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Artificial intelligence in scientific writing

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Artificial intelligence (AI) has long fascinated humanity and has been vividly depicted in several movies, such as "2001: A Space Odyssey" with HAL 9000 and "The Terminator" with Skynet. The topic has gained even more traction in recent years, both in the media and everyday life with the advent of tools such as ChatGPT (Open AI), which was launched in November 2022. These AI applications are now utilized for a wide range of tasks, from seeking travel advice to generating intricate mathematical tables for economic studies.

In this brief editorial, we will explore an AI application that significantly impacts the quality and volume of both general and medical science: the use of AI in scientific writing. According to ChatGPT, scientific writing "is a writing style used to present research information and results clearly, concisely, and accurately, following specific rules and structures. It is essential for the dissemination of scientific knowledge, enabling researchers, professionals, and the general population to understand, evaluate, and replicate studies and experiments".[1]

As conducting scientific research and preparing data for publication are tasks that demand substantial time and effort, even for seasoned authors, AI tools have garnered significant interest from numerous researchers. In 2024, Weidman[2] listed useful AI-based tools that are beneficial in various stages of the research process. These include tools for designing research questions (Elicit AI), identifying scientific databases (Search Smart), reviewing and analyzing the literature (Litmaps, Consensus, Connected Paper, ResearchRabbit, Scite, OpenRead), interpreting and synthetizing data (ChatGPT4, ResearchGPT, Lateral), structuring and writing academic papers and scientific articles for publication or for securing funding (Jenni.ai, Quillbot), translating texts into English (Google Translator, ChatGPT), and checking grammar (Grammarly).

AI tools can undoubtedly expedite various stages of scientific writing, including data analysis and statistics. They assist in recognizing data trends, providing contextual information, and enhancing linguistic accuracy, which is particularly crucial for non-native English-speaking authors. However, certain tasks still necessitate human intervention: reasoning, applying and integrating knowledge to address complex problems, demonstrating true creativity, and developing groundbreaking theories.[3] The value of AI-generated outputs heavily relies on the breadth and quality of the sources powering these tools.[2] Often, these sources lack transparency and exhibit inconsistent quality, both within a single tool and across tools, depending on how queries are formulated.

Authorship and plagiarism have also sparked considerable debate. As AI generates contents based on existing sources, and these sources may not be clearly referenced, the resulting material might be considered plagiarized.[4] This raises the question of who should receive credit for AI-generated content: the person who created the question, the one who typed the prompt, the programmer, or the AI owner?

Furthermore, the way human authors interpret and use AI-generated content is a cause for concern. According to Anderson and Rainie, "considering the lack of user understanding of how these models derive their outputs, there are significant concerns about objectivity, bias, and fairness. This can lower the quality of academic work and oversimplify subtle academic arguments, ultimately leading to a loss of innovation and original critical thinking".[5]

In conclusion, AI tools can significantly assist the scientific process by enhancing the construction of scientific knowledge. However, their proper and human-supervised use, along with addressing referencing and plagiarism issues, remain critical concerns that need to be debated and regulated by the global scientific community.

REFERENCES

1. OpenAI. ChatGPT (GPT-4 version). Available from: https://www.openai.com/chatgpt. Accessed in 2024 (Jul. 1st).
2. Weidmann AE. Artificial intelligence in academic writing and clinical pharmacy education: consequences and opportunities. Int J Clin Pharm. 2024;46(3):751-4. PMID: 38472596; https://doi.org/10.1007/s11096-024-01705-1.
3. Joksimovic S, Ifenthaler D, Marrone R, de Laat M, Siemens G. Opportunities of artificial intelligence for supporting complex problem-solving: findings from a scoping review. Comput Educ Artif Intell. 2023;4:100138. https://doi.org/10.1016/j.caeai.2023.100138.
4. Livberber T, Ayvaz S. The impact of artificial intelligence in academia: views of Turkish academics on ChatGPT. Heliyon. 2023;9(9):e19688. PMID: 37809772; https://doi.org/10.1016/j.heliyon.2023.e19688.
5. Anderson J, Rainie L. As AI Spreads, Experts predict the best and worst changes in digital life by 2035. Pew Research Center, June 21, 2023. Available from: https://www.pewresearch.org/internet/2023/06/21/as-ai-spreads-experts-predict-the-best-and-worst-changes-in-digital-life-by-2035/. Accessed in: 2024 (Jul. 1st).

Alcohol consumption during pregnancy by women from southern Brazil: a cross-sectional study

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ABSTRACT

BACKGROUND: Some maternal characteristics are related to alcohol intake during pregnancy, which irreversibly compromises the maternal-fetal binomial integrity.

OBJECTIVES: To identify the frequency, impact, and factors associated with alcohol consumption during pregnancy.

DESIGN AND SETTING: A cross-sectional study was performed at the Hospital Materno Infantil Presidente Vargas (HMIPV) in Porto Alegre/RS between March and December 2016.

METHODS: A structured questionnaire was administered along with a medical records review. They refer to the maternal sociodemographic and gestational status, alcohol consumption patterns, and characteristics of the fetus/newborn. In the statistical analysis, P values < 0.05 were considered significant.

RESULTS: The frequency of alcohol intake was 37.3%; this was characterized by the consumption of fermented beverages (89.3%), especially during the first trimester (79.6%). Risky consumption (high and/or early) occurred for 30.2% of participants. Risk factors associated with maternal alcohol consumption during pregnancy were tobacco use (P < 0.001) and abortion attempt (P = 0.023). Living with a partner (P = 0.002) and planning pregnancy (P = 0.009) were protective factors. Risky consumption was related to all of the aforementioned variables as well as threatened abortion (P = 0.023).

CONCLUSIONS: Alcohol intake during pregnancy is common and affects nearly one-third of pregnant women. Knowledge of the population at risk and protective factors is essential for the development of campaigns that seek to reduce consumption and, therefore, its consequences for the mother and fetus.

INTRODUCTION

Health problems related to alcohol consumption are usually associated with males. However, changes in the social role of women have led to a decrease in this difference.[1] Over time, a progressive rise in the use and abuse of alcohol by women has been observed,[2] even at childbearing age, which has led to an increasing number of obstetric and neonatal complications.[3] According to the World Health Organization (WHO), the global prevalence of alcohol intake is 9.8%.[4] In Brazil, this reality is even more concerning, with frequencies ranging from 6% to 60%.[5-7]

Some maternal characteristics are associated with an increased frequency and amount of alcohol intake during pregnancy. These include lifestyle, psychological factors, alcohol consumption patterns, concomitant drug use, social vulnerability, and aspects related to family structure, such as single motherhood.[8] The lack of prenatal care and pregnancy planning also appears to be important predisposing factors.[9,10]

Alcohol can cause injuries in one in every 100 live births exposed during pregnancy,[11] and there is no safe consumption amount. Therefore, abstinence is the best and safest conduct to be followed.[12] Alcohol directly acts on fetal and maternal-fetal tissue and, indirectly, on nutrients and oxygen supply, which can result in devastating and irreversible effects on the embryo/fetus.[13] Consequently, the spectrum of fetal consequences may be wider, ranging from only cognitive and behavioral disorders to fetal alcohol syndrome.[14,15]

Thus, these effects and consequences highlight the importance of early detection and profiling of women at risk of alcohol use during pregnancy. This will enable the development of more effective management and follow-up approaches.

OBJECTIVE

Considering the scarcity of Brazilian epidemiological studies related to this issue, our aim was to identify the impact and factors associated with alcohol intake in pregnant women who gave birth at a reference hospital in southern Brazil.

METHODS

This was a prospective cross-sectional study carried out at the Hospital Materno Infantil Presidente Vargas (HMIPV) that included pregnant and postpartum women and their respective newborns who utilized the hospital's obstetrics service at birth from March to December 2016. All patients were users of the Unified Health System (in Portuguese, Sistema Único de Saúde – SUS), which is the current public health system in Brazil. The HMIPV is located at Porto Alegre and is a reference hospital for maternal and child care in the State of Rio Grande do Sul (RS).

Trained members conducted a pilot study and applied the clinical protocol. Data were collected through direct interviews with puerperal women during rooming in shortly after delivery. The medical records of the mothers and their respective newborns were also reviewed. The data collected included sociodemographic and gestational history findings, fetuse/newborns characteristics, and the use of drugs, including alcohol, during pregnancy. The sample comprised 570 women who were divided into two groups: 1) those who did and 2) did not consume alcohol during pregnancy.

Maternal age was stratified into women aged 20 years or younger, those 21–34 years, and those 35 years or older.[16] Origin was classified by whether the patient lived in Porto Alegre, metropolitan region, or countryside town of the state. Puerperal women's education was classified as incomplete elementary education, complete elementary education, and complete secondary education to higher education.[17] The number of residents per house into two groups: from one to five and from six to 14 individuals.[18] Family income was categorized into one minimum wage (BRL 880.00 at the moment of the study) or more per household. Women were divided into primiparous or multiparous groups according to their number of pregnancies.[19] Prenatal care was divided by trimester of beginning (in first, second, or third)[20] and by consultations number (fewer than six or six or more).[21]

Women were asked about quarter(s) of alcohol consumption; alcohol amount consumed and intensity, frequency, and type of drink. All beverage measurements were converted and presented according to international (10 g of pure alcohol per serving)[22] and national standards (14 g of pure alcohol per serving). This corresponds to approximately 350 mL of beer, 150 mL of wine, or 45 mL of hard liquor.[2]

Alcohol consumption amount was categorized as low (1–20 g/day), moderate (21–40 g/day) or high (≥ 41 g/day).[23] Binge drinking episodes and heavy episodic drinking were assessed according to WHO guidelines and defined as the consumption of 60 g or more of pure alcohol, or about four servings or more on at least one occasion.[22] Drink types were questioned and classified into fermented (beer, sparkling wine, and wine) and distillates (whiskey, vodka, "cachaça," "caipirinha," and tequila). Consumption frequency was classified as monthly or less, two to four times a month, two to three times a week, or four or more times a week. Women who answered affirmatively to at least one of the following variables were categorized as engaging in risky consumption: period of use in the first trimester, consumption frequency of four or more times a week, high amount consumption (≥ 41 g/day), or positive for binge drinking episodes.[24]

Prematurity was defined as gestational age at birth less than 37 weeks[25] and low birth weight as below 2,500 grams.[26] For Apgar scores, values greater or less than 7 were considered at the first and fifth minutes of life.[27] When fetal malformations were present, they were classified as isolated or multiple and specified according to the medical records description. In assessing microcephaly, the measurement of the newborns head circumference was considered both for gestational age at birth (absolute) and after correction, considering baby's length (relative or true).[28]

The results for qualitative variables are presented as frequencies and percentages, and the quantitative variables are shown as averages and standard deviations. Normality was verified using the Shapiro-Wilk test and histogram inspection. Sociodemographic and gestational factors associated with alcohol consumption were evaluated using a Poisson regression analysis with robust variance adjustment. Prevalence ratio (PR) measurements are presented with a 95% confidence interval. For multivariate analysis, variables with $P < 0.20$ in the Wald test were selected. To evaluate the characteristics of fetuses and live births, Student's t-test and chi-square tests were applied, as was Fisher's exact test when appropriate. The results were considered statistically significant at $P < 0.05$. The analyses were performed using SPSS statistical software (SPSS Inc., Chicago, United States, Release 22.0, 2013).

This study was approved by the Research Ethics Committee of HMIPV on October 10, 2017 (CAAE 09909712.3.1001.5329), and the Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA) on January 12, 2018 (CAAE 9909712.3.3001.5345). The study was only performed after informed consent assignment.

RESULTS

The total sample consisted of 570 women, ages ranging from 12 to 45 years (mean 25.1, SD ± 7.1). Gestation was recognized at an average of 11.6 weeks. Paternal ages ranged from 15 to 60 years (mean 28.5, SD ± 8.5). The average number of maternal pregnancies was 2.32 (range 1–12).

Alcohol consumption was reported by 213 women (37.3%). Age was similar between women who consume and did not consume

alcohol (mean age of 24.9 [SD ± 6.8] and 25.2 years [SD ± 7.2] respectively; P = 0.5887). Most women who drank alcohol during pregnancy consumed low amounts (64.2%; moderate: 16.9%; high: 18.9%). However, approximately one in every four women (24.9%) reported binge drinking episodes. Fermented beverages were the main type of beverage consumed (89.3%), with beer representing the most common (82.1%), followed by vodka (17%) and wine (9.2%). Almost 13% of women drank both fermented and distilled beverages during pregnancy. Most drank monthly or less (63.9%; two to four times a month: 27.4%; two to three times a week: 6.7%; and four or more times a week: 1.9%). The first trimester was the most commonly reported period of alcohol use (79.6%), with a decreasing trend in the other trimesters (second trimester: 48.3%; third trimester: 33.6%). Continuous use throughout pregnancy was reported by 21.8% of women.

Table 1 presents the consumption of alcoholic beverages during pregnancy according to maternal sociodemographic characteristics. There was a significant association between presence of a partner and lower alcohol consumption (PR = 0.66; 95%CI: 0.53-0.83; P < 0.001). However, beverage consumption was significant in two situations: when the pregnancy was unplanned (41.9%; PR = 0.72; 95%CI: 0.57-0.91; P = 0.006) and when some abortive intervention was carried out (71.4%; PR = 1.93; 95%CI: 1.20-3.13; P = 0.007; **Table 2**).

Drinking during pregnancy was associated with both concomitant use of illicit (PR = 2.20; 95%CI: 1.72-2.80; P < 0.001) and licit drugs (tobacco; PR = 1.96; 95%CI: 1.61-2.39; P < 0.001) as well as use during the first trimester of pregnancy (P < 0.001). Alcohol intake during gestation occurred in 78.3% of women who had used illicit drugs and 59.6% of those who smoked. Approximately three out of four marijuana users had consumed alcohol. Only eight women reported using cocaine (3.8%), and three crack (1.4%). All of them reported using alcohol simultaneously (**Table 3**).

None fetal or newborn characteristic was associated with consumption of alcoholic beverages by women. However, 'multiple" malformations were most predominant in the group of fetuses exposed to alcohol (46.2%; **Table 4**).

Multivariate analysis showed that trying to terminate the pregnancy increased the chance of alcohol consumption by 63% (PR = 1.63; 95%CI: 1.04-2.54; P = 0.032), while smoking increased it by 90% (PR = 1.90; 95%CI: 1.55-2.32; P < 0.0001; **Table 5**). However, the presence of protective factors is noteworthy. The likelihood of alcohol consumption for a pregnant woman with a partner was 23% lower than that for women with no partner (PR = 0.77; 95%CI: 0.61-0.97; P = 0.024). In addition, planning the pregnancy reduced the chance of alcohol consumption by one quarter (PR = 0.75; 95%CI: 0.59-0.94; P = 0.013; **Table 5**).

Risky alcohol consumption was observed in 171 women (30.2%) and was associated with attempt to terminate the pregnancy (PR = 1.92; 95%CI: 1.17-3.13; P = 0.009), threat of abortion (PR = 1.45;95%CI: 1.05-1.99; P = 0.023), and tobacco use

Table 1. Consumption of alcoholic beverages according to maternal sociodemographic characteristics

Variables		Total* (n = 570)	Alcohol use (n = 213)	%	P value	PR	95%CI	
		n	n					
Age group	≤ 20 years	183	68	37.2		1		
	21 to 34 years	319	123	38.6	0.757	1.04	0.82	1.31
	≥ 35 years	68	22	32.4	0.489	0.87	0.59	1.29
Origin	Porto Alegre	391	155	39.6		1		
	Metropolitan area	151	49	32.5	0.132	0.82	0.63	1.06
	Countryside town	28	9	32.1	0.456	0.81	0.47	1.41
Employed (n = 568)*	Yes	228	90	39.5		1		
	No	340	123	36.2	0.424	0.92	0.74	1.14
Education	Incomplete elementary education	200	79	39.5		1		
	Complete elementary education	188	69	36.7	0.571	0.93	0.72	1.20
	Complete secondary education to higher education	178	62	34.8	0.351	0.88	0.68	1.15
Presence of partner	No	100	52	52.0		1		
	Yes	470	161	34.3	0.000	0.66	0.53	0.83
Family income (n = 550)*	Less than R$ 880	112	41	36.6		1		
	> R$ 880	438	164	37.4	0.871	1.02	0.78	1.34
Number of residents per house (n = 566)*	< 5 individuals	315	110	34.9		1		
	≥ 5 individuals	251	101	40.2	0.193	1.15	0.93	1.43

Quantitative variables are presented as means and standard deviations in the text; *Number of valid answers; PR = Crude prevalence ratio; CI = Confidence interval.

(PR = 2.10; 95%CI: 1.66-2.65; P < 0.0001). The presence of a partner (PR = 0.66; 95%CI: 0.51-0.86; P = 0.002) and planned pregnancy (PR = 0.74;95%CI: 0.56-0.97; P = 0.027) were protective factors against risky alcohol consumption (**Table 6**).

DISCUSSION

This study identified a high frequency of alcohol consumption in pregnant women (37.3%), similar to other Brazilian studies, such as those that took place in São Paulo (33.3%),[6] Rio de Janeiro (40.6%),[28] and Teresina (32.4%).[29] These frequencies are higher than those reported in developed countries (10.2%).[30] In addition to methodological and sampling differences, some factors, such as effectiveness of public health policies and cultural disparities, may have contributed to such inequalities.[26] In general, alcohol consumption in developed countries is seen more negatively than in Latin America.[31]

Table 2. Consumption of alcoholic beverages according to gestational characteristics

Variables		Total* (n = 570)	Alcohol use (n = 213)	%	P value	PR	95%CI	
		n	n					
Planned pregnancy	No	351	147	41.9		1		
	Yes	219	66	30.1	0.006	0.72	0.57	0.91
Number of gestations	Multiparous	340	128	37.6		1		
	Primiparous	230	85	37.0	0.867	0.98	0.79	1.22
Attempted abortion	No	563	208	36.9		1		
	Yes	7	5	71.4	0.007	1.93	1.20	3.13
Prenatal care	No	12	6	50.0		1		
	Yes	558	207	37.1	0.310	0.74	0.42	1.32
Number of consultations (n = 555)*	> = 6 consultations	430	157	36.5		1		
	< 6 consultations	125	50	40.0	0.471	1.10	0.85	1.40
Beginning of prenatal care (n = 558)*	1	375	132	35.2		1		
	2	166	71	42.8	0.087	1.22	0.97	1.52
	3	17	4	23.5	0.363	0.67	0.28	1.59
zz	No	518	189	36.5		1		
	Yes	51	24	47.1	0.110	1.29	0.94	1.76

*Number of valid answers; PR = Crude prevalence ratio; CI = Confidence interval.

Table 3. Consumption of alcoholic beverages according to concomitant use of drugs during pregnancy

Variables		Total* (n=570)	Alcohol use (n=213)	%	P value	PR	95%CI	
		n	n					
Use of illicit drugs during pregnancy	No	547	195	35.6		1		
	Yes	23	18	78.3	0.000	2.20	1.72	2.80
Use of illicit drugs during 1st trimester of pregnancy	No	548	196	35.8		1		
	Yes	22	17	77.3	0.000	2.16	1.68	2.78
Tobacco during pregnancy	No	434	132	30.4		1		
	Yes	136	81	59.6	0.000	1.96	1.61	2.39
Tobacco 1st trimester	No	437	134	30.7		1		
	Yes	133	79	59.4	0.000	1.94	1.59	2.36
Marijuana	No	550	198	36.0		1		
	Yes	20	15	75.0	0.000	2.08	1.58	2.75
Marijuana 1st trimester (n = 569)*	No	550	198	36.0		1		
	Yes	19	14	73.7	0.000	2.05	1.53	2.74
Cocaine	No	562	205	36.5		1		
	Yes	8	8	100	0.000	2.74	2.46	3.06
Cocaine 1st trimester (n = 569)*	No	562	205	36.5		1		
	Yes	7	7	100	0.000	2.74	2.46	3.06
Crack	No	567	210	37.0		1		
	Yes	3	3	100	0.000	2.70	2.43	3.01
Crack 1st trimester (n = 569)*	No	567	210	37.0		1		
	Yes	2	2	100	0.000	2.70	2.43	3.01

*Number of valid answers; PR = Crude prevalence ratio; CI = Confidence interval.

Table 4. Fetus or newborn characteristics according to maternal consumption of alcoholic beverages during pregnancy

Variables		Total[a]	Alcohol use	%	P value	PR	95%CI	
		n*	n*					
Malformation	No	550	204	37.1				
	Yes	33	13	39.4	0.787	1.06	0.69	1.64
Type of Malformation	Multiple	9	6	66.7		1		
	Isolated	24	7	29.2	0.037	0.44	0.20	0.95
Thoracic	No	580	214	36.9		1		
	Yes	3	3	100.0	0.000	2.71	2.44	3.01
Skeletal	No	580	215	37.1		1		
	Yes	3	2	66.7	0.154	1.80	0.80	4.03
Gastrointestinal	No	580	215	37.1		1		
	Yes	3	2	66.7	0.154	1.80	0.80	4.03
Urinary tract	No	572	212	37.1		1		
	Yes	11	5	45.5	0.542	1.23	0.64	2.36
Extremities	No	578	215	37.2		1		
	Yes	5	2	40.0	0.895	1.08	0.37	3.16
Abdomen	No	580	216	37.2		1		
	Yes	3	1	33.3	0.892	0.90	0.18	4.45
Central nervous system	No	573	215	37.5		1		
	Yes	10	2	20.0	0.322	0.53	0.15	1.85
Other	No	578	215	37.2		1		
	Yes	5	2	40.0	0.895	1.08	0.37	3.16
Prematurity	>=37	502	186	37.1		1		
	<37	73	28	38.4	0.828	1.04	0.76	1.41
Low birth weight	>=2,500g	506	187	37.0		1		
	<2,500g	69	27	39.1	0.723	1.06	0.77	1.45
Absolute microcephaly (n = 489)[a]	No	473	175	37.0		1		
	Yes	16	7	43.8	0.563	1.18	0.67	2.09
Relative microcephaly * (n = 489)[a]	No	482	179	37.1		1		
	Yes	42	16	38.1	0.902	1.03	0.68	1.54
Apgar 1 < 7* (n = 569)[a]	> = 7	518	185	35.7		1		
	< 7	51	25	49.0	0.040	1.37	1.01	1.86
Apgar 5 < 7* (n = 569)[a]	> = 7	562	206	36.7		1		
	< 7	7	4	57.1	0.181	1.56	0.81	2.99

*Relative microcephaly corrected for the length of the baby; Apgar 1<7/Apgar 5<7 = values greater or less than 7 in the first and fifth minutes of life; a. Number of fetuses/neonates, considering deaths and valid responses; PR = Crude prevalence ratio; CI = Confidence interval.

Table 5. Multiple regression analysis of factors associated with alcohol consumption during pregnancy

Variables	P value	PR	95%CI	
Marital status = With partner	0.024	0.77	0.61	0.97
Planned pregnancy = Yes	0.013	0.75	0.59	0.94
Attempted abortion = Yes	0.032	1.63	1.04	2.54
Smoking = Yes	0.000	1.90	1.55	2.32

Valid variables with P < 0.20 in the Wald test were included in the analysis: PR = Adjusted prevalence ratio; CI = Confidence interval.

Table 6. Multiple regression analysis of factors associated with risky consumption during pregnancy

Variables	P value	PR	95%CI	
Marital status = with partner	0.002	0.66	0.51	0.86
Planned pregnancy = Yes	0.027	0.74	0.56	0.97
Attempted abortion = Yes	0.009	1.92	1.17	3.13
Threat of abortion = Yes	0.023	1.45	1.05	1.99
Smoking = Yes	0.000	2.10	1.66	2.65

Valid variables with P < 0.20 in the Wald test were included in the analysis; Risk consumption considered women who answered affirmatively to at least one of the variables: quantity (high > = 41g/day), frequency (4 or > week), EBP (positive), and consumption in the first trimester; PR = Adjusted prevalence ratio; CI = Confidence interval.

The results obtained in our study about the use of alcohol in the first trimester of pregnancy and the occurrence of binge drinking episodes among pregnant women were cause for concern. They were similar to those reported by other authors[9,10] and highlight the progressive tendency of the female population to consume more alcohol at abusive levels.[32] Early consumption of alcohol within the first trimester has been associated with a 12-fold greater chance of fetal involvement. Moreover, excessive levels of alcohol intake have increased the risk for worse neonatal outcomes.[33]

Alcohol consumption most often occurred in an occasional way and in low quantities; this fact reflects the underestimation

of the harmful effects even for small amounts.[11] In addition, the drinks mainly consisted of fermented beverages, especially beer and derivatives, which may also demonstrate an underestimation of the potential risk of these beverages compared to distilled drinks.[34]

The absence of a partner has been shown to be closely related to alcohol consumption by women during pregnancy.[8,9,13] According to the Centers for Disease Control and Prevention (CDC), alcohol consumption is almost twice as common among pregnant women with no partner. In addition, the frequency of excessive consumption among these women is significantly higher.[35] This finding is often related to other risk factors for alcohol consumption, such as unplanned pregnancies, as well as low socioeconomic status, with the mothers usually being the main or only providers of income.[36] Notably, in the present study, the presence of a partner was a protective factor for alcohol consumption, which may be related to greater financial and emotional stability as well as family support.

Another protective factor identified in this study was pregnancy planning. There are reports in literature of substantially less alcohol consumption by women during pregnancy when there is intention and planning to become pregnant.[9,37] Failure to plan and, consequently, delay to recognize the pregnancy, can lead many women to engage in harmful behaviors, including the consumption of alcoholic beverages.[10] This fact helps to clarify the high frequency of alcohol intake (79.6%) during the first trimester observed in our study. In addition, women tend to be more careful about what they consume when pregnancy is planned, as they are more aware of possible risks for the fetus due to alcohol consumption.[38]

The use of pregnancy termination methods was associated with risky alcohol intake in our sample. This association is well described in the literature.[8,39] This may be linked to pregnancy rejection because it is unwanted.

Threatened abortion was the only variable that showed an exclusive association with at-risk alcohol consumption in this study. According to the literature,[40] women who consume more than five drinks per week have a significantly greater chance of miscarriage. This problem occurs because alcohol is one of the main substances responsible for childbirth-related problems.[41]

As previously described in the literature,[5,15,41] we found that smoking was an important factor associated with risky alcohol consumption. The simultaneous use of alcohol and tobacco can be explained by the legality and wide availability of these substances as well as by the common maternal risk factors for their use during pregnancy, which are usually related to the vulnerability presented by these women.[42] In addition, studies have identified neurotransmitters and nicotine receptors that interact with both substances and mediate effects involved not only in their sensitivity but also in dependence.[43]

The most discussed and described fetal malformations associated with alcohol consumption belong to the spectrum of findings observed in individuals with FAS.[14] However, some studies point to possible associations between maternal alcohol consumption and the occurrence of other anomalies.[43] In the present study, no major fetal/neonatal malformation was associated with the consumption of this substance. Alcohol can cross the placental barrier and directly interfere with embryonic and fetal development. However, there is no single mechanism that can explain all of the harmful effects of alcohol on the fetus or the precise alcohol amount that can cause malformations.[9]

Other factors have been associated with alcohol consumption during pregnancy, such as low education and socioeconomic level, advanced maternal age, and lack of prenatal care.[8,9,13] However, we did not find significant relationships among them in the present study.

Despite the care we took in terms of both sample size and data collection and analysis, we cannot rule out possible limitations such as memory bias. Previous literature indicates that parents who have children with malformations tend to remember more details about their previous history, such as the use of substances during pregnancy.[44]

CONCLUSION

Therefore, alcohol intake during pregnancy is common at our hospital. There is also high use during the first trimester as well as preferential consumption of fermented products and in abusive amounts, which represents important cause for concern. This risk of alcohol intake applies mainly to women who smoke, attempt pregnancy termination, or have a threat of miscarriage. However, there are protective factors such as the presence of a partner and pregnancy planning. Considering the unique characteristics of this vulnerable population, these findings may be important in the development of more effective campaigns for the avoidance of alcohol consumption by women during gestation.

Moreover, healthcare professionals should be prepared to identify efficient strategies during prenatal care, given the apparent lack of awareness in a considerable number of situations involving this issue in routine consultations.

REFERENCES

1. Marangoni SR, Oliveira ML. Fatores desencadeantes do uso de drogas de abuso em mulheres. Texto Context Enferm. 2013;22(3):662-70. https://doi.org/10.1590/S0104-07072013000300012.
2. De Andrade AG. Álcool e Saúde dos Brasileiros. 1st ed. Vol. 1. São Paulo: CISA; 2021. Available from: https://cisa.org.br/images/upload/Panorama_Alcool_Saude_CISA2021.pdf. Accessed in 2023 (May 21).
3. Santana RA, Almeida LF, Monteiro DL. Síndrome alcoólica fetal–revisão sistematizada. Rev HUPE. 2014;13(3):61-6. https://doi.org/10.12957/rhupe.2014.12128.

4. World Health Organization. Guidelines for the identification and management of substance use and substance use disorders in pregnancy. Geneva: WHO, 2014. Available from: https://www.who.int/publications/i/item/9789241548731. Accessed in 2023 (Jun. 21).
5. Rocha PC, Britto e Alves MT, Chagas DC, et al. Prevalence of illicit drug use and associated factors during pregnancy in the BRISA cohort. Cad Saude Publica. 2016;32(1):S0102-311X2016000100707. PMID: 26886368; https://doi.org/10.1590/0102-311x00192714.
6. Sbrana M, Grandi C, Brazan M, et al. Alcohol consumption during pregnancy and perinatal results: a cohort study. Sao Paulo Med J. 2016;134(2):146-52. PMID: 27007799; https://doi.org/10.1590/1516-3180.2015.02040211.
7. França VT, Ferrari L, Ebert JP, et al. Avaliação do uso de drogas por gestantes atendidas em hospital de ensino do interior do Rio Grande do Sul. Rev Epidemiol Control Infec. 2016;6(2):68-73. https://doi.org/10.17058/reci.v6i2.6976.
8. Montag AC. Fetal alcohol-spectrum disorders: identifying at-risk mothers. Int J Womens Health. 2016;8:311-23. PMID: 27499649; https://doi.org/10.2147/ijwh.s85403.
9. Mesquita MA, Segre CA. Freqüência dos efeitos do álcool no feto e padrão de consumo de bebidas alcoólicas pelas gestantes de maternidade pública da cidade de São Paulo. J Human Growth Developm. 2009;19(1):63-77. https://doi.org/10.7322/jhgd.19903.
10. Dejong K, Olyaei A, Lo JO. Alcohol use in pregnancy. Clin Obstet Gynecol. 2019;62(1):142-55. PMID: 30575614; https://doi.org/10.1097/grf.0000000000000414.
11. Carson G, Cox LV, Crane J, et al. Alcohol use and pregnancy consensus clinical guidelines. J Obstet Gynaecol Can. 2010;32(8 Suppl 3):S1-31. PMID: 21172102; https://doi.org/10.1016/s1701-2163(16)34633-3.
12. American College of Obstetricians and Gynecologists. Committee opinion no. 496: At-risk drinking and alcohol dependence: obstetric and gynecologic implications. Obstet Gynecol. 2011;118(2 Pt 1):383-8. PMID: 21775870; https://doi.org/10.1097/aog.0b013e31822c9906.
13. Tan CH, Denny CH, Cheal NE, Sniezek JE, Kanny D. Alcohol use and binge drinking among women of childbearing age - United States, 2011-2013. MMWR Morb Mortal Wkly Rep. 2015;64(37):1042-6. PMID: 26401713; https://doi.org/10.15585/mmwr.mm6437a3.
14. Suttie M, Foroud T, Wetherill L, et al. Facial dysmorphism across the fetal alcohol spectrum. Pediatrics. 2013;131(3):e779-88. PMID: 23439907; https://doi.org/10.1542/peds.2012-1371.
15. Segre CAM, coord. Efeitos do álcool na gestante, no feto e no recém-nascido. São Paulo: Sociedade de Pediatria de São Paulo; 2010. Available from: https://www.spsp.org.br/downloads/AlcoolSAF2.pdf. Accessed in 2023 (Jun. 21).
16. Santos GH, Martins MG, Sousa MS, Batalha SJ. Impact of maternal age on perinatal outcomes and mode of delivery. Rev Bras Ginecol Obstet. 2009;31(7):326-34. PMID: 19838577; https://doi.org/10.1590/S0100-72032009000700002.
17. Greco SMSS, coord. Empreendedorismo no Brasil: 2016. Curitiba: IBQP; 2017. Available from: https://ibqp.org.br/wp-content/uploads/2017/07/AF-GEM-Nacional-BAIXA.pdf. Accessed in 2023 (Jun. 21).
18. Fonseca VM, Sichieri R, Basilio L, Ribeiro LVC. Consumo de folato em gestantes de um hospital público do Rio de Janeiro. Rev Bras Epidemiol. 2003;6(4):319-27. https://doi.org/10.1590/S1415-790X2003000400006.
19. Linhares JJ, Macêdo NM, Arruda GM, et al. Factors associated with mode of delivery in women with pre-eclampsia. Rev Bras Ginecol Obstet. 2014;36(6):259-63. PMID: 25099465; https://doi.org/10.1590/s0100-720320140004812.
20. Linhares AO, Cesar JA. Suplementação com ácido fólico entre gestantes no extremo Sul do Brasil: prevalência e fatores associados. Ciên Saúde Colet. 2017;22(2):535-42. https://doi.org/10.1590/1413-81232017222.06302016.
21. Brasil. Humanização do parto – humanização no pré-natal e nascimento. Brasília-DF: Ministério da Saúde; 2002. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/parto.pdf. Accessed in 2023 (Jun. 21).
22. World Health Organization. Self-help strategies for cutting down or stopping substance use: a guide. Geneva: WHO; 2010. Available from: https://www.who.int/publications/i/item/9789241599405. Accessed in 2023 (Jun. 21).
23. World Health Organization, Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. AUDIT: The alcohol use disorders identification test: Guidelines for use in primary health care. Geneva: WHO; 2001. Available from: https://apps.who.int/iris/handle/10665/67205. Accessed in 2023 (Jun. 21).
24. World Health Organization. WHO recommendations for care of the preterm or low birth weight infant. Geneva: WHO; 2022. Available from: https://www.who.int/publications/i/item/9789240058262. Accessed in 2023 (Jun. 21).
25. World Health Organization. Global nutrition targets 2025: low birth weight policy brief. Geneva: WHO; 2014. Available from: https://www.who.int/publications/i/item/WHO-NMH-NHD-14.5. Accessed in 2023 (Jun. 21).
26. Brasil. Atenção à saúde do recém-nascido: guia para os profissionais de saúde. Brasília-DF: Ministério da Saúde; 2014. Available from: https://bvsms.saude.gov.br/bvs/publicacoes/atencao_saude_recem_nascido_v1.pdf. Accessed in 2023 (Jun. 21).
27. Margotto PR. Intrauterine growth curves: study of 4413 single live births of normal pregnancies. J Pediatr. 1995;71(1):11-21. PMID: 14689030; https://doi.org/10.2223/jped.696.
28. Moraes CL, Reichenheim ME. Screening for alcohol use by pregnant women of public health care in Rio de Janeiro, Brazil. Rev Saude Publica. 2007;41(5):695-703. PMID: 17923889; https://doi.org/10.1590/s0034-89102007000500002.
29. Veloso LU, de Souza Monteiro CF. Prevalence and factors associated with alcohol use among pregnant adolescents. Rev Lat Am Enfermagem. 2013;21(1):433-41. PMID: 23546329; https://doi.org/10.1590/s0104-11692013000100020.

30. Laranjeira R, Pinsky I, Sanches M, Zaleski M, Caetano R. Alcohol use patterns among Brazilian adults. Braz J Psychiatry. 2010;32(3):231-41. PMID: 19918673; https://doi.org/10.1590/s1516-44462009005000012.
31. Brasil. Conhecendo os efeitos do uso de drogas na gestação e as consequências para os bebês. Brasília-DF: Ministério da Cidadania; 2021. Available from: https://www.gov.br/mds/pt-br/pt-br/noticias-e-conteudos/desenvolvimento-social/noticias-desenvolvimento-social/ministerio-da-cidadania-lanca-cartilha-sobre-efeitos-e-consequencias-do-uso-de-drogas-na-gestacao/30042021_cartilha_gestantes.pdf. Accessed in 2023 (Jun. 21).
32. May PA, Blankenship J, Marais AS, et al. Maternal alcohol consumption producing fetal alcohol spectrum disorders (FASD): quantity, frequency, and timing of drinking. Drug Alcohol Depend. 2013;133(2):502-12. PMID: 23932841; https://doi.org/10.1016/j.drugalcdep.2013.07.013.
33. Meucci RD, Saavedra JS, Silva ES, et al. Alcohol intake during pregnancy among parturients in southern Brazil. Rev Bras Saude Mater Infant. 2017;17(4):653-61. https://doi.org/10.1590/1806-93042017000400003.
34. Denny CH, Acero CS, Naimi TS, Kim SY. Consumption of alcohol beverages and binge drinking among pregnant women aged 18-44 years - United States, 2015-2017. MMWR Morb Mortal Wkly Rep. 2019;68(16):365-8. PMID: 31022164; https://doi.org/10.15585/mmwr.mm6816a1.
35. Oliveira TR, Simões SMF. O consumo de bebida alcóolica pelas gestantes: um estudo exploratório. Esc Anna Nery. 2007;11(4):632-8. https://doi.org/10.1590/S1414-81452007000400012.
36. O'Keeffe LM, Kearney PM, McCarthy FP, et al. Prevalence and predictors of alcohol use during pregnancy: findings from international multicentre cohort studies. BMJ Open. 2015;5(7):e006323. PMID: 26152324; https://doi.org/10.1136/bmjopen-2014-006323.
37. Baptista FH, Rocha KBB, Martinelli JL, et al. Prevalence and factors associated with alcohol consumption during pregnancy. Rev Bras Saude Mater Infant. 2017;17(2):271-9. https://doi.org/10.1590/1806-93042017000200004.
38. Roberts SCM. The presence and consequences of abortion aversion in scientific research related to alcohol use during pregnancy. Int J Environ Res Public Health. 2019;16(16):2888. PMID: 31412544; https://doi.org/10.3390/ijerph16162888.
39. Kesmodel U, Wisborg K, Olsen SF, Henriksen TB, Secher NJ. Moderate alcohol intake during pregnancy and the risk of stillbirth and death in the first year of life. Am J Epidemiol. 2002;155(4):305-12. PMID: 11836194; https://doi.org/10.1093/aje/155.4.305.
40. Roberts SC, Pies C. Complex calculations: how drug use during pregnancy becomes a barrier to prenatal care. Matern Child Health J. 2011;15(3):333-41. PMID: 20232126; https://doi.org/10.1007/s10995-010-0594-7.
41. Guimarães VA, Fernandes KS, Lucchese R, et al. Prevalence and factors associated with alcohol use during pregnancy in a maternity hospital in Goiás, Central Brazil. Cien Saude Colet. 2018;23(10):3413-20. PMID: 30365860; https://doi.org/10.1590/1413-812320182310.24582016.
42. Falk DE, Yi HY, Hiller-Sturmhöfel S. An epidemiologic analysis of co-occurring alcohol and tobacco use and disorders: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. Alcohol Res Health. 2006;29(3):162-71. PMID: 17373404.
43. Kurita H, Motoki N, Inaba Y, et al. Maternal alcohol consumption and risk of offspring with congenital malformation: the Japan Environment and Children's Study. Pediatr Res. 2021;90(2):479-86. PMID: 33230193; https://doi.org/10.1038/s41390-020-01274-9.
44. Coughlin SS. Recall bias in epidemiologic studies. J Clin Epidemiol. 1990;43(1):87-91. PMID: 2319285. https://doi.org/10.1016/0895-4356(90)90060-3.

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Effects of bariatric surgery on renal function: a retrospective cohort study comparing one-year outcomes between one-anastomosis gastric bypass and Roux-en-Y gastric bypass

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ABSTRACT

BACKGROUND: Evidence on the effect of one-anastomosis gastric bypass (OAGB) on renal function is limited.

OBJECTIVE: To compare the evolution of estimated renal function observed 1 year after OAGB and Roux-en-Y gastric bypass (RYGB) in individuals with obesity.

DESIGN AND SETTING: Observational, analytical, and retrospective cohort study. Tertiary-level university hospital.

METHODS: This study used a prospectively collected database of individuals who consecutively underwent bariatric surgery. Renal function was assessed by calculating the estimated glomerular filtration rate (eGFR), according to the Chronic Kidney Disease Epidemiology Collaboration. The one-year variation in the eGFR was compared between the procedures.

RESULTS: No significant differences in age, sex, obesity-associated conditions, or body mass index were observed among individuals who underwent either OAGB or RYGB. OAGB led to a significantly higher percentage of total (P = 0.007) and excess weight loss (P = 0.026). Both OAGB and RYGB led to significantly higher values of eGFR (103.9 ± 22 *versus* 116.1 ± 13.3; P = 0.007, and 102.4 ± 19 *versus* 113.2 ± 13.3; P < 0.001, respectively). The one-year variation in eGFR was 11 ± 16.2% after OAGB and 16.7 ± 26.3% after RYGB (P = 0.3). Younger age and lower baseline eGFR were independently associated with greater postoperative improvement in renal function (P < 0.001).

CONCLUSION: Compared with RYGB, OAGB led to an equivalent improvement in renal function 1 year after the procedure, along with greater weight loss.

INTRODUCTION

In the recent decades, obesity has reached worrisome epidemic proportions worldwide, compromising the life expectancy and quality of life of affected individuals. According to World Health Organization estimates, nearly 3 million deaths each year are directly attributable to obesity, mainly because of major cardiovascular events.[1] Obesity and its related conditions are also significantly associated with impairment of renal function and the development of end-stage chronic kidney disease (CKD). Several key pathophysiological factors are seemingly involved in this association, such as insulin resistance, diabetes, hypertension, accumulation of visceral fat, chronic inflammation, and hyperuricemia.[2] Evidence has also been reported, demonstrating that obesity acts as an independent risk factor for progression to CKD, both indirectly through diabetes and hypertension, as well as through a so-called obesity-related glomerulopathy (ORG), which is pathologically defined as glomerulomegaly and segmental focal glomerulosclerosis occurring in individuals with obesity regardless of other obesity-related medical conditions.[3,4] Although the pathophysiology of ORG remains unclear, obesity may initially induce hyperfiltration and increases tubular sodium reabsorption, resulting in glomerular hypertension and activation of the renin–angiotensin–aldosterone system, associated with inflammation and imbalance of adipokines. The clinical course is characterized by stable or slowly progressing

proteinuria, and up to one-third of patients develop renal failure and end-stage CKD.[5-7]

Weight loss interventions are effective in mitigating or even resolving ORG.[8] Considering that bariatric surgery (BS) is the most effective method that leads to long-term significant and sustained weight loss in individuals with refractory obesity, it also reportedly improves long-term kidney function in individuals with obesity. Several studies have demonstrated the beneficial effects of Roux-en-Y gastric bypass (RYGB) on renal function.[9,10] Garcia et al.[11] analyzed individuals who underwent RYGB and observed significant improvement in the estimated glomerular filtration rate (eGFR) 1 year postoperatively. Moreover, evidence that improvement of renal function after BS may occur regardless of weight loss or glycemic control has been reported, thus corroborating the hypothesis that adipokine homeostasis, enterohormonal mechanisms, and reduction of systemic inflammation may play pivotal roles in post-BS nephroprotection.[12,13]

One-anastomosis gastric bypass (OAGB) has emerged more recently as a promising and highly effective operation to treat obesity, with reports indicating both weight loss and resolution rates of diabetes as superior to those observed after RYGB.[14,15] OAGB is based on a simplification of RYGB, with a single anastomosis (gastroenterostomy) and no enteroenterostomy, which is generally associated with a reduction in technical complexity and significantly lower operative times.[16] However, to date and to the best of our knowledge, data reporting the impact of OAGB on renal function are scarce. In a single study, Bassiony et al. evaluated creatinine clearance in 10 patients undergoing OAGB and 47 patients undergoing sleeve gastrectomy, demonstrating a significant reduction in glomerular hyperfiltration and urinary protein excretion 6 months after both operations, without significant difference between the techniques.[17]

OBJECTIVE

This study aimed to compare the evolution of estimated renal function observed 1 year after OAGB and RYGB in individuals with obesity.

METHODS

Study Design

This observational, analytical, and retrospective study was based on a prospectively collected database of individuals who consecutively underwent BS at a tertiary-level university hospital between 2018 and 2019. BS was performed during the implementation of OAGB at this facility when individuals underwent either OAGB or RYGB without pre-established differences in the indications for both operations. OAGB was performed on days when the entire research team responsible for the trial was identified at http://ensaiosclinicos.gov.br as RBR-59k78k was present; RYGB was performed in the remaining cases. The research team was available monthly.

The main outcome considered was the variation in renal function 1 year postoperatively, which was compared between the RYGB and OAGB groups.

The study was approved by the Ethical Committee of the Universidade Estadual de Campinas under reference number CAAE 55545422.9.0000.5404 on March 25, 2022. All participants signed an informed consent form. All procedures involving human participants performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all the participants.

Study Population

We included individuals aged 18–65 years of any sex who underwent either OAGB or RYGB between 2018 and 2019. Individuals with incomplete medical records, belonging to vulnerable groups (minors or with mental or intellectual disabilities), or who did not consent to study participation were excluded. Surgery was indicated according to the National Institutes of Health Consensus criteria (body mass index [BMI] ≥ 40 kg/m^2 or BMI ≥ 35 kg/m^2 with obesity-related medical conditions).

No specific criteria were established for the participants to undergo either OAGB or RYGB, except in situations where there were contraindications for OAGB (severe gastroesophageal reflux, preoperative esophagogastric intestinal metaplasia, or an antecedent of familial gastric cancer). All patients underwent consecutive operations and were informed of the technique adopted prior to the procedure. OAGB was performed on days when the entire research team gathered, whereas RYGB was performed on the remaining days. The selected patients for surgery followed a regular hospital schedule.

Surgical Techniques

OAGB

The main features of OAGB include approximately 15 cm gastric pouch alongside a 200 cm biliopancreatic limb and a common channel comprising the remainder of the small intestine. **Figure 1** presents a graphical representation of the surgical technique.

RYGB

The main features of RYGB include an approximately 30-mL gastric pouch, 100-cm biliopancreatic loop, 150-cm alimentary limb, and a common channel comprising the remainder of the small intestine. **Figure 2** presents a graphical representation of the surgical technique.

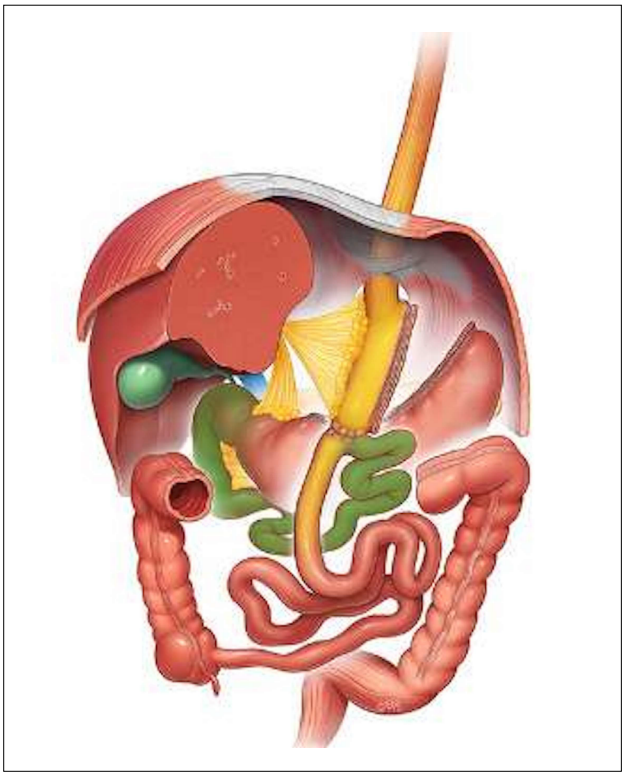

Figure 1. Graphic representation of one anastomosis gastric bypass. Source: © Dr Levent Efe, courtesy of IFSO.[48]

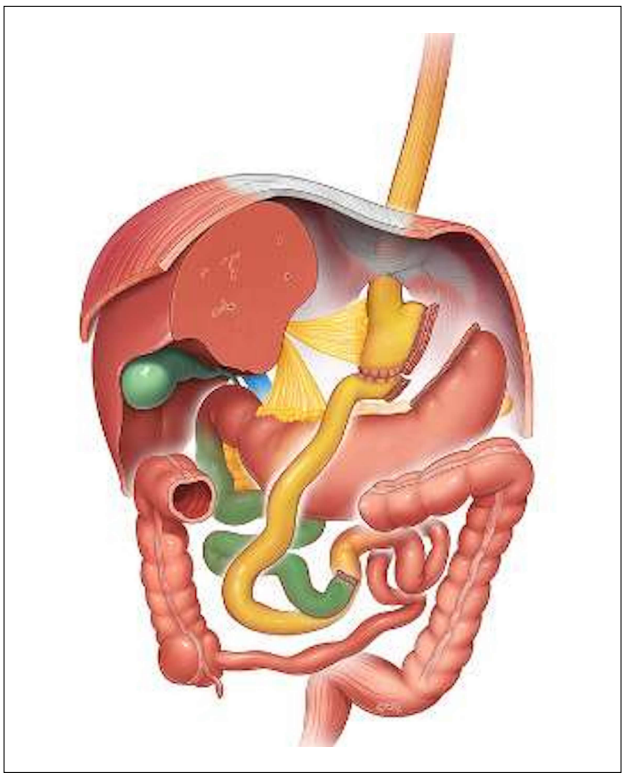

Figure 2. Graphic representation of Roux-en-Y gastric bypass. Source: © Dr Levent Efe, courtesy of IFSO.[48]

Study Variables

Demographic, Clinical, Anthropometric, and Biochemical Variables

The following variables were considered: age at surgery, sex, weight, BMI, and presence of obesity-associated medical conditions. Weight loss was analyzed as a percentage of total weight loss (%TWL) and excess weight loss (%EWL). Pre- and postoperative fasting glucose, serum urea, creatinine, and albumin levels were assessed. Percentage variations in these biochemical variables, considering their pre- and postoperative values, were calculated.

Renal Function Assessment

Renal function was assessed using eGFR, which was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula. The percentage variation in the CKD-EPI was calculated 1 year postoperatively.

The CKD-EPI formula was calculated according to the proposition of Levey et al.[18] It was used to evaluate the eGFR and has the advantage of not considering the patient's weight since, in individuals with obesity, the formulas that consider this variable tend to overestimate the true values of GFR.[19] The CKD-EPI formula is expressed as a single equation as follows:

$$eGFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if Black}]$$

Scr is serum creatinine (mg/dL), κ is 0.7 for women and 0.9 for men, α is −0.329 for women and −0.411 for men, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

Statistical Analysis

Proportions were compared using the chi-square test or Fisher's exact test, when necessary. Normality was assessed using the Shapiro–Wilk test. Comparisons of continuous or ordinal measurements between the two assessments were performed using the Mann–Whitney U test. To assess the associations of the study variables with the main outcome (one-year variation in GFR), simple and multiple regression analyses were performed. The level of significance was set at 5% ($P < 0.05$).

RESULTS

The average age of the study participants was 38.6 ± 9.1 years, and 87% were female. The mean preoperative BMI was 39 ± 5.8 kg/m^2; postoperatively, it significantly decreased to 27.9 ± 4.3 kg/m^2 ($P < 0.001$). Regarding obesity-related conditions, 43.2% presented with hypertension, and 26% had type 2 diabetes.

Overall, the participants experienced a %TWL of 23.2 ± 11.3% and %EWL of 77.3 ± 36.7%.

No significant differences in age, sex, obesity-associated conditions, or BMI were observed among individuals who underwent either OAGB or RYGB. OAGB led to significantly higher %TWL (P = 0.007) and %EWL (P = 0.026) (**Table 1**).

Regarding biochemical examinations, patients who underwent either RYGB or OAGB presented significantly decreased postoperative glucose, creatinine, hemoglobin, ferritin, and albumin levels. The urea, aminotransferase, and serum iron levels did not change significantly after either procedure. **Table 2** presents the evolution of the biochemical parameters after both procedures.

Considering the postoperative variation of renal function, both OAGB and RYGB led to significantly higher values of eGFR (103.9 ± 22 *versus* 116.1 ± 13.3; P = 0.007, and 102.4 ± 19 *versus* 113.2 ± 13.3; P < 0.001, respectively). The one-year variation of eGFR was 11 ± 16.2% after OAGB and 16.7 ± 26.3% after RYGB; no significant difference was observed between the two procedures (P = 0.3). The one-year postoperative variations in glucose, creatinine, and urea levels did not significantly differ between the procedures (**Table 1**).

In the univariate regression analysis enrolling the entire cohort, the main study outcome (one-year variation of GFR) was significantly associated with baseline creatinine (R = 0.80; P < 0.001) and baseline GFR (R = -0.85; P < 0.001); there was also a marginal association with age (R = 0.20; P = 0.07). Multivariate analysis was performed through multiple regression enrolling these three variables and showed that both age (R = −0.31; P < 0.001) and baseline GFR (R = -0.99; P < 0.001) were independently and negatively associated with the variation in GFR. Thus, the younger the age and the lower the GFR at surgery, the higher the postoperative increase in GFR. **Table 3** summarizes the results of the simple and multiple regression analyses.

DISCUSSION

The current study demonstrated that both OAGB and RYGB promoted the recovery of renal function after 1 year. Both procedures

Table 1. Comparison of baseline characteristics and postoperative outcomes between patients who underwent one anastomosis gastric bypass and those who underwent Roux-en-Y gastric bypass

	OAGB	RYGB	P value
N	46	100	NA
Age (years)	37.4 ± 8	39.2 ± 9.6	0.28
Sex	Male: 5 (10.9%) Female: 41 (89.1%)	Male: 14 (14%) Female: 86 (86%)	0.60
Preoperative BMI (kg/m²)	38.3 ± 5.4	37.3 ± 3.7	0.22
Postoperative BMI (kg/m²)	27 ± 3.9	28.4 ± 4.5	0.07
%TWL	26.9 ± 10.3%	21.4 ± 11.3%	**0.007**
%EWL	87.4 ± 30.7%	72.5 ± 38.5%	**0.026**
Preoperative glucose (mg/dL)	87.8 ± 14.7	91.6 ± 20.3	0.27
Postoperative glucose (mg/dL)	82 ± 8.5	81.8 ± 10	0.92
% Δ Glucose	−6.4 ± 15%	−6.9±15.5%	0.89
Preoperative creatinine (mg/dL)	0.8 ± 0.2	0.8 ± 0.2	0.99
Postoperative creatinine (mg/dL)	0.6 ± 0.1	0.6 ± 0.1	0.54
% Δ Creatinine	−14.6 ± 14.3%	−17 ± 20.5%	0.59
Preoperative urea (mg/dL)	24.7 ± 9.8	26.6 ± 9.8	0.29
Postoperative urea (mg/dL)	25.6 ± 6.8	25.1 ± 7	0.82
% Δ Urea	2.9 ± 20.9%	−4.7 ± 26.5%	0.39
Preoperative eGFR (mL/min/1.73m²)	103.9 ± 22	102.4 ± 19	0.69
Postoperative eGFR (mL/min/1.73m²)	116.1 ± 13.3	113.2 ± 13.3	0.33
% Δ eGFR	11 ± 16.2%	16.7 ± 26.3%	0.30
Preoperative obesity-associated conditions			
Type 2 diabetes – N (%)	15 (32.6%)	23 (23%)	0.22
Hypertension – N (%)	19 (41.3%)	44 (44%)	0.76
Postoperative obesity-associated conditions			
Type 2 diabetes – N (%)	1 (2.2%)	6 (6%)	0.31
Hypertension – N (%)	3 (6.5%)	9 (9%)	0.64
Diabetes remission rate (%)	93.3%	73.9%	0.13
Hypertension remission rate (%)	84.2%	79.5%	0.67

OAGB = one anastomosis gastric bypass; RYGB = Roux-en-Y gastric bypass; n = number of individuals; BMI = body mass index; eGFR = estimated glomerular filtration rate; % Δ = percentage of variation; %TWL = percentage of total weight loss; %EWL = percentage of excess weight loss.
Bold indicates statistical significance.

Table 2. Biochemical changes 1 year after one anastomosis gastric bypass and Roux-en-Y gastric bypass

One-anastomosis gastric bypass (n = 46)			
	Preoperative	**Postoperative**	**P value**
BMI (kg/m²)	38.3 ± 5.4	27 ± 3.9	**<0.001**
Glucose (mg/dL)	87.8 ± 14.7	82 ± 8.5	**0.047**
Creatinine (mg/dL)	0.8 ± 0.2	0.6 ± 0.1	**0.001**
Urea (mg/dL)	24.7 ± 9.8	25.6 ± 6.8	0.75
eGFR (mL/min/1.73m²)	103.9 ± 22	116.1 ± 13.3	**0.007**
AST (IU/L)	23.2 ± 9.6	23.8 ± 11.3	0.82
ALT (IU/L)	30.6 ± 24.2	27.2 ± 15.2	0.53
Hemoglobin (g/dL)	13.9 ± 1.1	13 ± 1.1	**0.002**
Ferritin (µg/L)	185.9 ± 103.2	94.2 ± 112.4	**0.03**
Serum iron (µg/dL)	69.1 ± 16.1	89.5 ± 32.9	0.08
Albumin (g/dL)	4.3 ± 0.3	4.1 ± 0.3	**0.01**
Roux-em-Y gastric bypass (n = 100)			
BMI (kg/m²)	37.3 ± 3.7	28.4 ± 4.5	**<0.001**
Glucose (mg/dL)	91.6 ± 20.3	81.8 ± 10	**0.002**
Creatinine (mg/dL)	0.8 ± 0.2	0.6 ± 0.1	**<0.0001**
Urea (mg/dL)	26.6 ± 9.8	25.1 ± 7	0.39
eGFR (mL/min/1.73m²)	102.4 ± 19	113.2 ± 13.3	**<0.0001**
AST (IU/L)	21.8 ± 7.3	22.8 ± 19.9	0.64
ALT (IU/L)	26.7 ± 16.1	26.6 ± 40.9	0.99
Hemoglobin (g/dL)	13.9 ± 1.3	13.1 ± 1.3	**0.01**
Ferritin (µg/L)	233.9 ± 249.3	138.8 ± 149	**0.01**
Serum iron (µg/dL)	71.2 ± 28.7	83 ± 38.1	0.08
Albumin (g/dL)	4.3 ± 0.3	4.1 ± 0.3	**<0.0001**

n = number of individuals; BMI = body mass index; AST = aspartate aminotransferase; ALT = alanine aminotransferase; eGFR = estimated glomerular filtration rate.
Bold indicates statistical significance.

Table 3. Correlation analyses between the main study outcome (one-year variation of glomerular filtration rate) and study variables

Univariate analysis (simple regression)		
Variable	**Regression coefficient**	**P value**
Age	*0.20*	*0.07*
BL BMI	0.07	0.41
%TWL	0.18	0.12
%EWL	0.17	0.14
BL glucose	0.13	0.26
BL insulin	−0.35	0.81
BL creatinine	0.80	**<0.001**
BL urea	0.14	0.74
BL albumin	0.03	0.77
BL hemoglobin A1c	0.06	0.69
BL eGFR	−0.85	**<0.001**
Multivariate analysis (multiple regression)		
Age	−0.31	**<0.001**
BL creatinine	−0.16	0.25
BL eGFR	−0.99	**<0.001**

BL = baseline; BMI = body mass index; %TWL = percentage of total weight loss; %EWL = percentage of excess weight loss; eGFR = estimated glomerular filtration rate.
Bold indicates statistical significance. *Italic* indicates a marginal association.

demonstrated statistically comparable results in terms of the percentage variation in eGFR. Meanwhile, regarding weight, OAGB led to significantly greater weight loss than RYGB. Thus, although both procedures lead to equivalent benefits in relation to renal function, OAGB is more advantageous in terms of weight loss.

Several case series, retrospective and prospective studies, and systematic reviews have demonstrated post-BS improvement in renal function in patients with obesity, in addition to various other benefits in quality of life, metabolic control, blood pressure, and other conditions related to excess weight.[20-24] Garcia et al.[11] analyzed 109 patients who underwent RYGB and demonstrated a significant improvement in GFR 1 year postoperatively, which was more pronounced in younger individuals without hypofiltration. Interestingly, in this study, no significant correlation was identified between the improvement in kidney function and presence of obesity-associated conditions, such as diabetes and hypertension, or with greater loss of excess weight. This finding of renal improvement independent of the magnitude of weight loss was reinforced by a systematic review conducted by Scheurlen et al.,[12] who enrolled 15 studies involving 2,145 patients undergoing RYGB and reported that patients had improved renal function regardless of weight loss or glycemic control.

However, the mechanisms underlying renal recovery after BS are unclear. They may be related to several different factors, which are seemingly linked, but far from restricted to, weight loss itself, as well as decreased visceral fat-associated inflammation, incretin activity on insulin sensitivity and pancreatic endocrine function, incretin natriuretic effect, improvement of hypertension, among others.[25] Both OAGB and RYGB are reportedly capable of producing massive weight loss alongside significant metabolic improvement, which are likely to positively affect renal function, as observed in the current study. Regarding enterohormonal secretion, an interesting study by DeBandt et al. demonstrated no significant differences in the postprandial levels of glucagon-like peptide-1 (GLP-1), peptide YY, or ghrelin between OAGB and RYGB; however, glucose-dependent insulinotropic polypeptide levels tended to be lower with OAGB than with RYGB.[26]

The possibility of superior weight loss provided by OAGB compared to RYGB in the current study has been previously reported, although this remains debatable. Two pioneering studies comparing these techniques, the Y-OMEGA[27] and Taiwan trial,[28] demonstrated that both procedures led to similar weight loss, although OAGB promoted more metabolic improvement in relation to glucose metabolism and diabetes resolution than RYGB, concluding that OAGB is a technically easier procedure and features better glycemic control than RYGB.[29] Li et al.,[30] in a systematic review that encompassed 8 randomized trials, have reported that OAGB was associated with higher one-year excess weight loss, significantly fewer early post-operative complications, and shorter operative time

compared to RYGB. Similarly, Uhe et al.[31] in a systematic review that analyzed 25 randomized trials have reported that OAGB was associated with a 10% higher 1-year %EWL than RYGB, a finding comparable to that observed in the present study. Nevertheless, a consensus has been reached regarding the higher potential of OAGB to cause malnutrition because of its malabsorptive nature compared with RYGB.[32] Thus, OAGB may lead to greater weight loss at the expense of more nutritional issues, which emphasizes the necessity of a rigorous postoperative multidisciplinary follow-up.

Younger age and worse baseline renal function were independent predictors of better postoperative renal outcomes in this study cohort. These findings are in accordance with previous evidence and, respectively, emphasize the importance of early surgical indication leading to better results, as well as the possibility of BS/metabolic surgery acting as a method to salvage individuals with already impaired renal function.[9-13] It should be emphasized that this applies to individuals without established severe kidney dysfunction, considering that this study did not involve patients with end-stage renal disease. In fact, BS evidently plays a nephroprotective role through multiple mechanisms, such as the decrease in visceral fat volume and consequent reduction of chronic low-grade inflammation, the improvement of glycemic metabolism mediated by the activation of incretins, and antihypertensive effects associated with natriuretic properties of GLP-1 alongside weight loss itself.[33] However, in individuals with kidney disease classified as stage 3 or worse already installed, the reversal rates after bariatric procedures are not significant, despite all other metabolic benefits.[34]

The long-term risk of biliary reflux-associated esophagogastric cancer after OAGB remains debatable. Recent studies by Keleidari et al.[35] and Braga et al.[36] have demonstrated that low rates of severe endoscopic and histopathological abnormalities were observed after 1 and 2 years after OAGB, respectively. One unique case of purely gastric cancer detected after OAGB was in the excluded stomach.[37] The remaining cases were diagnosed at the esophagogastric junction, both 2 years postoperatively. Interestingly, neither patient had undergone biopsies of the esophagogastric junction, and one patient did not even undergo preoperative esophagogastroscopy.[38,39] The commonly and historically described history of biliary reflux-associated cancer requires a significantly longer time of exposure, generally 20 years or more.[40,41] Considering that OAGB has been systematically performed at least since 1997, no surge in the diagnosis of this type of cancer has been observed over recent years, as it would have been expected in case this operation really carried such risk.[42,43] Nevertheless, continuous long-term endoscopic surveillance is warranted.

Considering the previously reported advantages of OAGB over RYGB, shorter operative time, lower perioperative morbidity, and greater weight loss and glycemic control,[44-47] the current study demonstrates that OAGB is at least equivalent to RYGB in another significant postoperative outcome, which is the recovery of renal function.

This study had some limitations that should be considered. The small sample size of patients with OAGB and its short follow-up time are significant and should ensure the performance of larger prospective studies with longer postoperative follow-up periods. This decrease in serum creatinine levels may be related to surgically induced weight loss-related sarcopenia, at least to a certain extent. The GFR estimation model was appropriate for this population study model, although it cannot provide the same accuracy as direct measurements through total 24-hour urine collection and calculation of clearance, which are expensive and more difficult to execute. Moreover, changes in body composition postoperatively may have biased our findings. Meanwhile, the main strength of the current study was the systematic collection of renal function laboratory examinations after BS, which is not very common in most services.

CONCLUSION

Compared to RYGB, OAGB led to an equivalent improvement in renal function 1 year postoperatively, along with higher weight loss.

REFERENCES

1. World Health Organization. Obesity and overweight factsheet. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed in 2023 (Apr 13).
2. Fritz J, Brozek W, Concin H, et al. The association of excess body weight with risk of ESKD is mediated through insulin resistance, hypertension, and hyperuricemia. J Am Soc Nephrol. 2022;33(7):1377-89. PMID: 35500938; https://doi.org/10.1681/asn.2021091263.
3. Declèves AE, Sharma K. Obesity and kidney disease: differential effects of obesity on adipose tissue and kidney inflammation and fibrosis. Curr Opin Nephrol Hypertens. 2015;24(1):28-36. PMID: 25470014; https://doi.org/10.1097/mnh.0000000000000087.
4. Wickman C, Kramer H. Obesity and kidney disease: potential mechanisms. Semin Nephrol. 2013;33(1):14-22. PMID: 23374890; https://doi.org/10.1016/j.semnephrol.2012.12.006.
5. Bagby SP. Obesity-initiated metabolic syndrome and the kidney: a recipe for chronic kidney disease? J Am Soc Nephrol. 2004;15(11):2775-91. PMID: 15504931; https://doi.org/10.1097/01.asn.0000141965.28037.ee.
6. Griffin KA, Kramer H, Bidani AK. Adverse renal consequences of obesity. Am J Physiol Renal Physiol. 2008;294(4):F685-96. PMID: 18234955; https://doi.org/10.1152/ajprenal.00324.2007.
7. Praga M, Morales E. The fatty kidney: obesity and renal disease. Nephron. 2017;136(4):273-6. PMID: 27414023; https://doi.org/10.1159/000447674.
8. Martínez-Montoro JI, Morales E, Cornejo-Pareja I, Tinahones FJ, Fernández-García JC. Obesity-related glomerulopathy: current approaches and future perspectives. Obes Rev. 2022;23(7):e13450. PMID: 35362662; https://doi.org/10.1111/obr.13450.

9. Huang H, Lu J, Dai X, et al. Improvement of renal function after bariatric surgery: a systematic review and meta-analysis. Obes Surg. 2021;31(10):4470-84. PMID: 34355340; https://doi.org/10.1007/s11695-021-05630-4.
10. Bilha SC, Nistor I, Nedelcu A, et al. The effects of bariatric surgery on renal outcomes: a systematic review and meta-analysis. Obes Surg. 2018;28(12):3815-33. PMID: 30054877; https://doi.org/10.1007/s11695-018-3416-4.
11. Garcia MS, Calderoni DR, Jimenez LS, et al. Renal function 1 year after bariatric surgery: influence of Roux-en-Y gastric bypass and identification of pre-operative predictors of improvement. Obes Surg. 2020;30(3):860-6. PMID: 31705414; https://doi.org/10.1007/s11695-019-04249-w.
12. Scheurlen KM, Probst P, Kopf S, et al. Metabolic surgery improves renal injury independent of weight loss: a meta-analysis. Surg Obes Relat Dis. 2019;15(6):1006-20. PMID: 31104957; https://doi.org/10.1016/j.soard.2019.03.013.
13. Fenske WK, Dubb S, Bueter M, et al. Effect of bariatric surgery-induced weight loss on renal and systemic inflammation and blood pressure: a 12-month prospective study. Surg Obes Relat Dis. 2013;9(4):559-68. PMID: 22608055; https://doi.org/10.1016/j.soard.2012.03.009.
14. Musella M, Milone M, Deitel M, Kular KS, Rutledge R. What a mini/one anastomosis gastric bypass (MGB/OAGB) is. Obes Surg. 2016;26(6):1322-3. PMID: 27091050; https://doi.org/10.1007/s11695-016-2168-2.
15. Singh B, Saikaustubh Y, Singla V, et al. One anastomosis gastric bypass (OAGB) vs Roux-en-Y gastric bypass (RYGB) for remission of T2DM in patients with morbid obesity: a randomized controlled trial. Obes Surg. 2023;33(4):1218-27. PMID: 36807043; https://doi.org/10.1007/s11695-023-06515-4.
16. Chaim EA, Ramos AC, Cazzo E. Mini-gastric bypass: description of the technique and preliminary results. Arq Bras Cir Dig. 2017;30(4):264-6. PMID: 29340551; https://doi.org/10.1590/0102-6720201700040009.
17. Bassiony AI, Sabry A, Shiha O, ElGeidie A, Nassar MK. The short-term renal effects of bariatric surgery: a comparative study between sleeve gastrectomy and one anastomosis gastric bypass operations among Egyptian patients with severe obesity. Obes Surg. 2020;30(11):4494-504. PMID: 32700183; https://doi.org/10.1007/s11695-020-04841-5.
18. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12. PMID: 19414839; https://doi.org/10.7326/0003-4819-150-9-200905050-00006.
19. Matsushita K, Mahmoodi BK, Woodward M, et al. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. JAMA. 2012;307(18):1941-51. PMID: 22570462; https://doi.org/10.1001/jama.2012.3954.
20. Moriconi D, Nannipieri M, Dadson P, et al. The beneficial effects of bariatric-surgery-induced weight loss on renal function. Metabolites. 2022;12(10):967. PMID: 36295869; https://doi.org/10.3390/metabo12100967.
21. Funes DR, Montorfano L, Blanco DG, et al. Sleeve gastrectomy in patients with severe obesity and baseline chronic kidney disease improves kidney function independently of weight loss: a propensity score matched analysis. Surg Obes Relat Dis. 2022;18(6):772-8. PMID: 35331642; https://doi.org/10.1016/j.soard.2022.02.006.
22. Favre G, Grangeon-Chapon C, Iannelli A. Renal function and bariatric surgery: an ongoing debate. Obes Surg. 2022;32(1):210-1. PMID: 34398381; https://doi.org/10.1007/s11695-021-05631-3.
23. Panagiotou OA, Markozannes G, Adam GP, et al. Comparative effectiveness and safety of bariatric procedures in medicare-eligible patients: a systematic review. JAMA Surg. 2018;153(11):e183326. PMID: 30193303; https://doi.org/10.1001/jamasurg.2018.3326.
24. Zhou X, Li L, Kwong JS, et al. Impact of bariatric surgery on renal functions in patients with type 2 diabetes: systematic review of randomized trials and observational studies. Surg Obes Relat Dis. 2016;12(10):1873-82. PMID: 27421689; https://doi.org/10.1016/j.soard.2016.05.003.
25. Docherty NG, le Roux CW. Bariatric surgery for the treatment of chronic kidney disease in obesity and type 2 diabetes mellitus. Nat Rev Nephrol. 2020;16(12):709-20. PMID: 32778788; https://doi.org/10.1038/s41581-020-0323-4.
26. De Bandt D, Rives-Lange C, Frigout Y, et al. Similar gut hormone secretions two years after one anastomosis gastric bypass and Roux-en-Y gastric bypass: a pilot study. Obes Surg. 2022;32(3):757-62. PMID: 34993850; https://doi.org/10.1007/s11695-021-05837-5.
27. Robert M, Espalieu P, Pelascini E, et al. Efficacy and safety of one anastomosis gastric bypass versus Roux-en-Y gastric bypass for obesity (YOMEGA): a multicentre, randomised, open-label, non-inferiority trial. Lancet. 2019;393(10178):1299-309. PMID: 30851879; https://doi.org/10.1016/s0140-6736(19)30475-1.
28. Lee WJ, Yu PJ, Wang W, et al. Laparoscopic Roux-en-Y versus mini-gastric bypass for the treatment of morbid obesity: a prospective randomized controlled clinical trial. Ann Surg. 2005;242(1):20-8. PMID: 15973097; https://doi.org/10.1097/01.sla.0000167762.46568.98.
29. Lee WJ, Almalki OM, Ser KH, Chen JC, Lee YC. Randomized controlled trial of one anastomosis gastric bypass versus Roux-en-Y gastric bypass for obesity: comparison of the YOMEGA and Taiwan studies. Obes Surg. 2019;29(9):3047-53. PMID: 31290104; https://doi.org/10.1007/s11695-019-04065-2.
30. Li X, Hu X, Fu C, et al. Efficacy and safety of one anastomosis gastric bypass versus Roux-en-Y gastric bypass for obesity: a meta-analysis and systematic review. Obes Surg. 2023;33(2):611-22. PMID: 36564618; https://doi.org/10.1007/s11695-022-06401-5.
31. Uhe I, Douissard J, Podetta M, et al. Roux-en-Y gastric bypass, sleeve gastrectomy, or one-anastomosis gastric bypass? A systematic review and meta-analysis of randomized-controlled trials. Obesity. 2022;30(3):614-27. PMID: 35137548; https://doi.org/10.1002/oby.23338.
32. Tourky M, Issa M, Salman MA, et al. Nutritional complications after laparoscopic Roux-en-Y gastric bypass and one-anastomosis gastric bypass: a comparative systematic review and meta-analysis. Cureus. 2022;14(1):e21114. PMID: 35036236; https://doi.org/10.7759/cureus.21114.

33. Docherty NG, le Roux CW. Bariatric surgery for the treatment of chronic kidney disease in obesity and type 2 diabetes mellitus. Nat Rev Nephrol. 2020;16(12):709-720. PMID: 32778788. https://doi.org/10.1038/s41581-020-0323-4.]
34. Lee Y, Anvari S, Chu MM, et al. Improvement of kidney function in patients with chronic kidney disease and severe obesity after bariatric surgery: A systematic review and meta-analysis. Nephrology (Carlton). 2022;27(1):44-56. PMID: 34375462. https://doi.org/10.1111/nep.13958.
35. Keleidari B, Mahmoudieh M, Davarpanah Jazi AH, et al. Comparison of the bile reflux frequency in one anastomosis gastric bypass and Roux-en-Y gastric bypass: a cohort study. Obes Surg. 2019;29(6):1721-5. PMID: 30767188; https://doi.org/10.1007/s11695-018-03683-6.
36. Braga JGR, Callejas GH, da Silva Costa LC, et al. Endoscopic and histopathological assessment of individuals undergoing one anastomosis gastric bypass: a 2-year follow-up. Surg Endosc. 2023;37(5):3720-7. PMID: 36650354; https://doi.org/10.1007/s00464-023-09884-0.
37. Wu CC, Lee WJ, Ser KH, et al. Gastric cancer after mini-gastric bypass surgery: a case report and literature review. Asian J Endosc Surg. 2013;6(4):303-6. PMID: 24308590; https://doi.org/10.1111/ases.12052.
38. Runkel M, Pauthner M, Runkel N. The first case report of a carcinoma of the gastric cardia (AEG II) after OAGB-MGB. Obes Surg. 2020;30(2):753-4. PMID: 31667674; https://doi.org/10.1007/s11695-019-04193-9.
39. Aggarwal S, Bhambri A, Singla V, Dash NR, Sharma A. Adenocarcinoma of oesophagus involving gastro-oesophageal junction following mini-gastric bypass/one anastomosis gastric bypass. J Minim Access Surg. 2020;16(2):175-8. PMID: 30777997; https://doi.org/10.4103/jmas.jmas_320_18.
40. Safatle-Ribeiro AV, Ribeiro Jr U, Reynolds JC. Gastric stump cancer: what is the risk? Dig Dis. 1998;16(3):159-68. PMID: 9618135; https://doi.org/10.1159/000016860.
41. Cazzo E, de Saito HPA. Mixed adenoneuroendocrine carcinoma of the gastric stump following Billroth II gastrectomy: case report and review of the literature. Sao Paulo Med J. 2016;134(1):84-7. PMID: 25885489; https://doi.org/10.1590/1516-3180.2013.9080911.
42. Musella M, Berardi G, Bocchetti A, et al. Esophagogastric neoplasms following bariatric surgery: an updated systematic review. Obes Surg. 2019;29(8):2660-9. PMID: 31129886; https://doi.org/10.1007/s11695-019-03951-z.
43. Rutledge R, Deitel M, Carbajo MA, et al. Commentary: Cancer after the OAGB-MGB. Obes Surg. 2020;30(2):755-8. PMID: 31832935; https://doi.org/10.1007/s11695-019-04313-5.
44. Castro MJ, Jimenez JM, Carbajo MA, et al. Long-term weight loss results, remission of comorbidities and nutritional deficiencies of sleeve gastrectomy (SG), Roux-En-Y gastric bypass (RYGB) and one-anastomosis gastric bypass (OAGB) on type 2 diabetic (T2D) patients. Int J Environ Res Public Health. 2020;17(20):7644. PMID: 33092117; https://doi.org/10.3390/ijerph17207644.
45. Cazzo E, Valerini FG, Chaim FHM, et al. Early weight loss outcomes and glucose metabolismo parameters after banded versus non-banded one anastomosis gastric bypass: a prospective randomized trial. Arq Gastroenterol. 2019;56(1):15-21. PMID: 31141062; https://doi.org/10.1590/s0004-2803.201900000-14.
46. Cazzo E, Jimenez LS, Valerini FG, et al. Weight loss and vomiting 1 year after banded versus non-banded one anastomosis gastric bypass: a prospective randomized trial. Obes Surg. 2020;30(5):1719-25. PMID: 31942688; https://doi.org/10.1007/s11695-020-04393-8.
47. Taha O, Abdelaal M, Abozeid M, Askalany A, Alaa M. Outcomes of one anastomosis gastric bypass in 472 diabetic patients. Obes Surg. 2017;27(11):2802-10. PMID: 28534188; https://doi.org/10.1007/s11695-017-2711-9.
48. Efe L; International Federation for Surgery of Obesity & Metabolic Disorders. Atlas of bariatric and metabolic surgery. Available at: https://www.ifso.com/atlas-of-bariatric-and-metabolic-surgery/. Accessed: September 07th, 2023.

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Comparison between use of a pleural drainage system with flutter valve and a conventional water-seal drainage system after lung resection: a randomized prospective study

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ABSTRACT

BACKGROUND: There is still a debate regarding the most appropriate pleural collector model to ensure a short hospital stay and minimum complications.

OBJECTIVE: To study aimed to compare the time of air leak, time to drain removal, and length of hospital stay between a standard water-seal drainage system and a pleural collector system with a unidirectional flutter valve and rigid chamber.

DESIGN AND SETTING: A randomized prospective clinical trial was conducted at a high-complexity hospital in São Paulo, Brazil.

METHODS: Sixty-three patients who underwent open or video-assisted thoracoscopic lung wedge resection or lobectomy were randomized into two groups, according to the drainage system used: the control group (WS), which used a conventional water-seal pleural collector, and the study group (V), which used a flutter valve device (Sinapi® Model XL1000®). Variables related to the drainage system, time of air leak, time to drain removal, and time spent in hospital were compared between the groups.

RESULTS: Most patients (63%) had lung cancer. No differences were observed between the groups in the time of air leak or time spent hospitalized. The time to drain removal was slightly shorter in the V group; however, the difference was not statistically significant. Seven patients presented with surgery-related complications: five and two in the WS and V groups, respectively.

CONCLUSIONS: Air leak, time to drain removal, and time spent in the hospital were similar between the groups. The system used in the V group resulted in no adverse events and was safe.

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INTRODUCTION

Chest drains are essential in the post-operative period of lung resection because they enable air escape and the drainage of secretions produced by surgery.[1]

Conventional pleural drains with a single bottle using a water seal became the standard for this purpose at the beginning of the 20th century and are currently the most used devices worldwide.[2] Keeping them in place for longer periods frequently limits the time of hospital discharge and directly influences the cost of hospital stay as well as the anxiety levels of patients and their caregivers.

There is still a debate on the most appropriate pleural collector model to ensure a short hospital stay and minimum complications, principally considering the reality of health services in developing countries.

The need to reduce adverse events related to pleural drains, and to make them easier to use, motivated Heimlich, in 1968, to create a one-way valve for this purpose, which is referred to by his name.[3] It is a mechanical device, designed to isolate the external environment from the sub-atmospheric intrapleural environment.[4,5] Since then, other drainage systems have been developed that aim to replace water-seal drains and make hospital stays shorter.[6]

In view of the options currently available, there is a need to identify systems that are easy to handle, reduce the time for which the pleural drain needs to remain in place, can be emptied,

have a rigid reservoir, are low cost, are perceived by the patient as safe, and enable suction when necessary.[4,7]

OBJECTIVE

This study aimed to compare the time of air leak, time to drain removal, and length of hospital stay between two systems: (a) a standard water-seal drainage system and (b) a pleural collector system employing a unidirectional flutter valve and a rigid chamber after lung resection and to report any complications related to patients and/or the systems.

METHODS

This randomized clinical trial included patients who underwent open or video-assisted thoracoscopic lung resection surgery (VATS) at Hospital do Servidor Público Estadual Francisco Morato de Oliveira (IAMSPE), São Paulo, Brazil, between October 2020 and May 2022. The same surgical team performed all the surgeries.

The study was approved by the Ethics and Research Committee of IAMSPE on February 11, 2020, under protocol no. 3.832.730. All patients signed an informed consent form prior to enrollment.

Patients included in the study were adults aged >18 years indicated for elective lung wedge resection or lobectomy, with predicted post-operative forced expiratory volume in one second (FEV_1ppo) ≥ 40%. Patients with any type of present or past pleural infection, those needing concomitant chest wall resection, those presenting with diffuse adhesions in the intraoperative period, and those who died before the chest drain was removed were excluded from the study.

Air leaks were controlled by mechanical stapling of the fissure (Echelon Flex, Ethicon, Johnson & Johnson®) and manual sutures. In all surgeries, only one tubular pleural drain, nº 28 Fr, was used.

Patients were randomized into groups, according to the drainage system to be used: 1) the control group (WS), which used a conventional water-seal pleural collector, and 2) the study group (V), which used a flutter valve device, the Sinapi® Model XL1000® pleural collector employing a flutter valve.

The decision on which drainage system to use was randomized using the randomization calculator available on the website *calculatorsoup.com,* allocating participants randomly to the V or WS groups. The surgeon was informed of the type of system to be used only after the completion of the surgical procedure.

In the WS group, the pleural collector comprised of a polyvinyl chloride bottle with a volume of 2 L, under an initial sterile water seal of 2 cm (**Figure 1**).

In the V group the pleural collector was a chamber in the form of a rectangular transparent rigid prism of acrylonitrile butadiene styrene polymer, with numbering on its external surface to identify the volume stored and an internal capacity of 1,000 mL. This had a half-turn type evacuation nozzle on the interior surface. It was connected to a tubular drain using a silicone tube with an adapter for various drains of different calibers. Connected to the silicone tube, in the initial part of the rigid prism, was a one-way mechanical anti-reflux 'flutter' valve, with the same format and effect as the Heimlich valve. The flap in the flutter valve was made of an anti-adherent polymer. Additionally, a compressible suction valve made of silicone was connected to the end of the connection tube of the drain close to the flutter valve. When pressed, this bulb created a vacuum in the drain system, allowing air leaks to be detected. If the bulb was squeezed and did not immediately return to its resting inflated position, it was assumed that there was no air leakage through the pleural drain. (**Figure 2**).

All patients underwent anteroposterior chest radiography within 24 hours post operation to check for pneumothorax or

Figure 1. Water seal pleural collector comprised a polyvinyl chloride (PVC) bottle with volume of 2L, under an initial sterile water seal of 2 cm.

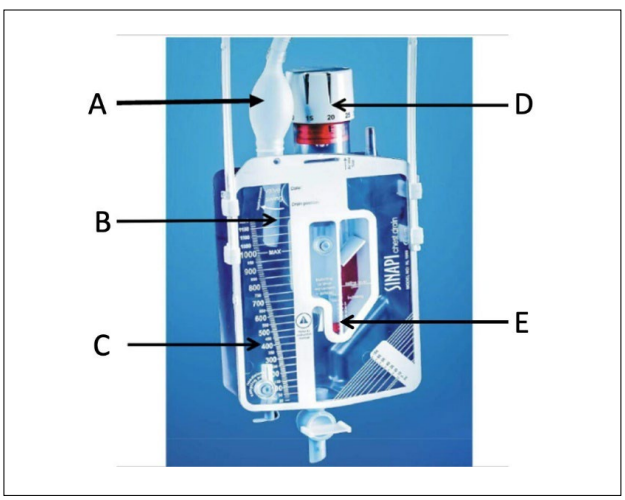

Figure 2. Pleural collector with valve. A: suction bulb; B: one-way flutter valve; C: calibrated liquid collection chamber; D: suction regulation valve; E: level scale for checking air bubbles.

pleural collection. Patients whose radiographs showed a residual pleural space in the post-operative period underwent suction using the drainage system.

In the WS group, pleural suction of 10 cmH_2O was applied (maximum capacity in that common bottle) with the standard system of three bottles. Patients in the V group who presented with residual pleural space or for whom the bulb did not remain compressed after compression were assumed to have residual air leaks and underwent pleural suction of 20 cmH_2O.

Air leaks were considered to be stopped:

- In the WS group, when there was no air bubbling through the water seal during coughing with exertion.
- In the V group, when the bulb remained collapsed for 10 minutes after compression, indicating air leaks were completely absent.

In both groups, the drain was removed when (i) there was no air leak, (ii) the liquid drawn was <200 mL in 24 hours, and (iii) a prior chest radiograph showed complete lung expansion.

A further chest radiograph was obtained at the return outpatient visit seven days after hospital discharge.

The following variables were recorded:

- Time of air leak (TAL) (days);
- Time to removal of drain (TRD) (days);
- Time in hospital (TIH) (days);
- Total liquid drained during the entire hospitalization period (TLD) (mL);
- The number and type of post-operative complications; and
- Any dysfunctions related to the drainage system.

The following were considered complications related to the patients: empyema, subcutaneous emphysema, hospital discharge with a Heimlich valve, readmission to the hospital, re-draining, or prolonged air leak (defined as an air leak through the drain for six days or more). The following complications were considered system-related: prolonged clamping, empty water-seal system, mechanical valve clogging, and unintentional disconnections.

The sample size was determined based on the descriptive statistics of a pilot study, adopting an alpha of 0.05 and a beta of 0.20, which indicated the need to evaluate a minimum of 61 patients.

The data are presented using descriptive statistics, average and standard deviation for quantitative variables, and absolute numbers and relative percentages for categorical variables.

The quantitative variables were compared between the groups using the Independent Samples T Test for the variables age and VEF_1ppo and the Mann-Whitney test for the variables total drain volume, TRD, TAL, and TIH. Categorical variables were compared using Pearson's chi-squared test. All analyses were performed using R software (version 4.2 for Mac iOS), with a significance level of 5% ($P < 0.05$).

Sinapi® model XL1000® pleural collectors were donated by the manufacturer (Sinapi Biomedical, Idasvallei, Stellenbosch, 7599, South Africa). Although the manufacturers supplied the device, they had no interference of any form during the study.

RESULTS

The study sample comprised 64 patients. One patient who died before drain removal was excluded. Therefore, the data from 63 patients were analyzed: 31 and 32 in the WS and V groups, respectively. **Table 1** shows the demographic, clinical, and surgical characteristics of the study participants. There was a small predominance of women – 33 patients (52%), with age varying from 18 to 81 years (average age: 65 ± 13 years). There were no significant demographic differences between the two groups.

The majority (63%) of patients had lung cancer, and there was no difference in the diagnoses between the two groups. The most commonly performed surgery was wedge resection (52% of the cases, 45% in the WS group and 59% in the V group). Thirty-four surgeries were performed using VATS with a similar distribution between the two groups. Pleural suction was applied in 18 patients: four (6%) in the WS group and 14 (21%) in the V group.

The TAL and TIH were similar between the two groups. TAL varied from one to 20 days, with a median of two days. TIH varied from one to 23 days.

The TRD was similar between the two groups, with the median time for removal being four days [Interquartile range(IQR) 3–6] in the WS group and three days [IQR 2–4] in the V group; however, this difference was not statistically significant.

Four patients died after drain removal (two in each group). The causes of death were pneumonia due to Coronavirus disease (COVID-19) in three cases and massive lung thromboembolism in one case.

Seven patients presented with surgery-related complications: five in the WS group and two in the V group (Table 1). There were a total of 14 complications in these patients; in the V group, each patient had one complication, and in the WS group, the patients presented with two or three associated complications. The most frequent complications were prolonged air leak (in four patients) and empyema (in three patients). All cases of prolonged air leaks were observed in the WS group. Furthermore, hospital discharge with the Heimlich device in place, readmission, re-drainage, and drain malfunction were observed in the WS group.

DISCUSSION

In this study, no significant differences were observed in TAL, TRD and TIH between the two collectors evaluated, although the medians for TRD and TIH were lower in the V group. Flutter valves have been used as an option for reducing TIH for patients who have undergone surgery;[5] however, other studies

Table 1. Demographic, clinical, and surgery characteristics of the total sample and the two groups

Variables	Total n = 63	Control group (Water seal) n = 31	Study group (Valve) n = 32	P
Gender				0.80*
Female	33 (52)	17 (53)	16 (50)	
Male	30 (48)	14 (47)	16 (50)	
Age (years)	65 ± 13	67 ± 9	63 ± 16	0.70†
VEF_1ppo (mL)	67 ± 15	66 ± 13	68 ± 17	0.70†
Diagnoses				0.48*
Lung cancer	37 (63)	21 (70)	16 (55)	
Granuloma	6 (10)	2 (6.7)	4 (14)	
Metastasis	5 (8.5)	3 (10)	2 (6.9)	
Blebs	2 (3.4)	0 (0)	2 (6.9)	
Hamartoma	3 (5.1)	2 (6.7)	1 (3.4)	
Other	6 (10)	2 (6.7)	4 (14)	
Type of surgery				0.31*
Wedge	33 (52)	14 (45)	19 (59)	
Lobectomy	30 (48)	17 (55)	13 (41)	
Type of surgery				0.45*
Open surgery	29 (46)	15 (48)	13 (41)	
VATS	34 (54)	16 (52)	19 (59)	
Total liquid drained (mL)	400 [200-1100]	425 [115-1100]	350 [200-1350]	0.46‡
TAL	2 [1-4]	2 [1-3]	2 [1-4]	0.81‡
TRD	3 [2-5]	4 [3-6]	3 [2-4]	0.08‡
TIH	4 [2-6]	4.5 [3-7]	3 [2-5]	0.11‡
Complications	7 (12)	5 (16)	2 (6.2)	0.26*
Deaths	4 (6.2)	2 (6.2)	2 (6.2)	0.90*

*Pearson Chi-squared test (^{2}); †T-test for independent variables; ‡Mann-Whitney test.
SD = standard deviation; VEF1ppo = predicted post-operative forced expiratory volume in one second; VATS = video thoracoscopy; TAL = time of air leak (days); TRD = time to removal of drain; TIH = time in hospital (days). [a]Amounts expressed as n (%), average ± standard deviation, or median [interquartile interval].

with a one-way valve have not shown any difference in TRD when compared with a water seal.[5,7-10]

Pleural suction was used more frequently in the V group than in the WS group. This is explained by the fact that suction was applied to the WS group only when the chest radiograph showed incomplete expansion. Chest radiography may fail to diagnose pneumothorax in up to 39% of cases when compared to chest ultrasound examination.[11]

Suction was applied in a larger number of patients in the V group, since the bulb of the drainage system, with its function of compression followed by observation of whether it inflated again, helped in the evaluation of complete expansion. The valve system used in this study enabled a more objective assessment of air leakage using a silicone vacuum bulb.

In the WS group, pleural suction was performed using three bottles. In this system, there was a limit of 10 cm for the difference in the levels of liquid, indicating suction pressure. In the V group, suction at 20 cmH_2O was easily established using a numbered pressure regulator.

Dysfunctions of water-seal pleural chest drains are known to occur and have been reported in the literature. Previous studies have described inadequate connections, low volume of liquid in the bottle, loss of connection between the drain and the chest tube, kinks in the system's connecting tube, inadequate clamping, blockage of the air output relief valve, failure in suction, and consequences of placement of the system above the level of the chest.[12,13] In our study, there was one dysfunction in the water-seal system: the patient, in a moment of confusion, emptied the collector, which led to lung collapse, prolonged air leak, and empyema.

One experimental study[6] showed that a flutter valve is physiologically more efficacious than a water seal for treating post-operative air leaks. This is partly explained by the fact that with the valve, there is no movement of the lungs against the chest wall, which occurs with the water seal through the movement of the liquid in the bottle. Other authors[14] considered it possible that the use of the flutter valve, in isolation or using malleable collector bags, was discouraged in some cases owing to the presence of adverse events as well as the absence of a rigid reservoir, and thus the possibility of suction. One study reported complications such as hypertensive pneumothorax due to blockage of the valve.[15] Another study comparing the use of a valve and a water-seal collector for lung

surgeries reported two cases of valve obstruction by blood clots, one disconnection of the valve, and the need to change the water seal in one patient.[16]

The materials used to manufacture valves have evolved. In a randomized study published in 2006,[7] which compared the TRD between a water-seal system and a new flutter valve model in patients who underwent pleural drainage following blunt and perforating lung trauma in a referral hospital in South Africa, no clogging by blood was reported with the flutter-valve system. In our study, no adverse events were directly associated with the flutter-valve drain system.

In addition to the systems used in this study, there are now digital systems that enable a numerical and objective evaluation of the air leak flow and the amount of liquid withdrawn.[17] These tend to be lighter than the common water-seal system; however, these are not emptiable, and their standard reception canister has a maximum volume of 800 mL. In addition, these require a non-disposable electronic pump for functioning, which costs approximately US$ 4,000.

Patient access to various types of pleural drainage systems is not uniform because ex-factory and retail prices vary between the types of devices and where they are produced, duty, and taxes. As illustrative examples: (i) the ex-factory price of the water-seal pleural drain with a simple bottle (used in the WS group) is approximately US$ 7; (ii) the ex-factory price of the Sinapi® XL 1000 valve system (used in the V group) is approximately US$ 20; and (iii) the ex-factory price of the disposable canister and the connecting tubes of the digital drain is approximately US$ 40, and this system requires a permanent pump. With taxes, charges, and other costs, these values could increase significantly.

Notably, the data used in this study were collected during the COVID-19 pandemic. Elective surgeries were interrupted for four (non-consecutive) months during this period, and COVID-19 was a factor in the mortality that occurred in this study. Of the four deaths observed, three were directly related to COVID-19 and tested positive in the post-operative period after the appearance of symptoms. The fourth patient died because of acute thromboembolism. A relationship with COVID-19 was suspected, although not confirmed, possibly because of limitations in the interpretation of diagnostic methods at the beginning of the pandemic. Other studies have reported an increase in mortality due to COVID-19 following chest surgery.[18,19]

CONCLUSION

In conclusion, the results for air leak, time to drain removal, and TIH were similar between the V group (using a flutter valve) and the group using a conventional water-seal system. The tested valve system did not exhibit any adverse events and was proven to be safe.

REFERENCES

1. Satoh Y. Management of chest drainage tubes after lung surgery. Gen Thorac Cardiovasc Surg. 2016;64(6):305-8. PMID: 27048219; https://doi.org/10.1007/s11748-016-0646-z.
2. Meyer JA. Gotthard Bülau and closed water-seal drainage for empyema, 1875-1891. Ann Thorac Surg. 1989;48(4):597-9. PMID: 2679468; https://doi.org/10.1016/s0003-4975(10)66876-2.
3. Heimlich HJ. Valve drainage of the pleural cavity. Dis Chest. 1968;53(3):282-7. PMID: 5640897; https://doi.org/10.1378/chest.53.3.282.
4. Kam AC, O'Brien M, Kam PC. Pleural drainage systems. Anaesthesia. 1993;48(2):154-61. PMID: 8460765; https://doi.org/10.1111/j.1365-2044.1993.tb06859.x.
5. McKenna RJ Jr, Fischel RJ, Brenner M, Gelb AF. Use of the Heimlich valve to shorten hospital stay after lung reduction surgery for emphysema. Ann Thorac Surg. 1996;61(4):1115-7. PMID: 8607667; https://doi.org/10.1016/0003-4975(96)00034-3.
6. Waller DA, Edwards JG, Rajesh PB. A physiological comparison of flutter valve drainage bags and underwater seal systems for postoperative air leaks. Thorax. 1999;54(5):442-3. PMID: 10212112; https://doi.org/10.1136/thx.54.5.442.
7. Cooper C, Hardcastle T. Xpand chest drain: assessing equivalence to current standard therapy--a randomised controlled trial. S Afr J Surg. 2006;44(4):131-5. PMID: 17330628.
8. Vuorisalo S, Aarnio P, Hannukainen J. Comparison between flutter valve drainage bag and underwater seal device for pleural drainage after lung surgery. Scand J Surg. 2005;94(1):56-8. PMID: 15865119; https://doi.org/10.1177/145749690509400114.
9. Wu MH, Wu HY. Pleural drainage using drainage bag for thoracoscopic lobectomy. Asian Cardiovasc Thorac Ann. 2018;26(3):212-7. PMID: 29448831; https://doi.org/10.1177/0218492318760876.
10. Vuorisalo S, Hannukainen J, Aarnio P. Flutter valve drainage bag is a useful device for the pleural drainage. Ann Chir Gynaecol. 2001;90(4):294-6. PMID: 11820420.
11. Galbois A, Ait-Oufella H, Baudel JL, et al. Pleural ultrasound compared with chest radiographic detection of pneumothorax resolution after drainage. Chest. 2010;138(3):648-55. PMID: 20382717; https://doi.org/10.1378/chest.09-2224.
12. Hashmi U, Nadeem M, Aleem A, et al. Dysfunctional Closed Chest Drainage - Common Causative Factors and Recommendations for Prevention. Cureus. 2018;10(3):e2295. PMID: 29750136; https://doi.org/10.7759/cureus.2295.
13. Talpur AA, Khaskheli AB, Hashmi SF, Jamal A. Analysis of 200 cases of tubethoracostomies performed by general surgeons. JLUMHS. 2014;13(1):22-6. Available from: https://www.lumhs.edu.pk/jlumhs/Vol13No01/pdfs/6.pdf. Accessed in 2023 (Sept. 5).
14. Lodi R, Stefani A. A new portable chest drainage device. Ann Thorac Surg. 2000;69(4):998-1001. PMID: 10800782; https://doi.org/10.1016/s0003-4975(99)01567-2.

15. Paul AO, Kirchhoff C, Kay MV, et al. Malfunction of a Heimlich flutter valve causing tension pneumothorax: case report of a rare complication. Patient Saf Surg. 2010;4(1):8. PMID: 20565768; https://doi.org/10.1186/1754-9493-4-8.
16. Vega NA, Ortega HA, Tincani AJ, Toro IF. Use of a one-way flutter valve drainage system in the postoperative period following lung resection. J Bras Pneumol. 2008;34(8):559-66. PMID: 18797739; https://doi.org/10.1590/s1806-37132008000800004.
17. Chang PC, Chen KH, Jhou HJ, et al. Promising Effects of Digital Chest Tube Drainage System for Pulmonary Resection: A Systematic Review and Network Meta-Analysis. J Pers Med. 2022;12(4):512. PMID: 35455628; https://doi.org/10.3390/jpm12040512.
18. Peng S, Huang L, Zhao B, et al. Clinical course of coronavirus disease 2019 in 11 patients after thoracic surgery and challenges in diagnosis. J Thorac Cardiovasc Surg. 2020;160(2):585-92. PMID: 32414594; https://doi.org/10.1016/j.jtcvs.2020.04.005.
19. Gomes WJ, Rocco I, Pimentel WS, et al. COVID-19 in the Perioperative Period of Cardiovascular Surgery: the Brazilian Experience. Braz J Cardiovasc Surg. 2021;36(6):725-35. PMID: 34882365; https://doi.org/10.21470/1678-9741-2021-0960.

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Association between hepatitis A seropositivity and bone mineral density in adolescents and adults: a cross-sectional study using NHANES data

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Supplementary material form this article can be seen in the link: https://github.com/FearlessYu/SPMJ-2023-0266.R1.Supplementary-material.git

ABSTRACT

BACKGROUND: Osteoporosis, characterized by decreased bone density and increased fracture risk, imposes significant physical, psychosocial, and financial burdens. Early detection and prevention are crucial for managing osteoporosis and reducing the risk of fractures.

OBJECTIVES: To investigate the relationship between Hepatitis A seropositivity and bone mineral density (BMD) in adolescents and adults and to explore the potential link between Hepatitis A infection and osteoporosis risk.

DESIGN AND SETTING: This cross-sectional study used data from the National Health and Nutrition Examination Survey (NHANES) from 2011 to 2018 to evaluate the association between hepatitis A seropositivity and BMD in 15,693 participants.

METHODS: Multivariable regression analysis was used to calculate the mean BMD and standard error for adolescents and adults, followed by an independent z-test to determine whether there was a significant difference between the seropositive and seronegative groups.

RESULTS: Hepatitis A seropositive adolescents and adults had lower BMD than their seronegative counterparts, with significant differences in lumber spine (mean difference = -0.03 g/cm2, $P < 0.01$ for both age groups) and pelvis BMDs (mean difference = -0.02 g/cm2, $P < 0.01$ for the adult age groups), after adjusting for various covariates.

CONCLUSIONS: This study confirmed that both adolescent and adult individuals seropositive for Hepatitis A antibodies had reduced BMD among both adolescents and adults, especially in the adult group. This finding suggests a possible link between Hepatitis A infection and risk of osteoporosis.

INTRODUCTION

Osteoporosis, a medical condition characterized by decreased bone density and increased fracture risk, often progresses silently until a fracture occurs.[1] The condition primarily affects postmenopausal women and results from a loss of calcium and collagen in the bones.[2] Notably, osteoporosis is not limited to any specific population or age group and can cause significant physical, psychosocial, and financial burdens across all populations and ages.[3-6] Early detection and prevention are crucial for managing osteoporosis and reducing the risk of fracture.[2,7]

Bone mineral density (BMD) tests can aid in early detection by comparing an individual's bone density to that of a healthy person of the same age and sex.[8] The most commonly used BMD test is the central dual-energy x-ray absorptiometry (DXA) test, which measures the grams of calcium and other bone minerals packed into a segment of bone using X-rays. The spine, hip, and forearm are the most commonly tested bones.

Hepatitis A is an inflammation of the liver that can range from asymptomatic infection to severe illness.[9] The Hepatitis A virus (HAV), a positive-strand RNA virus, is transmitted through ingestion of contaminated food and water or through direct contact with an infectious person.[9,10] The incidence rate of reported Hepatitis A cases in the United States was one case per 100,000 population.[11] Although almost everyone recovers fully from Hepatitis A with a lifelong immunity, a very small proportion of people infected with Hepatitis A could die from fulminant hepatitis.[12-14] A safe and effective vaccine is available to prevent Hepatitis A.[9]

Previous studies have suggested that viral hepatitis may negatively affect bone metabolism and health. For example, chronic hepatitis B and C infections have been associated

with lower BMD and a higher risk of osteoporosis in adults.[15-19] Hepatitis A is a viral infection whose symptoms are clinically indistinguishable from other types of acute viral hepatitis.[20] Therefore, it was hypothesized that Hepatitis A seropositivity may be related to a lower BMD and higher osteoporosis risk in adolescents and adults.

The National Health and Nutrition Examination Survey (NHANES), a program designed to assess the health and nutritional status of adults and children in the United States, combines interviews and physical examinations and covers a wide range of health and nutrition measurements. The survey examines a nationally representative sample of approximately 5,000 persons each year and collects data on various demographic, socioeconomic, dietary, and health-related factors. The survey results are used to determine the prevalence of major diseases and risk factors to assess nutritional status and their association with health promotion and disease prevention.[21]

This study aimed to investigate the relationship between Hepatitis A seropositivity and BMD in adolescents and adults using data from the NHANES. The potential link between Hepatitis A infection and osteoporosis risk was also explored, and the implications for bone health and prevention strategies are discussed.

METHODS

Design and setting

A cross-sectional design was used to examine the association between Hepatitis A seropositivity and BMD, which enabled the measurement of the prevalence of the outcome and exposure at a certain moment in time, and the identification of potential correlations.

Data source and research participants

All patient information was based on data obtained from the NHANES. Four datasets (2011–2012, 2013–2014, 2015–2016, and 2017–2018) were used to combine the study population. The inclusion criteria required individuals to be tested for Hepatitis A antibodies (anti-HAV) and to undergo a DXA examination concurrently. Patients who were seropositive (+) for anti-HAV antibodies were compared to those who were seronegative (-).

Subpopulation definitions

According to the World Health Organization (WHO), individuals between the ages of 10 and 19 years are classified as adolescents.[22] Conversely, individuals > 19 years are considered adults. In the adult female population, those < 51 years are designated as premenopausal, while their counterparts are deemed postmenopausal, given that the average age of menopause in the United States is 51.[23]

BMD testing

BMD testing for the full participant set (incorporated into the final evaluation) was performed using DXA examinations, which were performed by qualified and registered radiology technologists using Hologic Discovery model A densitometers (Hologic, Inc., Bedford, Massachusetts, USA) with the software version Apex 3.2. More specifics are furnished on the NHANES website.[24] Lumbar spine and pelvis were chosen for evaluating the association as they have a higher risk of fracture compared to the skull bones, arms, legs, ribs, thorax and trunk bones.[25]

Total serum anti-HAV assay

Serum specimens from the complete participant set (incorporated into the final evaluation) were processed, stored, and shipped to the Division of Viral Hepatitis, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA for analysis. The Division uses the VITROS Immunodiagnostic Products Anti-HAV Total Reagent Pack and the VITROS Immunodiagnostic Products Anti-HAV Total Calibrator on the VITROS ECi/ECiQ or VITROS 3600 Immunodiagnostic System to detect IgG and IgM. Further details are provided in the NHANES Laboratory Procedures Manual.[26]

Covariates

Covariates were added to improve the accuracy of this study; these are variables that are not of primary interest but can influence the outcome of a study.[27,28] In the present study, several covariates were considered for both adult and adolescent populations. For adults, age, race, education level, income level, body mass index (BMI), smoking status, alcohol consumption, diabetes, physical activity level, and serum 25-hydroxyvitamin D [25(OH)D] levels were included as covariates. For adolescents, the same covariates were considered with the exception of smoking status and alcohol consumption. Detailed data on the covariates are listed in **Supplemental Table 1**.

Statistical evaluation

All evaluations were based on the participants' complete data. Individuals with missing covariate data were excluded from the final evaluation. The NHANES sample weights assigned by the Centers for Disease Control and Prevention (USA) based on the sample design for each survey year were used. Therefore, as some of the variables included in this study were captured at the mobile examination center (MEC), we used the MEC exam weight (WTMEC2YR) for evaluation.

Furthermore, the sample weight used in the final evaluation was equal to one-fourth the value of "WTMEC2YR" because we combined four NHANES survey cycles. Baseline characteristics were indicated by the weighted mean and standard error (SE)

Table 1. Baseline characteristics of participants incorporated into the final evaluation

		Adolescents		Adults	
		anti-HAV(-) (n = 916)	anti-HAV(+) (n = 2014)	anti-HAV(-) (n = 4459)	anti-HAV(+) (n = 3107)
Sex, n (%)	Female	414 (45.15)	971(48.22)	**2180 (48.90)**	**1345 (43.28)**
	Male	502 (54.85)	1043 (51.78)	**2279 (51.10)**	**1762 (56.72)**
Age [year], mean (SE)		**15.83 (0.10)**	**15.43 (0.07)**	**39.91 (0.23)**	**37.78 (0.29)**
Race, n (%)	Non-Hispanic white	**622 (67.93)**	**993 (49.31)**	**3323 (74.52)**	**1381 (44.43)**
	Mexican American	**51 (5.53)**	**410 (20.37)**	**191 (4.28)**	**668 (21.51)**
	Other Hispanic	**42 (4.64)**	**180 (8.92)**	**176 (3.94)**	**394 (12.67)**
	Non-Hispanic black	**136 (14.83)**	**235 (11.66)**	**478 (10.72)**	**282 (9.08)**
	Other races	**65 (7.07)**	**196 (9.74)**	**291 (6.54)**	**382 (12.31)**
Annual family income, n (%)	Under $20,000	153 (16.72)	358 (17.77)	**623 (13.98)**	**546 (17.57)**
	$20,000 and over	763 (83.28)	1656 (82.23)	**3836 (86.02)**	**2561 (82.43)**
Education level, n (%)	Lower than 5th grade	**30 (3.26)**	**86 (4.25)**	-	-
	5th grade to 8th grade	**423 (46.21)**	**1056 (52.44)**	-	-
	Higher than 8th grade	**463 (50.53)**	**872 (43.31)**	-	-
	Below high school	-	-	**406 (9.11)**	**530 (17.05)**
	High school or equivalent	-	-	**981 (22.00)**	**651 (20.96)**
	Above high school	-	-	**3072 (68.89)**	**1926 (61.99)**
BMI [kg/m2] , mean (SE)		24.52 (0.28)	23.99 (0.16)	**28.93 (0.12)**	**28.06 (0.14)**
Diabetes, n (%)	Yes	4 (0.38)	9 (0.44)	250 (5.60)	162 (5.21)
	No	907 (99.16)	1992 (98.93)	4136 (92.76)	2899 (93.29)
	Borderline	5 (0.46)	13 (0.63)	73 (1.64)	46 (1.50)
Serum 25(OH)D [nmol/L], mean (SE)		**65.16 (0.98)**	**62.54 (0.77)**	**68.51 (0.50)**	**64.10 (0.70)**
High-risk drinking, n (%)	Yes	-	-	**716 (16.05)**	**412 (13.25)**
	No	-	-	**3743 (83.95)**	**2695 (86.75)**
Smokers, n (%)	Yes	-	-	**2113 (47.38)**	**1219 (39.23)**
	No	-	-	**2346 (52.62)**	**1888 (60.77)**
AST [U/L], mean (SE)		23.91 (0.65)	23.87 (0.38)	25.08 (0.32)	26.04 (0.45)
ALT [U/L], mean (SE)		19.84 (0.74)	19.41 (0.37)	**25.46 (0.34)**	**27.83 (0.50)**

% = weighted proportion. 25(OH)D = 25-hydroxyvitamin D; AST = aspartate transaminase; ALT = alanine transaminase; BMI = body mass index; SE = standard error; HAV = hepatitis A virus; High-risk drinking = men who consumed more than five drinks every day and women who consumed more than four drinks every day; smokers = smoking at least 100 cigarettes in life.
Bold indicates statistical difference.

(continuous variables) and weighted proportion (categorical variables). Furthermore, since the four NHANES survey cycles were combined, the sample weight used in the final evaluation was equal to one-fourth the value of "WTMEC2YR". The baseline characteristics are presented as weighted proportions (categorical variables) and weighted means and SE (continuous variables). The weights used for these evaluations were chosen according to the guidelines delineated in the NHANES database.[29]

Multivariable regression analysis for BMD was implemented with adjustment for age, race, and BMI in Model 1, and adjusted for age, race, education level, income level, BMI, smoking status, alcohol consumption, diabetes, physical activity level, and serum 25(OH)D levels in Model 2.

Kolmogorov–Smirnov tests were used to determine whether the BMD variables conformed to the normal distribution, and logarithmic transformation was utilized for those that did not conform to the normal distribution.

Independent z-tests were used to assess the statistical significance of differences in BMD between the seropositive and seronegative groups for Hepatitis A antibodies.

All evaluations were performed using R software (version 4.2.3; https://www.R-project.org). Statistical significance was set at $P < 0.05$.

RESULTS

Segmentation and baseline characteristics

A flowchart of the segmentation process is shown in **Figure 1**. Data from 39,415 participants were obtained from the NHANES over four cycles: 2011–2012 (n = 10,015), 2013–2014 (n = 10,175), 2015–2016 (n = 9,971), and 2017–2018 (n = 9,254).

First, following the elimination of 23,722 participants from the original 39,415 owing to missing data on BMD or Hepatitis A antibodies, 15,693 participants meeting the inclusion

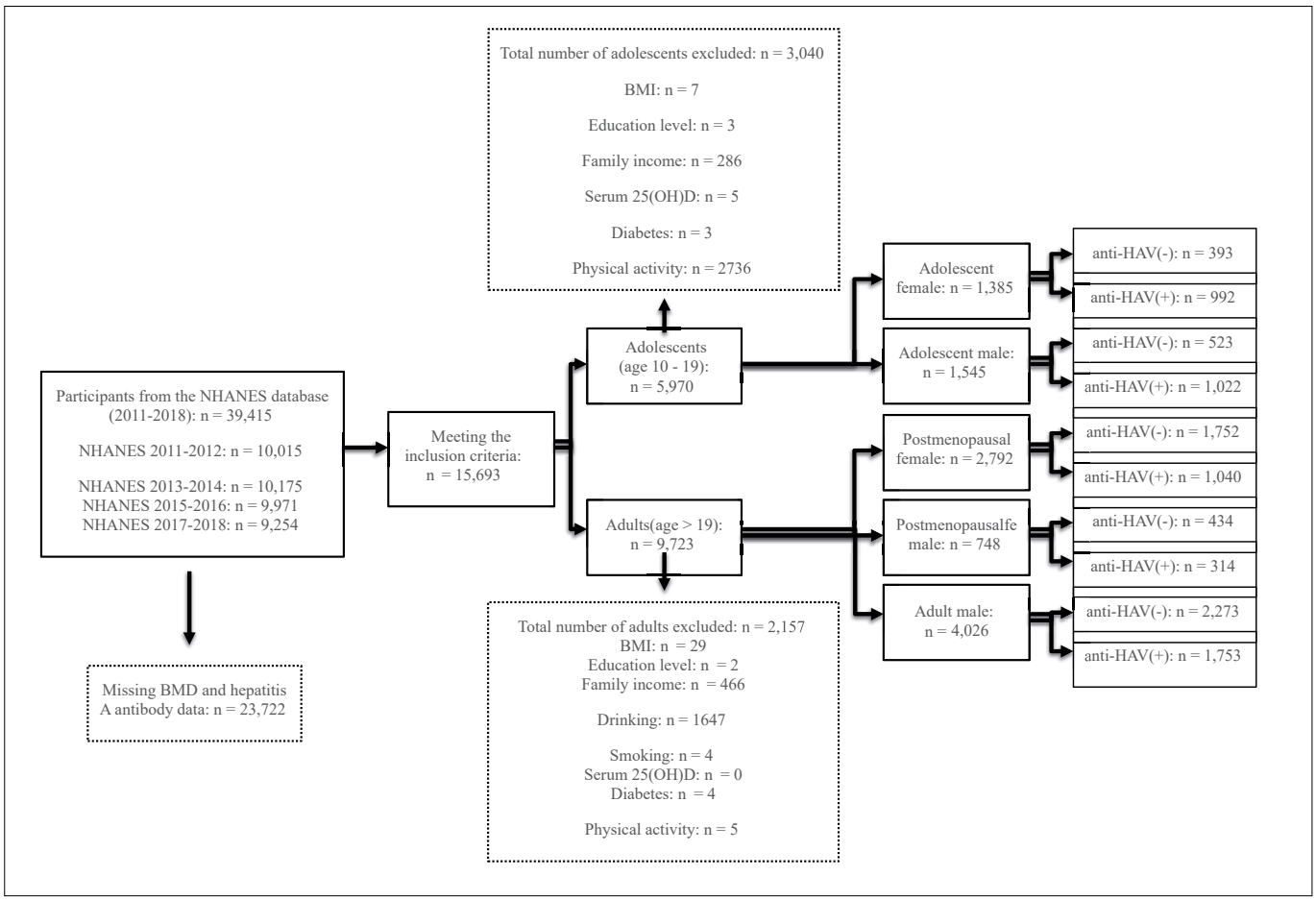

Figure 1. Flow chart of the study design.

criteria were included for subsequent analysis. Each participant's Hepatitis A antibody status and BMD were evaluated concurrently within these respective cycles to ensure temporal alignment of the measurements.

Second, the participants were stratified into adolescents (n = 5,970) and adults (n = 9,723) based on age. The covariates for adults included age, race, education level, income level, BMI, smoking status, alcohol consumption, diabetes, physical activity level, and serum 25 (OH) D levels. For adolescents, the covariates were the same except for smoking and alcohol use, which are illegal for minors. After excluding participants with missing covariates, 2,930 adolescents and 7,566 adults were included for further analysis.

Third, stratification of the adolescent and adult participants by sex yielded five groups: adolescent females (n = 1,385) and males (n = 1,545), premenopausal (n = 2,792) and postmenopausal (n = 748) adult females, and adult males (n = 4,026). Each of these five groups was then dichotomized as having either seronegative or seropositive Hepatitis A antibody status, providing 10 categories for subsequent analysis.

The baseline characteristics of the groups are presented in **Table 1**. In both adolescents and adults, the weighted mean age of the seronegative individuals was higher than that of the seropositive individuals. Specifically, the seronegative adolescents had a weighted mean age of 15.83 ± 0.10 years compared with 15.43 ± 0.07 years of the seropositive adolescents. Similarly, the seronegative adults had a weighted mean age of 39.91 ± 0.23 years compared with 37.78 ± 0.29 years of the seropositive adults. Regardless of age, the weighted proportion of non-Hispanic whites in the seropositive population was lower than that in the seronegative population **(Supplemental Figure S1).** Furthermore, the seronegative individuals were found to have higher levels of weighted mean serum 25(OH)D levels than the seropositive individuals in both age groups; detailed information on other variables is available in **Table 1 with P values in Supplemental Table S2.**

Adolescents' association between anti-HAV and BMD

Lumbar spine and pelvic BMDs of all subpopulations were tested using the Kolmogorov–Smirnov test to determine whether they

conformed to the normal distribution. Those who did not conform to the normal distribution at first conformed to the normal distribution after logarithmic transformation.

Multivariable regression analysis was used to calculate the mean BMD and SE for adolescents **(Table 2).** Two models were used: Model 1, adjusted for age, race, and BMI; and Model 2, adjusted for age, race, BMI, education level, annual family income, diabetes, physical activity level, and serum 25(OH)D levels. Whether BMD was more likely to be lower in the anti-HAV (+) participants than in the anti-HAV (-) participants was determined using independent z-tests with a statistical significance threshold of $P < 0.05$. The results showed that lumbar spine BMD was significantly lower in the anti-HAV (+) adolescent males than in the anti-HAV (-) adolescent males in both models (Model 1: mean difference = -0.018 g/cm2, $P = 0.002$; Model 2: mean difference = -0.021 g/cm2, $P < 0.001$). No other significant differences were observed between groups.

Adults' association between anti-HAV and BMD

Adults, divided into premenopausal and postmenopausal females and males were examined using multivariable regression analysis to calculate their mean BMD and SE (**Table 3**). Two models were used: Model 1, adjusted for age, race, and BMI; and Model 2, adjusted for age, race, BMI, education level, annual family income, diabetes, physical activity level, high-risk drinking, smoking, and serum 25(OH)D levels. Independent z-tests were used to determine whether BMD was more likely to be lower in anti-HAV (+) participants than in anti-HAV (-) participants, with a statistical significance threshold of $P < 0.05$. The results showed that the lumbar spine and pelvic BMDs were significantly lower in the anti-HAV (+) participants than in the anti-HAV (-) participants in all groups (premenopausal females, postmenopausal females, and males) in both models (all $P < 0.05$). Lumbar spine and pelvis BMDs of Models 1 and 2 for all subpopulations of adolescents and adults are illustrated in **Figure 2**.

Table 2. Association between anti-hepatitis A virus and bone mineral density in adolescents

	Model 1			Model 2		
	anti-HAV (-)	anti-HAV (+)	P	anti-HAV (-)	anti-HAV (+)	P
Lumbar Spine						
Female	0.999 ± 0.003	0.995 ± 0.002	0.343	1.002 ± 0.004	0.996 ± 0.002	0.142
Male	0.955 ± 0.005	0.937 ± 0.003	**0.002**	0.958 ± 0.005	0.937 ± 0.003	**<0.001**
Pelvis						
Female	1.182 ± 0.004	1.190 ± 0.003	0.134	1.187 ± 0.004	1.191 ± 0.003	0.476
Male	1.183 ± 0.006	1.174 ± 0.004	0.206	1.188 ± 0.006	1.175 ± 0.004	0.071

Model 1: Adjusted for age, race (non-Hispanic white, Mexican American, other Hispanic, non-Hispanic black, and other races), and body mass index.
Model 2: Adjusted for age, race (non-Hispanic white; Mexican American; other Hispanic; non-Hispanic black; other races), body mass index, education level (lower than 5th grade; 5th grade to 8th grade; higher than 8th grade), annual family income (under $20,000; $20,000 and over), diabetes (yes, no, borderline), physical activity level (vigorous work activity, moderate work activity, walking or cycling, vigorous recreational activities, and moderate recreational activities), and serum 25-hydroxyvitamin D levels.
HAV = hepatitis A virus.
All bone mineral density scores are in g/cm^2.
Bold indicates statistical difference.

Table 3. Association between anti-hepatitis A virus and bone mineral density in adults

	Model 1			Model 2		
	anti-HAV(-)	anti-HAV(+)	P	anti-HAV(-)	anti-HAV(+)	P
Lumbar Spine						
Pre	1.065 ± 0.001	1.049 ± 0.001	**< 0.001**	1.066 ± 0.001	1.050 ± 0.001	**< 0.001**
Post	0.995 ± 0.001	0.948 ± 0.003	**< 0.001**	1.001 ± 0.002	0.948 ± 0.003	**< 0.001**
Male	1.036 ± 0.001	1.016 ± 0.001	**< 0.001**	1.037 ± 0.001	1.017 ± 0.001	**< 0.001**
Pelvis						
Pre	1.238 ± 0.001	1.235 ± 0.001	**0.019**	1.239 ± 0.001	1.235 ± 0.001	**0.028**
Post	1.160 ± 0.001	1.137 ± 0.002	**< 0.001**	1.163 ± 0.002	1.138 ± 0.003	**<0.001**
Male	1.274 ± 0.001	1.270 ± 0.001	**0.005**	1.278 ± 0.001	1.272 ± 0.002	**<0.001**

Model 1: Adjusted for age, race (non-Hispanic white, Mexican American, other Hispanic, non-Hispanic black, and other races), and body mass index.
Model 2: Adjusted for age, race (non-Hispanic white; Mexican American; other Hispanic; non-Hispanic black; other races), body mass index, education level (below high school, high school, or equivalent; above high school), annual family income (under $20,000; $20,000 and over), diabetes (yes, no, borderline), physical activity level (vigorous work activity; moderate work activity; walk or bicycle; vigorous recreational activities; moderate recreational activities), high-risk drinking, smoking, and serum 25-hydroxyvitamin D levels.
HAV = hepatitis A virus.
All bone mineral density scores are in g/cm^2.
Bold indicates statistical difference.
Pre premenopausal female, Post postmenopausal female.

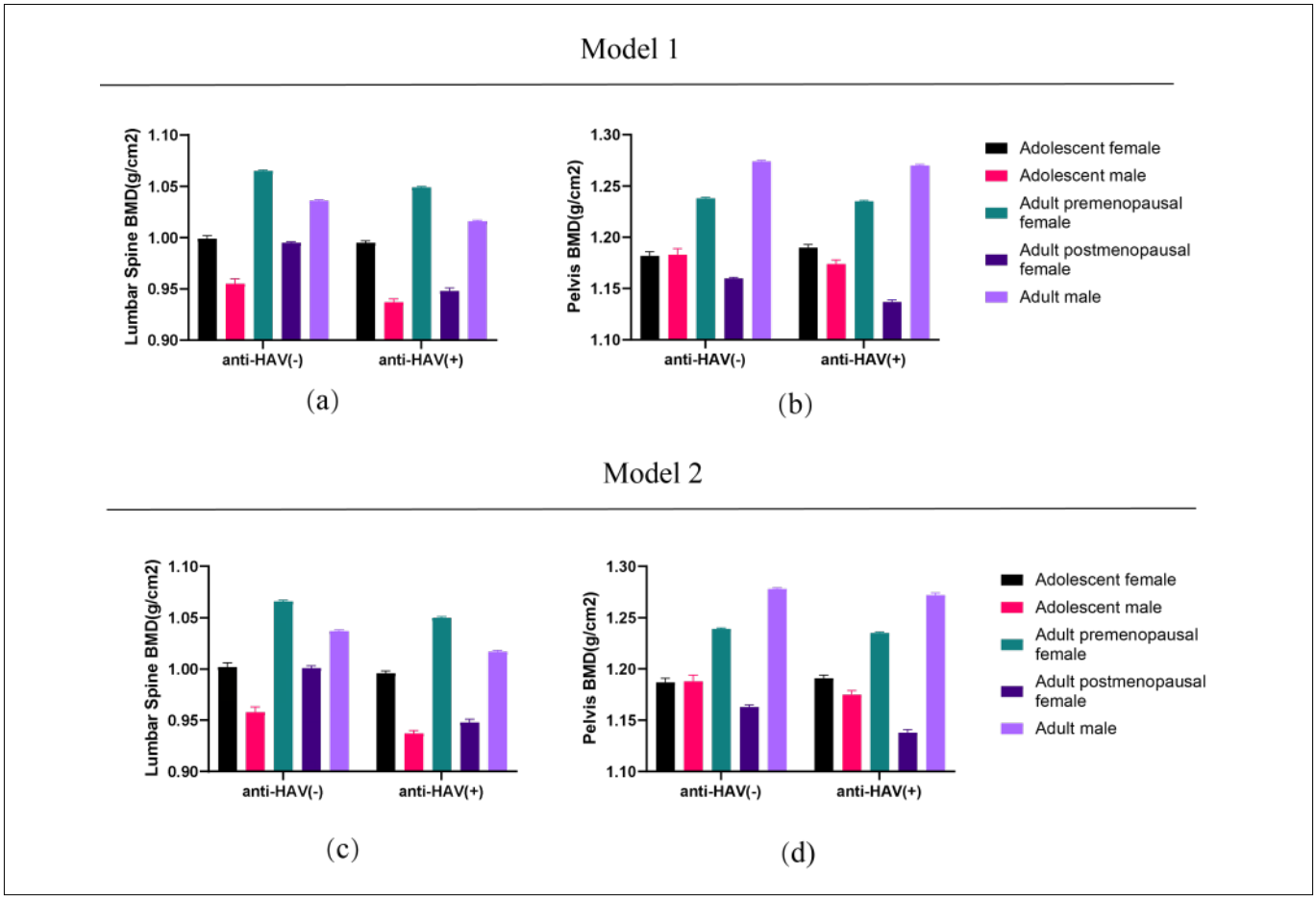

Figure 2. Comparative analysis of lumbar Spine and pelvis bone mineral density in two models across 10 subpopulations. **(a)** Lumbar spine bone mineral density distribution in model 1; **(b)** Pelvis bone mineral density distribution in model 1; **(c)** Lumbar spine bone mineral density distribution in model 2; **(d)** Pelvis bone mineral density distribution in model 2. The height of each histogram represents the mean value and the bars represent the standard error.

DISCUSSION

Examination of the relationship between Hepatitis A seropositivity and BMD revealed that both adolescents and adults who tested positive for Hepatitis A antibodies had lower BMDs than their seronegative counterparts. This association persisted even after controlling for several covariates that differed between the two groups, suggesting an increased risk of osteoporosis in patients with Hepatitis A seropositivity. Bone mineral density is a measure of the amount of minerals such as calcium and phosphorus in bones, which are essential for maintaining bone strength and preventing fractures. Hepatitis A can cause an increase of liver enzymes to above normal levels in the bloodstream, similar to other types of acute viral hepatitis, indicating liver dysfunction and a risk of liver damage.[30] Therefore, it may have a negative effect on nutrient metabolism absorption. Besides, the cytokines including interleukin-10, interleukin-1α, interleukin-6, interleukin-8, interleukin-13, tumor necrosis factor-alpha, and transforming growth factor-beta, are released in a Hepatitis A infection.[31-33] These cytokines may increase the risk of reduction of BMD by stimulating the receptor activator of nuclear factor κ-β ligand-receptor activator of nuclear factor κ-β-osteoprotegerin (RANKL-RANK-OPG) system, which regulates the balance between bone formation and resorption.[34] Multivariable regression is a method used to construct models that investigate the statistical relationship between a response variable (Y) and explanatory variables (Xi), with multivariable linear regression used when Y is continuous and approximately normal.[35] In this study, Y was the BMD of the lumbar spine or pelvis, which are continuous variables, and the covariates were considered as Xi. Therefore, it was reasonable to use multivariable linear regression to construct the two models, in which the means and SEs of the lumbar spine and pelvic BMDs were calculated after adjusting for covariates. The association in adolescents was less significant than that in adults, which may be attributable to the bone growth features of adolescents. Although adolescents and adults experience different changes in BMD, BMD is important in both age groups. During

adolescence, bone growth occurs rapidly, leading to an increase in overall BMD. This process slows down considerably after the age of approximately 20 years, when most people reach peak bone mass (PBM).[36] In contrast, adults face various factors that can negatively affect their BMD, including aging, hormonal changes (e.g., menopause), certain medications, or chronic diseases like osteoporosis.[37] The results illustrated in Figure 2 demonstrate that adolescents have lower lumbar spine and pelvic BMDs than adults (premenopausal females included), and postmenopausal women have lower BMD than premenopausal women in the same model and anti-HAV subgroup. These results confirm the robustness of the multivariable linear regression analysis. As people age, their bones tend to lose density, making them more prone to breakage, even with minimal trauma. Poor bone mass acquisition during growth, leading to lower than optimal levels of PBM, increases the risk of developing osteoporosis or other related conditions.[36,38,39] Moreover, osteoporosis is not only common in white postmenopausal women as it occurs in other populations of all ages, with significant physiological, mental, and economic consequences.[3-6] Therefore, it is important for individuals of all ages to prevent long-term complications associated with low BMD levels, regardless of whether they are adolescents or adults.

In this study, a link between Hepatitis A and bone loss was discovered for the first time; however, similar findings have been reported for other forms of hepatitis, with several studies showing an association between osteoporosis and Hepatitis B. Patients with a Hepatitis B infection tend to experience bone loss and may even develop osteoporosis or bone fractures. Zhang et al. found that patients with Hepatitis B cirrhosis had lower BMD and higher prevalence of osteoporosis than healthy controls.[18] Dessordi et al. reported that patients with a Hepatitis B infection had lower BMD and higher serum levels of osteoclast markers than controls, suggesting that chronic viral infection may enhance bone resorption independently of antiretroviral therapy.[16] Oh et al. reported that patients with chronic Hepatitis B infection in South Korea had increased risks of osteoporosis compared to the general population, as evidenced by a 9% higher fracture rate and an upward trend of osteoporotic fractures from 2007 to 2016.[17] Baeg et al. reported that male patients with Hepatitis B virus infection had lower BMD in the femur and lumbar spine than those without the infection.[15] Wei et al. reported that antiviral therapy for chronic Hepatitis B with tenofovir disoproxil fumarate or entecavir did not increase the risk of osteopenia or osteoporosis in Asian patients during a median follow-up of 4–5 years.[40] Research on Hepatitis C and other chronic active hepatitis has also shown a loss of bone. Wijarnpreecha et al., in a meta-analysis of four studies, reported that Hepatitis C virus infection was associated with an increased risk of osteoporosis.[19] Clements and Rhodes reported a case of a 41-year-old female patient with chronic active hepatitis who had a high rate of bone loss, in the context of increased incidence of osteoporosis in patients with chronic liver disease.[41] Hepatic osteodystrophy (HOD), a condition of bone loss in patients with chronic liver diseases, which leads to an increased risk of osteoporosis and osteoporotic fractures, has been proposed as a theory to explain this phenomenon. The pathogenesis of HOD is complex and multifactorial, and involves hormonal, inflammatory, nutritional, and genetic factors.[34, 41-44]

Hepatitis A is an acute disease that does not result in a chronic infection,[10] unlike HOD, which occurs only in patients with chronic liver disease. The anti-HAV assay used in this study measures total anti-HAV (IgG or IgM) in human serum or plasma, indicating past or present infection with HAV or vaccination against HAV.[26] Interestingly, the incidence rate of reported Hepatitis A cases in the United States (one case per 100,000 population) was significantly lower than the seropositive rate of anti-HAV in the study population (68.74% in adolescents and 41.06% in adults). This suggests that the high seropositivity rate of anti-HAV may not be due to infection but rather vaccination. However, the association between vaccination and bone loss has not yet been reported.

The present study was limited by the use of a total serum anti-HAV assay that detected total anti-HAV antibodies (including IgG or IgM). This assay does not allow for the differentiation of IgG and IgM, which can affect the BMD. Additionally, the study was cross-sectional, which means that it was not possible to establish the temporality between HAV infection and reduced BMD. Finally, this study did not assess whether a reduction in BMD leads to clinically relevant diseases. These limitations should be considered when interpreting the results of this study.

CONCLUSIONS

This study confirmed that Hepatitis A seropositivity was associated with reduced BMD in both adolescents and adults, suggesting that it is a potential risk factor for osteoporosis. Individuals seropositive for Hepatitis A should be aware of this risk and take preventive measures. Further research is needed to verify the causal effects of Hepatitis A antibodies on bone tissue and elucidate the underlying mechanisms. These findings may have implications for public health and inform the development of targeted interventions to prevent osteoporosis.

REFERENCES

1. Blanchard R, Thomas CDL, Hardiman R, et al. Structural and Material Changes of Human Cortical Bone With Age: Lessons from the Melbourne Femur Research Collection. In: Narayan R, editor. Encyclopedia of Biomedical Engineering. Oxford: Elsevier; 2019. p. 246-264. https://doi.org/10.1016/B978-0-12-801238-3.99928-8.
2. Ebeling PR, Nguyen HH, Aleksova J, et al. Secondary Osteoporosis. Endocr Rev. 2022;43(2):240-313. PMID: 34476488; https://doi.org/10.1210/endrev/bnab028.

3. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet. 1999;353(9156):878-882. PMID: 10093980; https://doi.org/10.1016/s0140-6736(98)09075-8.
4. Prasad D, Nguyen MH. Chronic hepatitis, osteoporosis, and men: under-recognised and underdiagnosed. Lancet Diabetes Endocrinol. 2021;9(3):141. PMID: 33607040; https://doi.org/10.1016/s2213-8587(21)00020-6.
5. The Lancet Diabetes Endocrinology. Osteoporosis: overlooked in men for too long. Lancet Diabetes Endocrinol. 2021;9(1):1. PMID: 33285120. https://doi.org/10.1016/s2213-8587(20)30408-3.
6. NIH Consensus Development Panel on Osteoporosis Prevention D, and Therapy. Osteoporosis prevention, diagnosis, and therapy. JAMA. 2001;285(6):785-795. PMID: 11176917; https://doi.org/10.1001/jama.285.6.785.
7. Reid IR. Revisiting osteoporosis guidelines. Lancet Diabetes Endocrinol. 2021;9(12):805-806. PMID: 34688355; https://doi.org/10.1016/s2213-8587(21)00283-7.
8. Stevenson MO, Tangpricha V. Osteoporosis and Bone Health in Transgender Persons. Endocrinol Metab Clin North Am. 2019;48(2):421-427. PMID: 31027549; https://doi.org/10.1016/j.ecl.2019.02.006.
9. Linder KA, Malani PN. Hepatitis A. JAMA. 2017;318(23):2393. PMID: 29094153; https://doi.org/10.1001/jama.2017.17244.
10. Nelson NP, Weng MK, Hofmeister MG, et al. Prevention of Hepatitis A Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices, 2020. MMWR Recomm Rep. 2020;69(5):1-38. PMID: 32614811; https://doi.org/10.15585/mmwr.rr6905a1.
11. Centers for Disease Control and Prevention. Surveillance for viral hepatitis—United States. Available from: https://www.cdc.gov/hepatitis/statistics/SurveillanceRpts.htm. Accessed in2023 (Oct. 24).
12. Jacobsen KH, Koopman JS. Declining hepatitis A seroprevalence: a global review and analysis. Epidemiol Infect. 2004;132(6):1005-1022. PMID: 15635957; https://doi.org/10.1017/s0950268804002857.
13. Jung YM, Park SJ, Kim JS, et al. Atypical manifestations of hepatitis A infection: a prospective, multicenter study in Korea. J Med Virol. 2010;82(8):1318-1326. PMID: 20572083; https://doi.org/10.1002/jmv.21822.
14. Lefilliatre P, Villeneuve JP. Fulminant hepatitis A in patients with chronic liver disease. Can J Public Health. 2000;91(3):168-170. PMID: 10927841; https://doi.org/10.1007/bf03404264.
15. Baeg MK, Yoon SK, Ko SH, et al. Males seropositive for hepatitis B surface antigen are at risk of lower bone mineral density: the 2008-2010 Korea National Health and Nutrition Examination Surveys. Hepatol Int. 2016;10(3):470-477. PMID: 26850597; https://doi.org/10.1007/s12072-015-9672-7.
16. Dessordi R, Watanabe LM, Guimarães MP, et al. Bone loss in hepatitis B virus-infected patients can be associated with greater osteoclastic activity independently of the retroviral use. Sci Rep. 2021;11(1):10162. PMID: 33986322; https://doi.org/10.1038/s41598-021-89486-9.
17. Oh H, Jun DW, Lee IH, et al. Increasing comorbidities in a South Korea insured population-based cohort of patients with chronic hepatitis B. Aliment Pharmacol Ther. 2020;52(2):371-381. PMID: 32542860; https://doi.org/10.1111/apt.15867.
18. Zhang Y, Gao X, Liu T, et al. Association between osteoporosis and hepatitis B cirrhosis: a case-control study. Afr Health Sci. 2020;20(4):1610-1616. PMID: 34394221; https://doi.org/10.4314/ahs.v20i4.13.
19. Wijarnpreecha K, Thongprayoon C, Panjawatanan P, Phatharacharukul P, Ungprasert P. Hepatitis C virus infection and risk of osteoporosis: A meta-analysis. Saudi J Gastroenterol. 2017;23(4):216-221. PMID: 28721974; https://doi.org/10.4103/sjg.SJG_452_16.
20. Lednar WM, Lemon SM, Kirkpatrick JW, et al. Frequency of illness associated with epidemic hepatitis A virus infections in adults. Am J Epidemiol. 1985;122(2):226-233. PMID: 3860002; https://doi.org/10.1093/oxfordjournals.aje.a114093.
21. Centers for Disease Control and Prevention. About the National Health and Nutrition Examination Survey. Available from: https://www.cdc.gov/nchs/nhanes/about_nhanes.htm. Accessed in 2023 (Oct. 24).
22. World Health Organization. Adolescent health. Available from: https://www.who.int/health-topics/adolescent-health#tab=tab_1. Accessed in 2023 (Oct. 24).
23. Mayo Clinic. Menopause. Available from: https://www.mayoclinic.org/diseasesconditions/menopause/symptoms-causes/syc-20353397. Accessed in 2023 (Oct. 24)..
24. Centers for Disease Control and Prevention. NHANES Body Composition Procedures Manual. 2018. Available from: https://wwwn.cdc.gov/nchs/data/nhanes/2017-2018/manuals/Body_Composition_Procedures_Manual_2018.pdf. Accessed in 2023 (Oct. 24).
25. Kanis JA, Johnell O, Oden A, et al. Long-term risk of osteoporotic fracture in Malmö. Osteoporos Int. 2000;11(8):669-674. PMID: 11095169; https://doi.org/10.1007/s001980070064.
26. Centers for Disease Control and Prevention. Hepatitis A Antibody Laboratory Procedure Manual. 2019. Available from: https://wwwn.cdc.gov/nchs/data/nhanes/2017-2018/labmethods/HEPA-J-MET-HEPATITIS-A-ANTIBODY-508.pdf. Accessed in 2023 (Oct. 24)..
27. Ni G, van der Werf J, Zhou X, et al. Genotype-covariate correlation and interaction disentangled by a whole-genome multivariate reaction norm model. Nat Commun. 2019;10(1):2239. PMID: 31110177; https://doi.org/10.1038/s41467-019-10128-w.
28. Sukegawa S, Fujimura A, Taguchi A, et al. Identification of osteoporosis using ensemble deep learning model with panoramic radiographs and clinical covariates. Sci Rep. 2022;12(1):6088. PMID: 35413983; https://doi.org/10.1038/s41598-022-10150-x.
29. Centers for Disease Control and Prevention. Weighting. Available from: https://wwwn.cdc.gov/nchs/nhanes/tutorials/Weighting.aspx. Accessed in 2023 (Oct. 24).
30. Giannini EG, Testa R, Savarino V. Liver enzyme alteration: a guide for clinicians. Cmaj. 2005;172(3):367-379. PMID: 15684121; https://doi.org/10.1503/cmaj.1040752.

31. Fierro NA, Castro-Garcia FP, Panduro A. Rethinking cytokine function during hepatitis A and hepatitis C infections. Advances in Bioscience and Biotechnology. 2013;4(7A):13-18. PMID; https://doi.org/10.4236/abb.2013.47A1003.
32. XinHuan W, YaLi L, Jing Z, Wei L. Expression and significance of cytokines in children with acute hepatitis A. - Journal of Clinical Hepatology. 2019;35(9):1942. PMID; https://doi.org/-10.3969/j.issn.1001-5256.2019.09.011.
33. Shin EC, Sung PS, Park SH. Immune responses and immunopathology in acute and chronic viral hepatitis. Nat Rev Immunol. 2016;16(8):509-523. PMID: 27374637; https://doi.org/10.1038/nri.2016.69.
34. Jeong HM, Kim DJ. Bone Diseases in Patients with Chronic Liver Disease. Int J Mol Sci. 2019 Aug 31;20(17):4270. PMID: 31480433. https://doi.org/10.3390/ijms20174270.
35. Alexopoulos EC. Introduction to multivariate regression analysis. Hippokratia. 2010;14(Suppl 1):23-28. PMID: 21487487.
36. Xue S, Kemal O, Lu M, et al. Age at attainment of peak bone mineral density and its associated factors: The National Health and Nutrition Examination Survey 2005-2014. Bone. 2020;131:115163. PMID: 31760214; https://doi.org/10.1016/j.bone.2019.115163.
37. Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society. Menopause. 2021;28(9):973-997. PMID: 34448749; https://doi.org/10.1097/gme.0000000000001831.
38. Zhu X, Zheng H. Factors influencing peak bone mass gain. Front Med. 2021;15(1):53-69. PMID: 32519297; https://doi.org/10.1007/s11684-020-0748-y.
39. Gordon CM, Zemel BS, Wren TA, et al. The Determinants of Peak Bone Mass. J Pediatr. 2017;180:261-269. PMID: 27816219; https://doi.org/10.1016/j.jpeds.2016.09.056.
40. Wei MT, Le AK, Chang MS, et al. Antiviral therapy and the development of osteopenia/osteoporosis among Asians with chronic hepatitis B. J Med Virol. 2019;91(7):1288-1294. PMID: 30776311; https://doi.org/10.1002/jmv.25433.
41. Clements D, Rhodes J. Hormone replacement therapy in chronic active hepatitis; a case report. Gut. 1993;34(11):1639-1640. PMID: 8244156; https://doi.org/10.1136/gut.34.11.1639.
42. Danford CJ, Trivedi HD, Bonder A. Bone Health in Patients With Liver Diseases. J Clin Densitom. 2020;23(2):212-222. PMID: 30744928; https://doi.org/10.1016/j.jocd.2019.01.004.
43. Nakchbandi IA, van der Merwe SW. Current understanding of osteoporosis associated with liver disease. Nat Rev Gastroenterol Hepatol. 2009;6(11):660-670. PMID: 19881518; https://doi.org/10.1038/nrgastro.2009.166.
44. Schmidt T, Schmidt C, Strahl A, et al. A System to Determine Risk of Osteoporosis in Patients With Autoimmune Hepatitis. Clin Gastroenterol Hepatol. 2020;18(1):226-233.e223. PMID: 31163277; https://doi.org/10.1016/j.cgh.2019.05.043.

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Interdisciplinary training program for pediatric cardiorespiratory arrest using rapid cycle deliberate practice: A descriptive cross-sectional study

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ABSTRACT

BACKGROUND: cardiorespiratory arrest (CRA) is a severe public health concern, and clinical simulation has proven to be a beneficial educational strategy for training on this topic.

OBJECTIVE: To describe the implementation of a program for pediatric cardiac arrest care using rapid-cycle deliberate practice (RCDP), the quality of the technique employed, and participants' opinions on the methodology.

DESIGN AND SETTING: This descriptive cross-sectional study of pre- and post-performance training in cardiopulmonary resuscitation (CPR) techniques and reaction evaluation was conducted in a hospital in São Paulo.

METHODS: Multidisciplinary groups performed pediatric resuscitation in a simulated scenario with RCDP mediated by a facilitator. The study sample included professionals working in patient care. During the simulation, the participants were evaluated for their compliance with the CRA care algorithm. Further, their execution of chest compressions was assessed pre- and post-intervention.

RESULTS: In total, 302 professionals were trained in this study. The overall quality of CPR measured pre-intervention was inadequate, and only 26% had adequate technique proficiency, whereas it was 91% ($P < 0.01$) post-intervention. Of the participants, 95.7% responded to the final evaluation and provided positive comments on the method and their satisfaction with the novel simulation. Of these, 88% considered that repetition of the technique used was more effective than traditional simulation.

CONCLUSIONS: The RCDP is effective for training multidisciplinary teams in pediatric CPR, with an emphasis on the quality of chest compressions. However, further studies are necessary to explore whether this trend translates to differential performances in practical settings.

INTRODUCTION

Cardiorespiratory arrest (CRA) is considered among the most severe public health problems due to its significant healthcare burden, with significantly high morbidity and mortality rates.[1-3]

In pediatric patients, this condition is infrequent, and when it occurs, it is usually the result of respiratory failure progression. For this reason, asystole and pulseless electrical activity (PEA) are the most frequently presented rhythms, as evidenced in a study by Skellett et al. in the United Kingdom.[4-6] In this scenario, defibrillation is not recommended, and high-quality cardiopulmonary resuscitation (CPR) is the most preferred intervention in this population.[4,7]

Each year, approximately 19,900 pediatric cardiac arrests occur in the United States, according to the United States of America CRA registry publication.[3,8,9]

In Brazil, the database analysis of a tertiary pediatric hospital emphasized that in 15 years, an increase of 6% was observed in the reestablishment rate of spontaneous circulation and that of 13.8% in survival at hospital discharge.[9,10] This improvement is likely due to multifactorial reasons that can be attributed to earlier recognition and management of at-risk patients, improved quality of basic and advanced life support, post-CRA care, and patient care team training.[3]

Despite evidence supporting that CPR (cardiopulmonary resuscitation) is the best practice in CRA treatment, the technique quality provided to pediatric patients in simulated and real CRA situations[11,12] is often inadequate and may negatively impact survival rates.[13-15]

Therefore, effective CPR training requires the use of innovative educational strategies to achieve optimal results,[14] and clinical simulation has proven to be a beneficial educational strategy.

It supports skill development by reproducing a desired clinical context in a safe and controlled environment.[16]

Traditionally, clinical simulation consists of complete scenario development by a group of participants, followed by debriefing mediated by a facilitator.[17] After which the scenario is terminated without the participants having the opportunity to practice the required tasks again in the correct manner.[17,18]

To solve this problem, a study by Anders Ericsson[19] suggested deliberate practice as the most effective method to achieve perfection in performance. This method aims to maximize performance through well-defined learning objectives, focused and repetitive practice, accurate performance measures, and informative feedback.[19,20]

Given these conditions, the use of the rapid-cycle deliberate practice (RCDP), a simulation strategy created by Hunt, has been recommended.[21] This is a simulation-based model of education in which learners develop their actions repeatedly (deliberate practice) for a short period (rapid cycle) in the same clinical scenario until the desired skill is mastered by the participant. When the objectives of one cycle are achieved, a new cycle begins, increasing the complexity of the tasks required.[18,20]

The RCDP described by Hunt is characterized by a combination of personalized directive feedback and practice, which is repeated according to the participating students' performance. It modifies the debriefing from traditional post-simulation feedback to directive feedback within an event.[22,18] In this novel approach, whenever there is a non-conformity, the scenario is paused, the students are interrupted, and the instructor provides brief, pertinent corrective information.[21-23] After the corrections, the scenario continues, but this time follows the correct process. It allows participants to have multiple opportunities to perform the technique correctly by receiving focused guidance until they master the desired skills.[24,25]

OBJECTIVE

The main objective of this study was to describe the implementation of a simulation-based interdisciplinary training program using RCDP specific to the context of CRA in pediatrics. Other objectives were to describe the quality of performance of the professionals at the beginning and end of the training and to report the participants' opinions regarding the methodology used.

METHODS

This descriptive cross-sectional study was conducted in a private hospital providing pediatric care exclusively in the city of São Paulo from November 2020 to May 2022.

For this training project, the focus was a pediatric CRA with a high-performance team. For this purpose, a fully simulation-based multidisciplinary small group activity was established and supported by the most updated methodology and evidence in the field of medicine.

The convenience sample comprised 302 professionals including nurses, physical therapists, and physicians who work at the institution, regardless of hierarchical level and area of work, who agreed to participate in the study and signed an informed consent form. Those who did not participate in the training or sign the informed consent form were excluded.

The participants were invited to participate in the study and informed of its objectives. Participation was voluntary, and confidentiality was maintained.

After they consented to participate, they received an online form to fill in the demographic data, a brief instruction with a review of the Pediatric Advanced Life Suport (PALS-2020)[26] algorithm, guidance on the methodology to be used in training, and its objectives. They then began the care of a simulation case using a high-fidelity manikin sequenced in cycles. With each cycle, additional steps of the pediatric resuscitation algorithm were added.

The performance of the participants selected for chest compressions was evaluated in the first cycle of care (without instructor intervention) for frequency, depth, and quality of technique using the RescueNet Code Review software (standard edition) from Zoll Medical Corporation (Chelmsford, Massachusetts, USA), which captures information from electrodes positioned on the manikin and archives it for later analysis.

The parameters configured in the software as the quality standard for the technique were based on the guidelines determined by the American Heart Association (AHA).[26] For the variable compression frequency, the range of 100–120 compressions/min was defined, for depth compressions with 4–5 cm anteroposterior chest diameter. To determine the quality of the technique according to this guideline, parameters such as frequency and depth must occur simultaneously.

During the simulation, participants were evaluated for compliance with the CRA care algorithm. Therefore, when the instructor noticed a failure to reach a goal for that round, the scenario was paused and feedback was provided to correct the error, after which the activity was restarted from the beginning of that round, allowing the participants to practice the skills correctly.

The scenario was completed once the team achieved its goals for all cycles. Finally, in the goal-achieved cycle, the participants' performance in chest compressions was also recorded, collecting data following the same parameters as those in the first cycle.

At the end of the training, a reaction survey was made available to the participants to evaluate the training without identifying the respondents. The form consisted of basic demographic information, multiple-choice questions using a Likert scale to collect information on perceived practicality and possible points for improvement, basic information on the participants, and a space for comments.

Data from the reaction evaluation questionnaire and the feedback software were statistically analyzed. The average and standard

deviation were calculated for the continuous variable of CPR quality with a t-test comparison of the average recorded pre- and post-training.

This study was approved by the Ethics Committee of Universidade Federal de São Paulo (approval number: 4,195,837) on August 6, 2020.[27] Its results will only be disclosed anonymously, and it will not be possible to identify its participants in compliance with the General Data Protection Law.[28]

RESULTS

For simulation, a pediatric CRA case was adapted for use in the RCDP methodology. Cycles were created to provide the participants with adequate repetition of established goals and new challenges at each stage. This case was then used to train instructors.

During training, each instructor had the opportunity to lead a round of simulations, while the others enacted the clinical case. In addition, all trainers who participated in the additional training focused on deliberate practice methodology.

The safe learning environment generated integration and engagement from the instructors, and important contributions were made to enhance the performance of the simulated scenario. Moreover, they clarified doubts, defined expected standards for the participants, discussed and aligned the proposed learning objectives, and practiced the adopted methodology.

This qualification was an important part of the project as it enabled standardized training for all instructors. In this process, the challenge was to transition from the traditional simulation methodology, already well-established by previous training, to RCDP.

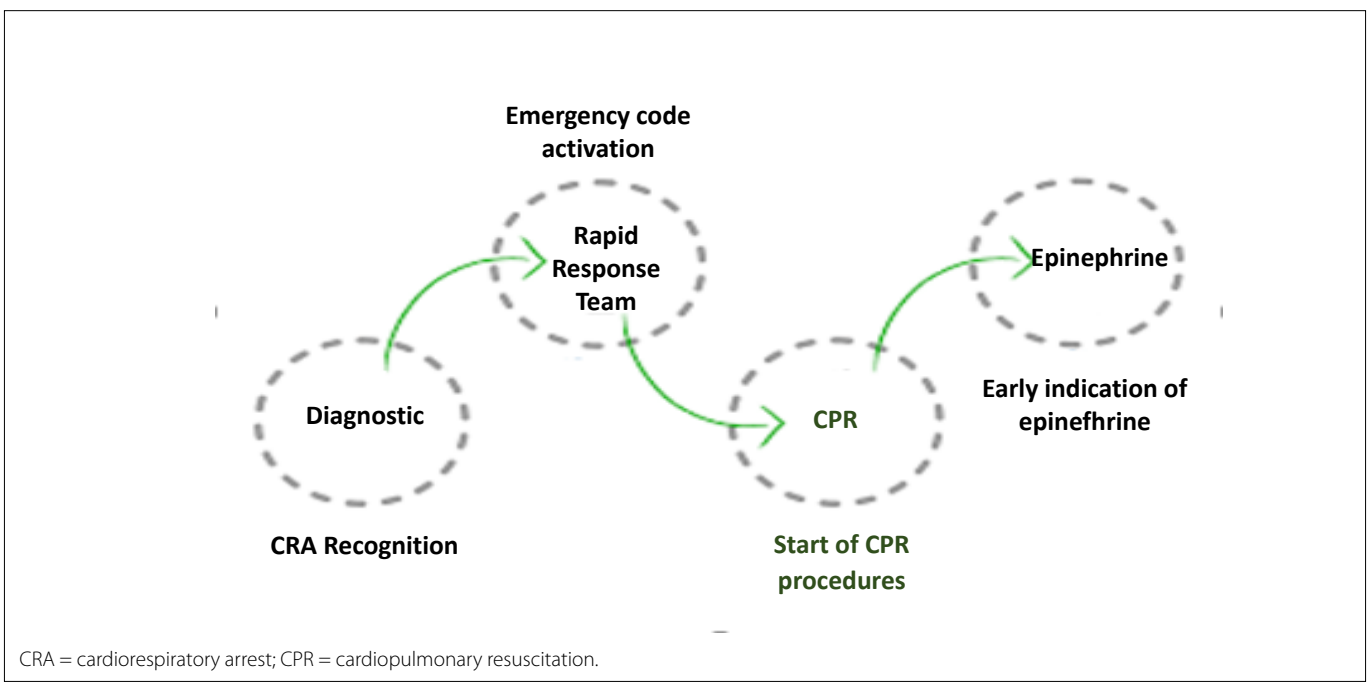
The clinical case scenario corresponded to a CRA in the PEA rhythm resulting from severe respiratory failure and had four objective goals (**Figure 1**).

Each program round was conducted by two instructors: one responsible for operating the scenario and the other for recording and extracting performance data from the equipment.

The group sessions were 1 h long and divided into 50 min of instructional time and 10 min of course feedback and evaluation (**Figure 2**).

The sessions were conducted from November 2020 to May 2022, and each session had six participants, as determined by the institution's CRA care protocol. The data resulting from the maneuvers of the two professionals who took turns performing chest compressions were recorded in the defibrillator equipment software in the first and last cycles of training and used later for the analysis.

The 50 min of instruction time was divided as follows: the first 10 min for presenting the objectives, program strategy, and a punctual review of the CRA care algorithm determined by the AHA in 2020. The next 10 min were for observation of the care provided by the team in the CRA scenario without interruptions or interventions by the instructors (recording of pre-intervention domain training data). Finally, the remaining 30 min were allocated to the same scenario but this time with the RCDP methodology applied. The progress of the service was paused when an action was incorrect, feedback was directed at failure, and the team was provided another opportunity to correctly perform the technique. Post-intervention compression data were also recorded during the last cycle of care in this scenario.



CRA = cardiorespiratory arrest; CPR = cardiopulmonary resuscitation.

Figure 1. Goals set for each training session.

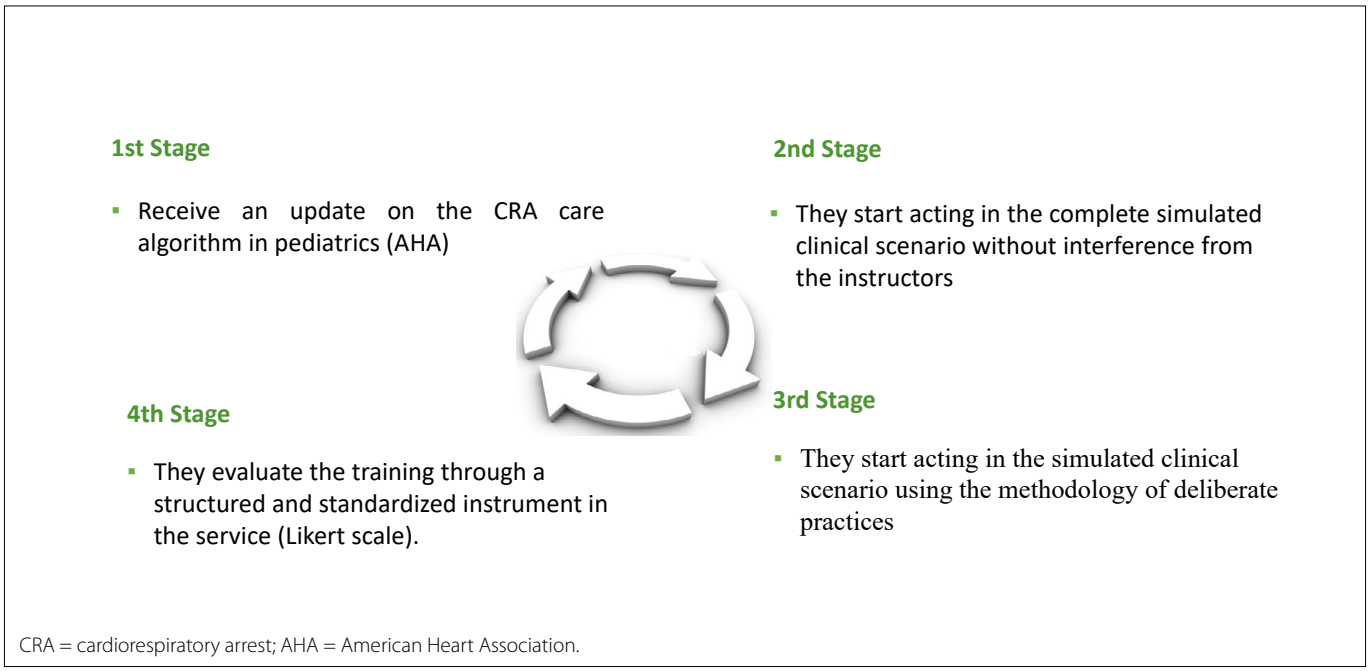


Figure 2. Steps established for each training session – rapid-cycle deliberate practice.

Finally, 10 min were reserved for closing feedback, in which each group was presented with a graph of the quality of chest compressions before and after the training so that they could visualize the difference in performance. Further, a course feedback evaluation using a structured online form was made available in the end.

Owing to the Sars-CoV-2 pandemic, the institutional norms related to infection control were adjusted, and the training sessions were linked to their compliance to ensure the safety of participants and instructors.

These new guidelines directly impacted the planning of this project. To comply with these guidelines, the number of professionals in the training area was limited, and the location was changed to an external area of the hospital (outdoors), adapted, and prepared with pediatric emergency equipment.

In addition, the attendees wore a mandatory N95 mask during the entire training period, hand sanitization with alcohol gel usage was imposed at the beginning and end of each session, and the equipment and materials used were sanitized with standardized hospital disinfectants at the end of each group.

All support materials and training forms were made available electronically so that participants could access them from their cell phones and, as such, did not share materials.

The entire project was studied and evaluated to ensure that safety protocols were strictly adhered to, guaranteeing safety for participants and instructors while not compromising training dynamics.

Overall, 302 professionals were trained during the study period, and all records of the participants' performance in chest compressions and responses to the reaction evaluation form were included in the analysis. The sample comprised 48% nurses, 41% physicians, and 11% physical therapists. Most participants performed their care activities in the intensive care unit, followed by inpatient units, emergency rooms, and operating rooms (**Graph 1**).

Among the training participants, 89% had already participated in a course on CRA care in pediatrics (**Table 1**).

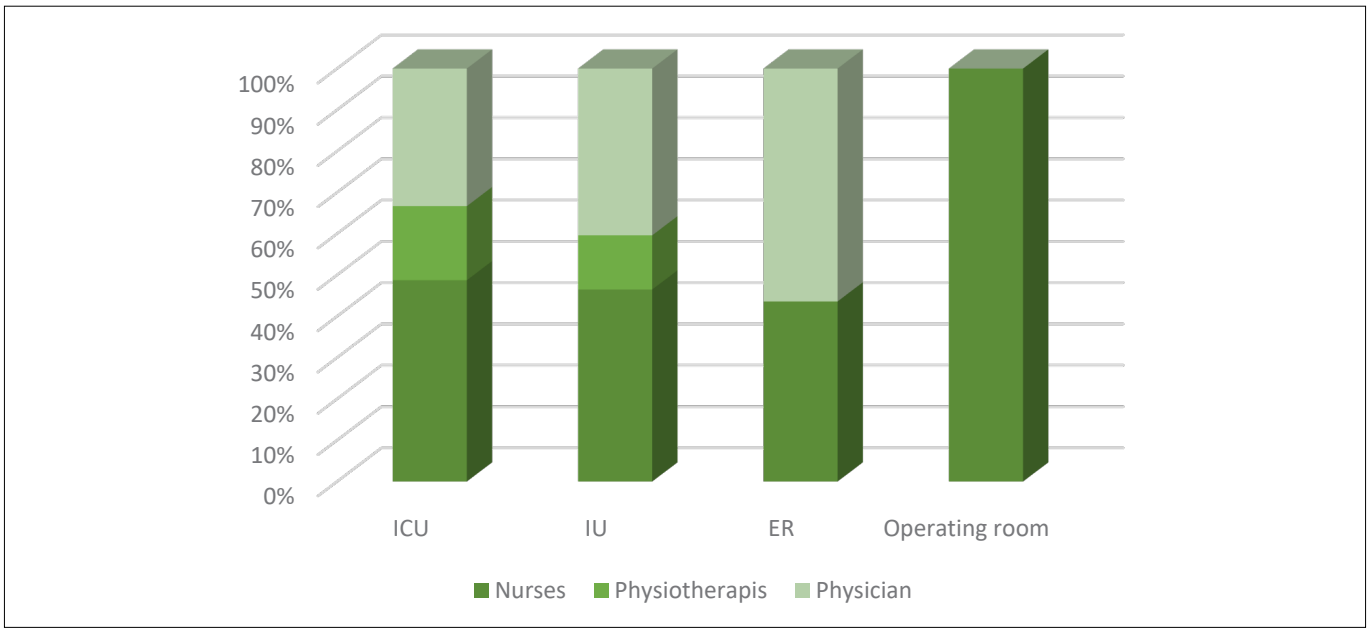
The overall quality of chest compressions measured at the pre-intervention educational mastery training time was inadequate, and only approximately 26% had technique quality within the given standards. In the post-intervention analysis, 91%, on average, reported the quality of the technique used according to the guidelines (**Table 2**).

In the statistical analysis comparing the mean quality of the pre- and post-training proficiency using the t-test for paired samples, the difference was significant ($P < 0.01$).

Regarding the evaluation of the training, 289 answers were obtained from the form made available; that is, 95.7% of the participants registered their impressions of the training (**Graph 2**).

We observed that 97% of the respondents agreed that the theme was important for the practice of their daily assistance activities, and 95% agreed that the activity contributed to their performance improvement in direct patient care.

Analyzing the instructors' performance directly, 96% agreed that they were encouraged to participate and ask questions during the training and that the instructors were objective and clear in their teaching.



Graph 1. Distribution of CPR training participants with RCDP by activity unit; nov 2020 to mar 2022. (n = 302)––

Table 1. Participation in a previous pediatric CRA course

	N	Yes N(%)	No N(%)
Nurses	145	128 (88%)	17 (12%)
Physiotherapists	34	24 (71%)	10 (29%)
Physician	123	119 (97%)	4 (3%)

Regarding the method instituted for skill mastery training, 78% agreed that repetition of the technique used in this methodology was more effective than the traditional simulation of previous pieces of training.

DISCUSSION

A team without appropriate knowledge of how to act in a crisis presents difficulties in the consistent execution of the guidelines that form the basis of CRA care. Therefore, professional education is important for improving survival outcomes in these cases.

This educational opportunity took advantage of the RCDP, which is best employed in simulations that require a participant to follow a clearly defined script under time pressure, as is the case in resuscitation scenarios. Therefore, the adopted methodology met the for skill requirements associated with the learning objectives defined for this project.

Among the training participants, 89% had attended a course on pediatric CRA on another occasion. Even with this prior theoretical knowledge and the review of current guidelines conducted immediately before training, the average performance measured in the pre-intervention scenario presented an inadequate quality of the chest compression technique.

From these findings, and consistent with other publications, it is possible to conclude that although theoretical presentations have a clear impact on learning that can be evidenced by knowledge assessment, they are not enough to ensure the transfer of knowledge acquired into practice during simulated clinical scenarios.[29,30]

The information extracted from the software showed that the average frequency and depth of the chest compressions executed before the intervention, despite being within the ranges determined by the AHA protocols, were of inadequate quality. Therefore, in most resuscitation movements, these two variables are not present simultaneously in the pattern.

This condition noticeably improved performance measured after training. Recording the resuscitation technique employed in the last RCDP cycle revealed that the frequency and depth averages remained within the given standards, and the quality of the technique employed was recorded as adequate in approximately 91% of the sessions.

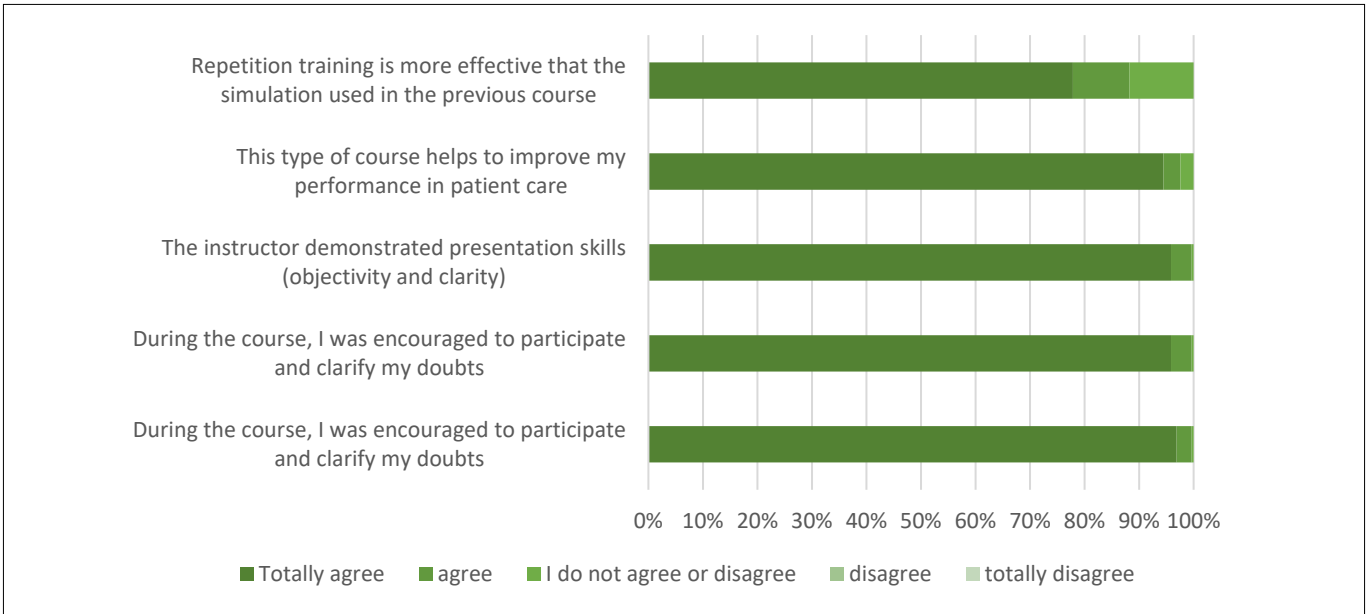
The analysis comparing the average pre- and post-training proficiency using the paired samples t-test revealed that the training intervention resulted in significant improvement in technique quality ($P < 0.01$). This methodology can improve CPR skill quality.

This result aligns with the current literature, which shows immediate improvement in skills and, consequently, in individual and team performance when simulations using the RCDP technique are used in pediatric CPR.[31-34]

One of these studies was a pilot study by Lemke et al., which demonstrated a trend toward improved staff performance during pediatric CRA care after training with RCDP compared with

Table 2. Performance of professionals in the CPR technique

compressions	N	AHA guideline	Pre-training average	DP	Pos-training average	DP
Frequency	302	100–120	109,62	14,36	109,59	5,89
Depth	302	4–5	4,41	0,83	4,21	0,86
Quality of CPR	**AHA guideline**		**Pre-training**		**Pos-training**	
	100%		26%		91%	



Graph 2. Reaction evaluation of CPR training participants with PDCR; nov 2020 to mar 2022. (n = 289)

traditional simulation. The study emphasized that the technique was well-received by students, but they reported fatigue due to repetition.[34]

Another study corresponding to our results is that of Hunt et al., who developed a teaching approach with RCDP that focused on the rapid acquisition of resuscitation and teamwork skills in the first 5 min of pediatric CRA care. The results revealed that training was associated with better resident performance during care for almost all measurable measures.[33]

Focusing on prehospital CRA care, Kosoko et al. developed training with RCDP and showed that this intervention was an effective way to educate professionals about this medical emergency.[35]

Regarding the evaluation of the training feedback, almost all respondents considered the topic covered in the training to be important for their practice. Among the placements in the free evaluation field, the most common one regards CRA as a severe situation, which is infrequent, and thus needs to be trained periodically to be performed with quality and safety.

These results also demonstrated that the training provided greater self-confidence in resuscitation skills. Participants perceived the proficiency they had achieved at the end of the sessions and were able to evaluate differences in technique performance after the RCDP cycles.

Consistent with the findings of this study, the mastery learning methodology is increasingly associated with better educational outcomes, especially concerning resuscitation topics,[20,31-34] as highlighted by Magee et al.[32]

The survey items that evaluated the instructors emphasized the relevance of previous training and instructor involvement in scenario construction and clinical cases. These steps provided standardization in the process and commitment to the stipulated learning objectives.

In the last statement of the form, participants were encouraged to compare the traditional simulation performed earlier with the RCDP. The responses revealed that the participants perceived that their ability to practice repeatedly enhanced their learning regardless of how time-consuming it was.

Finally, the comments were almost entirely positive and allowed us to state that the dynamism of RCDP was well-received by the study participants. In line with the findings of Chancey et al.[36]

Regarding perceived effectiveness, most participants exhibited a high degree of satisfaction in recognizing the relevance of the

content and skills learned. It is noteworthy that the present report is surprising at the results of the pre- and post-training comparisons. In fact, a large proportion realized and recorded that the techniques they believed they knew properly fell short of what was expected for a high-quality procedure.

Another important issue was the perception that it was productive to learn from other members of the multidisciplinary team because working in a cohesive team is a determining factor in successfully handling an emergency.

Although future studies are necessary to evaluate the translation of knowledge and skills from the learning environment to the clinical setting, this study revealed that it is critical to devote efforts to developing innovative health education strategies based on current scientific evidence for an improved care. These interventions can lead to differences in excellent and safe care for pediatric patients.

The results of this study reflect a specific simulated context, making it difficult to predict whether they can be directly generalized to actual patient care.

Another limitation is the lack of data on the improvement in CPR quality observed in previous training courses for comparison with the data obtained in this study.

Because it is a single-event training program, a higher limitation is the non-evaluation of skill retention. Therefore, it is impossible to assess how often training is required to maintain adequate professional performance.

CONCLUSIONS

The results of this study suggest that the RCDP is an appropriate and effective methodology for interdisciplinary team training in pediatric CPR, with an emphasis on the quality of the chest compression technique.

The measurable data revealed a significant improvement in participants' performance in the last cycle of the scenario compared to the first cycle. This demonstrates that this method contributed to the improvement of adequate technical skills in compression during CPR care in a simulated environment.

However, further studies are needed to explore whether this presented trend translates into differential performance in a practical setting, whether these acquired skills are sustained in the long term, and for how long.

This program was effective, well-received, and well-evaluated by the participants, who considered it better, more practical, and more dynamic than the simulation methodology previously adopted as a standard.

Nevertheless, further research is needed to determine whether the perceived benefits of this mastery training program translate into clinical practice by reducing errors, improving team performance, and, most importantly, improving the prognosis of children who rely on high-quality CPR.

REFERENCES

1. Bimerew M, Wondmieneh A, Gedefaw G, et al. Survival of pediatric patients after cardiopulmonary resuscitation for in-hospital cardiac arrest: A systematic review and meta-analysis. Ital J Pediatr. 2021;47(1):118. PMID: 34051837; https://doi.org/10.1186/s13052-021-01058-9.
2. Bastarrica EG, dos Santos F, Conte M, Baldo APV. Epidemiological profile of cardiorespiratory parede patientes: An integrative review. RSD. 2020;9(12):e1559126024. https://doi.org/10.33448/rsd-v9i12.6024.
3. Hamzah M, Othman HF, Almasri M, Al-Subu A, Lutfi R. Survival outcomes of in-hospital cardiac arrest in pediatric patients in the USA. Eur J Pediatr. 2021;180(8):2513-20. PMID: 33899153; https://doi.org/10.1007/s00431-021-04082-3.
4. Meaney PA, Bobrow BJ, Mancini ME, et al. Cardiopulmonary resuscitation quality: improving cardiac resuscitation outcomes both inside and outside the hospital: a consensus statement from the American Heart Association. Circulation. 2013;128(4):417-35. PMID: 23801105; https://doi.org/10.1161/cir.0b013e31829d8654.
5. Skellett S, Orzechowska I, Thomas K, Fortune PM. The landscape of paediatric in-hospital cardiac arrest in the United Kingdom National Cardiac Arrest Audit. Resuscitation. 2020;155:165-71. PMID: 32768496; https://doi.org/10.1016/j.resuscitation.2020.07.026.
6. Mick NW, Williams RJ. Pediatric Cardiac Arrest Resuscitation. Emerg Med Clin North Am. 2020;38(4):819-39. PMID: 32981620; https://doi.org/10.1016/j.emc.2020.06.007.
7. Girotra S, Spertus JA, Li Y, et al. Survival trends in pediatric in-hospital cardiac arrests: an analysis from Get With the Guidelines-Resuscitation. Circ Cardiovasc Qual Outcomes. 2013;6(1):42-9. PMID: 23250980; https://doi.org/10.1161/circoutcomes.112.967968.
8. da Silva WM, Santos MP, Silva CAO, et al. Atualizações em parada cardiorrespiratória pediátrica: uma revisão. Int J Develop Res. 2021;11(5):47001-5. https://doi.org/10.37118/ijdr.21925.05.2021.
9. Shimoda-Sakano TM, Schvartsman C, Reis AG. Epidemiology of pediatric cardiopulmonary resuscitation. J Pediatr. 2020;96(4):409-21. PMID: 31580845; https://doi.org/10.1016/j.jped.2019.08.004.
10. Shimoda-Sakano TM, Paiva EF, Schvartsman C, Reis AG. Factors associated with survival and neurologic outcome after in-hospital cardiac arrest in children: A cohort study. Resusc Plus. 2023;13:100354; PMID: 36686327; https://doi.org/10.1016/j.resplu.2022.100354.
11. Cheng A, Hunt EA, Grant D, et al. Variability in quality of chest compressions provided during simulated cardiac arrest across nine pediatric institutions. Resuscitation. 2015;97:13-9. PMID: 26417701; https://doi.org/10.1016/j.resuscitation.2015.08.024.
12. Sutton RM, Niles D, French B, et al. First quantitative analysis of cardiopulmonary resuscitation quality during in-hospital cardiac arrests of young children. Resuscitation. 2014;85(1):70-4. PMID: 23994802; https://doi.org/10.1016/j.resuscitation.2013.08.014.
13. Lurie KG, Nemergut EC, Yannopoulos D, Sweeney M. The Physiology of Cardiopulmonary Resuscitation. Anesth Analg. 2016;122(3):767-83. PMID: 26562060; https://doi.org/10.1213/ane.0000000000000926.

14. Lin Y, Cheng A, Grant VJ, Currie GR, Hecker KG. Improving CPR quality with distributed practice and real-time feedback in pediatric healthcare providers: a randomized controlled trial. Resuscitation. 2018;130:6-12. PMID: 29944894; https://doi.org/10.1016/j.resuscitation.2018.06.025.
15. Idris AH, Guffey D, Aufderheide TP, et al. Relationship between chest compression rates and outcomes from cardiac arrest. Circulation. 2012;125(24):3004-12. PMID: 22623717; https://doi.org/10.1161/circulationaha.111.059535.
16. Gross IT, Abrahan DG, Kumar A, et al. Rapid cycle deliberate practice (RCDP) as a method to improve airway management skills–a randomized controlled simulation study. Cureus. 2019;11(9):e5546. PMID: 31523589; https://doi.org/10.7759/cureus.5546.
17. Castro LT, Couto TB. Prática Deliberada em Ciclos Rápidos: uma estratégia moderna de simulação. Sci Med. 2018;28(1):ID28849. https://doi.org/10.15448/1980-6108.2018.1.28849.
18. Taras J, Everett T. Rapid cycle deliberate practice in medical education - a systematic review. Cureus. 2017;9(4):e1180. PMID: 28540142; https://doi.org/10.7759/cureus.1180.
19. Anders Ericsson K. Deliberate practice and acquisition of expert performance: a general overview. Acad Emerg Med. 2008;15(11):988-94. PMID: 18778378; https://doi.org/10.1111/j.1553-2712.2008.00227.x.
20. Patricia K, Arnold J, Lemke DS. Rapid Cycle Deliberate Practice: Application to Neonatal Resuscitation. MedEdPORTAL Publications. 2017;13:10534. PMID: 30800736; https://doi.org/10.15766/mep_2374-8265.10534.
21. Hunt EA, Vera K, Diener-West M, et al. Delays and errors in cardiopulmonary resuscitation and defibrillation by pediatric residents during simulated cardiopulmonary arrests. Resuscitation. 2009;80(7):819-25. PMID: 19423210; https://doi.org/10.1016/j.resuscitation.2009.03.020.
22. Sawyer T, Eppich W, Brett-Fleegler M, Grant V, Cheng A. More than one way to debrief: A critical review of healthcare simulation debriefing methods. Simul Healthc. 2016;11(3):209-17. PMID: 27254527; https://doi.org/10.1097/sih.0000000000000148.
23. Van Heukelom JN, Begaz T, Treat R. Comparison of postsimulation debriefing versus in-simulation debriefing in medical simulation. Simul Healthc. 2010;5(2):91-7. PMID: 20661008; https://doi.org/10.1097/sih.0b013e3181be0d17.
24. Brown KM, Mudd SS, Hunt EA, et al. A multi-institutional simulation boot camp for pediatric cardiac critical care nurse practitioners. Pediatr Crit Care Med. 2018;19(6):564-71. PMID: 29533354; https://doi.org/10.1097/pcc.0000000000001532.
25. Cheng A, Nadkarni VM, Mancini MB, et al. Resuscitation education science: educational strategies to improve outcomes from cardiac arrest: a scientific statement from the American Heart Association. Circulation. 2018;138(6):e82-122. PMID: 29930020; https://doi.org/10.1161/cir.0000000000000583.
26. Topjian AA, Raymond TT, Atkins D, et al. Part 4: Pediatric basic and advanced life support: American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2020;142(16 suppl 2):s469-523. PMID: 33081526; https://doi.org/10.1161/cir.0000000000000901.
27. Brasil. Conselho Nacional de Saúde. Resolução nº 466, de 12 de dezembro de 2012. Dispõe sobre assegurar os direitos e deveres que dizem respeito aos participantes da pesquisa, à comunidade científica e ao Estado e atualiza a resolução 196. DOU. 2013;(12 seção 1):59.
28. Brasil. Lei nº 13.709, de 14 de agosto de 2018. Dispõe sobre a proteção de dados pessoais e altera a Lei nº 12.965, de 23 de abril de 2014 (Marco Civil da Internet). Diário oficial da União. 2018;155(157 seção 1):59-64.
29. Ericsson KA. Acquisition and maintenance of medical expertise: a perspective from the expert-performance approach with deliberate practice. Acad Med. 2015;90(11):1471-86. PMID: 26375267; https://doi.org/10.1097/acm.0000000000000939.
30. Hunt EA, Duval-Arnould JM, Chime NO, et al. Integration of in-hospital cardiac arrest contextual curriculum into a basic life support course: A randomized, controlled simulation study. Resuscitation. 2017;114:127-32. PMID: 28323084; https://doi.org/10.1016/j.resuscitation.2017.03.014.
31. Gupta R, Fitzgibbons C, Ramsay C, et al. Development and pilot of an interprofessional pediatric resuscitation program for non-acute care inpatient providers. Med Educ Online. 2019;24(1):1581521. PMID: 30811308; https://doi.org/10.1080/10872981.2019.1581521.
32. Magee MJ, Farkouh-Karoleski C, Rosen TS. Improvement of immediate performance in neonatal resuscitation through rapid cycle deliberate practice training. J Grad Med Educ. 2018;10(2):192-7. PMID: 29686759; https://doi.org/10.4300/jgme-d-17-00467.1.
33. Hunt EA, Duval-Arnould JM, Nelson-McMillan KL, et al. Pediatric resident resuscitation skills improve after "Rapid Cycle Deliberate Practice" training. Resuscitation. 2014;85(7):945-51. PMID: 24607871; https://doi.org/10.1016/j.resuscitation.2014.02.025.
34. Lemke DS, Fielder EK, Hsu DC, Doughty CB. Improved team performance during pediatric resuscitations after rapid cycle deliberate practice compared with traditional debriefing. Pediatr Emerg Care. 2019;35(7):480-6. PMID: 27741071; https://doi.org/10.1097/pec.0000000000000940.
35. Kosoko AA, Glomb NW, Laba B, et al. Evaluating a Novel Simulation Course for Prehospital Provider Resuscitation Training in Botswana. West J Emerg Med. 2019;20(5):731-9. PMID: 31539330; https://doi.org/10.5811/westjem.2019.6.41639.
36. Chancey RJ, Sampayo EM, Lemke DS, Doughty CB. Learners' experiences during rapid cycle deliberate practice simulations. Simul Healthc. 2019;14(1):18-28. PMID: 30216277; https://doi.org/10.1097/sih.0000000000000324.

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Cognitive and social adaptation in autism spectrum disorder: A prospective cohort study

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ABSTRACT

BACKGROUND: During development, children face a number of demands and cognitive, behavioral, and social challenges necessary for growth. Cognitive skills make individuals competent and allow them to interact with their environment.

OBJECTIVE: To identify the cognitive skills that promote better social insertion in children with autism spectrum disorder within 12 months.

DESIGN AND SETTING: Prospective cohort study

METHODS: In this study, 21 children aged 3–12 years were assessed, and their mothers were interviewed. Children were enrolled in regular or special autistic schools. Twelve months after the first assessment, the same children participated in the second assessment. In individual interviews, mothers provided data by answering the Vineland Adaptive Behavior Scale. Each child was assessed individually using the fourth edition of the Stanford Binet Intelligence Scale 4th Edition.

RESULTS: In the first assessment, the Stanford Binet areas and total scores correlated with the communication domains, daily life abilities, socialization, and total score of the Vineland Scale. After 12 months, a correlation was observed between the Stanford Binet areas and the total and communication domains, daily life abilities, socialization, motor abilities, and total score on the Vineland Scale.

CONCLUSION: Logic mathematics and memory promote better social insertion in children with autism spectrum disorder. General cognitive ability promotes communication.

INTRODUCTION

During development, children face a number of demands and cognitive, behavioral, and social challenges necessary for growth. Child development involves these different aspects, and its purpose is to make children skilled in responding to their needs and the demands of their environment. The interrelation between these aspects makes the development a complex and intriguing process.[1,2]

From a cognitive standpoint, children develop flexibility in thought, the ability to come up with strategies for problem solving, and the capability to establish spatial, temporal, and causal relationships between objects.[3] From a social standpoint, they develop social skills for communicating and performing activities of daily living that make them independent; they also develop behavior that helps them relate better to others.[4-6]

Intelligence is an important parameter in the structuring and dynamics of global child development.[7] It is conceived as a general cognitive skill made up of mental abilities directed at social adaptation, such as language, logical-mathematical reasoning, visual-spatial reasoning, and short-term memory.[8] Cognitive skills involve responses for problem solving.[9] These responses are concretely expressed in the performance of daily activities and influence the performance of adaptive skills, such as communication, daily living skills, socialization, and motor skills, necessary for children to be socially included and experience personal autonomy.[2]

Qualitative failures in adaptation to social demands over time lead to diagnoses such as autism spectrum disorder (ASD).[10] In these syndromes of global development abnormalities, adaptive disabilities go hand-in-hand with communication problems as well as interest and activity restrictions.[10] The manifestations vary considerably with regard to the degree of severity and intellectual level of each child, which affects the performance of the daily activities necessary for autonomy.[11] The difficulties in social adaptation found in children with ASD may be linked to

failures in cognitive processes related to intelligence. Thus, it is supposed that correlations between cognitive and adaptive skills change throughout development, and specific cognitive skills promote greater social inclusion in children with these conditions.[12]

Cognitive profiles have revealed specific skills that interfere with the adaptive profiles of children with ASD.[13,14]

Executive functions enable mental manipulation of ideas, thinking before acting, facing new and unforeseen challenges, resisting temptations, and focusing. In this sense, executive functions generally comprise three components: working memory, cognitive flexibility, and inhibitory or self-control.[15] Thus, the executive functions have been studied and highlighted as important in the development of the pragmatic dimension of language, because the integrated operation of these functions allows to maintain and update the conversation without losing relevant information arising from the manipulation of facts in working memory and inhibition of off-topic responses. This study found a positive correlation between executive functions and theory of mind, which are considered predictors of the severity of autism symptoms.[16] Executive functions can be identified in the absence or scarcity of symbolic play in children with ASD as well as in the presence of restricted and repetitive patterns of interest and activity.[17]

Cognitive delay manifests as logical and intuitive reasoning deficits related to expressive language. These deficits interfere with knowledge of the world, interaction with people, and expression of their desires.[18] Increased cognitive performance and Intelligence Quotient (IQ) influence expressive language skills and are not related to social communication skills or diagnosis of ASD.[18,19] Cognitive skills such as low non-verbal quotient are also related to expressive language deficits. Studies have shown that nonverbal quotients predict patterns of increased simultaneous and longitudinal expressive language and sentence speech acquisition in children with ASD,[18] although intellectual disabilities commonly co-occur with low expressive language in this condition.[20]

The literature investigated social skills, executive functions, and theory of mind in six (6) children diagnosed with ASD.[21] They observed that the language development level of these children is important for the interaction and understanding of social processes, and that executive functions and social skills are directly influenced by the developmental level of verbal language.

The development of children's memory is strongly linked to that of communication and oral language in children with ASD, and the range of memory in these children remains intact.[22,23] However, recent studies have shown that children and adults with ASD have difficulties with short-term memory, especially serial order memory. This variation in memory function patterns cannot be explained by intelligence or language skills but is likely related to memory processing.[24] Furthermore, recent research has shown that individuals with ASD demonstrate difficulty with verbal and non-verbal short-term memory, especially in serial order, but not with item retrieval.[25] Visual memory is an important skill for children with ASD; however, it depends on the complexity of the stimulus, that is, whether they depend on verbal skills as well as on the effect of age and IQ.[22,26]

Some children with autism spectrum disorder have an impressive memory for memorizing, but the memorized information does not generalize to different contexts. When memory is stimulated by the environment, it becomes an important skill for social adaptation, as it facilitates communication and learning for activities of daily living, such as tying shoes, putting on clothes, buttoning shirt.[22]

The literature shows that deficits in divided attention and verbal fluency are related to social disabilities as well as impairments in working memory, which play a role in adaptive social difficulties.[27,28]

Another important aspect is that children with ASD show excellent performance in visual and spatial perceptual functions, such as detecting objects changing positions, known routes or paths, color discrimination, and simple visual tracking tasks. Although visuospatial perception may contribute to the high skills of these children,[29] they present difficulties when asked, in this organizational process, to understand a sequence of images, both in sentence construction and telling a story as well as difficulty in linking sensory information into a unified perception.[30]

OBJECTIVE

The aim of the present study was to identify the cognitive skills that promote greater social insertion in children with ASD on two separate evaluation occasions with a 12-month interval.

METHODS

This prospective cohort study was approved by the Ethics Committee of the Universidade Federal de São Paulo (Brazil), with the authorization of the services involved (CEP no 0334/06, dated April 13, 2006). The parents/guardians of the participants signed informed consent forms.

Participants

This study was conducted on two occasions. Twenty-six children aged between 3 and 12 years participated in the evaluation along with their mothers. All children had been previously diagnosed with ASD, confirmed by a specialized multidisciplinary team via interviews with parents, clinical evaluations, and based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders Index (DSM-5).[10,31] The children were involved in intervention programs at a specialized municipal school in São Paulo (Friends of Autism Association) and the Center for Speech and Hearing Investigation of Language in Global Development Disorders at the Teaching Clinic of the Sector of Human Communication Disorders, Department of Speech and Hearing

Therapy, Universidade Federal de São Paulo. Twelve months after the first evaluation, 21 of the same mother/child pairs participated in the second evaluation, during which the children were aged between 4 and 13 years.

The inclusion criteria were as follows: boys and girls aged between 3 and 12 years (and their mothers) involved in regular public or private educational programs. The exclusion criteria were as follows: comorbidities such as hearing loss, encephalopathy, or tuberous sclerosis; non-adherence to the reassessment of the children 1 year after the beginning of the study; and abandonment of the educational program.

Instruments

The Stanford Binet Intelligence Scale, 4th Edition[32] was employed to measure children's cognitive skills. This scale measures the general cognitive capacity and skills. It is made up of 15 subtests and furnishes an estimate of the general cognitive level and standard of cognitive skills in four areas: 1) Verbal Reasoning Subtests: Vocabulary, Comprehension, Absurdities, and Verbal Relations; 2) Visual-Abstract Reasoning Subtests: Pattern Analysis (Cubes), Copying, Matrices, Paper Folding, and Cutting; 3) Quantitative Reasoning Subtests: Quantitative, Numerical Series, Equation Building; 4) Short-Term Memory Subtests: Bead Memory, Memory for Sentences, Memory for Objects, and Memory for Digits.

All subtests were divided into levels beginning at 2 years of age. Each age group was determined using two items of approximately equal difficulty. The levels are composed of items arranged in increasing order of difficulty. The administration begins with the Vocabulary subtest, which uses chronological age and determines the mental age from the score the child achieves; the mental age then defines the starting point for the other tests. When a child makes a mistake in one of the items, the administration of the test should return to the items on the previous levels until two consecutive items are answered correctly. The test was administered until the child consecutively answered three of the four items or four items for two consecutive levels incorrectly. The scores achieved in each subtest were converted into standardized scores for age in the corresponding tables. The score was considered normal when the average was 50, and the standard deviation was 8. The composite standard age score (SAS) is considered normal when the average was 100, with a standard deviation of 16. The SAS of the Stanford Binet Intelligence Scale is equivalent to the intelligence quotient (QI) or general reasoning skills.[32]

The Vineland Adaptive Behavior Scale (VABS)[33] was used to measure adaptive skills.

The VABS[33] aims to assess the adaptive development of children and adolescents in their daily lives. Adaptive behavior on the scale is subdivided into four domains and sub-domains: 1) Communication (67 questions), subdivided into receptive, expressive, and written; 2) Daily Living Skills (92 questions), personal, domestic, and community skills; 3) Socialization (66 questions), interpersonal relationships, play and leisure time, and coping skills; and 4) Motor Skills (36 questions), gross and fine motor skills.

An optional index (36 questions) was designed to evaluate maladaptive behaviors such as obstinacy, impulsiveness, stubbornness, aggressiveness, anxiety, introversion, negativism, and mood swings.

The responses were scored in the following manner: 2 – usually, 1 – sometimes, 0 – never. N denotes no opportunity (does not apply), and DK is used when the respondent does not know the answer. The responses were recorded on the form. The raw scores obtained for each subdomain are converted into standardized scores for age in the corresponding tables. A normal score was defined as a mean score of 90–110 points. In the present study, the raw scores were not converted into standardized scores for age; we only considered correct answers. To obtain the profile of children with ASD from the total score and scores per category and subcategory, the administration of the scale commenced with item 1 on all sections. Higher scores on the VABS indicated greater social adaptation in children with ASD.

Procedure

In the individual interviews, mothers provided data on adaptive skills in response to the VABS. An intellectual assessment was performed on each child individually by a psychologist with experience in the administration of intellectual tests and trained in the administration of the Stanford-Binet Intelligence Scale 4th edition.

Statistical Analysis

Sample power was calculated to determine the precision and reliability of the samples. The test revealed a sample power of 83% for 21 children. Spearman's correlation coefficient was calculated to correlate the domains and total of the VABS test, and the areas and total of the Stanford-Binet test; as this statistical method is non-parametric and can be applied in more general cases when non-normal distribution is presumed.[34] Spearman's correlation coefficient was calculated for the first evaluation, second evaluation and to determine differences between the two evaluation moments. Statistical significance was set at $P < 0.05$.

RESULTS

The results demonstrated that children with ASD had specific cognitive skills that only correlated with specific adaptive domains in both evaluations. The tables below display the descriptive measures of the total Stanford-Binet and VABS for both evaluations, the values for the Spearman correlation coefficients (r) between

the areas of the Stanford-Binet and VABS domains, and the p-values of the significance tests of these coefficients.

Table 1 displays the descriptive measures for the total Stanford-Binet and VABS at both evaluation times.

Table 2 displays the values of the Spearman correlation coefficients for the areas and total of the Stanford-Binet with the domains and total VABS in the first evaluation.

All areas of the Stanford-Binet were correlated with Communication, Daily Living Skills, Socialization, and total VABS ($P < 0.05$), whereas the areas of the Stanford-Binet were not correlated with the Behavior Problems domain of the VABS ($P > 0.05$).

Table 1. Descriptive measures for the total of the Stanford-Binet and VABS in both evaluation times

Scales/ instruments	1st evaluation	2nd evaluation	P value
	Mean (SD)	Mean (SD)	
Stanford-Binet	53.76 (67.15)	60.00 (73.50)	0.001
VABS	212.86 (84.47)	243.67 (83.49)	0.002

* Significant at $P < 0.005$; VABS = Vineland Adaptive Behavior Scale; SD = standard deviation.

Table 3 displays the values of the Spearman correlation coefficients for the areas and total of the Stanford-Binet with the domains and total VABS in the second evaluation.

All areas and the total Stanford- Binet had a direct correlation with Communication, Daily Living Skills, Socialization, Motor Skills domains, and total VABS ($P < 0.05$).

Table 4 shows the values of the Spearman correlation coefficients for the Stanford-Binet areas with the VABS domains for both evaluations.

The Visual-Abstract Reasoning area had an inverse correlation with total VABS ($P = 0.04$) over the course of 12 months. The Quantitative Reasoning area had a direct correlation with the Daily Living Skills domain ($P = 0.03$) and VABS total ($P = 0.03$) over the course of 12 months. The Short-Term Memory area had a direct correlation with the total VABS ($P = 0.01$) over the course of 12 months. The Stanford-Binet total score was directly correlated with the Communication domain ($P = 0.01$) over the course of 12 months. No correlations were observed between the areas and total of the Stanford-Binet with the Communication, Daily Living Skills, Socialization, Motor skills domains, and total VABS ($P < 0.05$) after 12 months.

Table 2. Spearman correlation coefficients between the areas and total of the Stanford-Binet and the domains and total of the VABS in the first evaluation

VABS	Stanford-Binet				
	Verbal Reasoning	Visual Abstract Reasoning	Quantitative Reasoning	Short Term Memory	Total
Communication	r = 0.90*	r = 0.75*	r = 0.78*	r = 0.85*	**r = 0.87***
Daily Living Skills	r = 0.83*	r = 0.81*	r = 0.80*	r = 0.76*	**r = 0.82***
Socialization	r = 0.75*	r = 0.70*	r = 0.79*	r = 0.73*	**r = 0.78***
Motor Skills	r = 0.37	r = 0.47	r = 0.50	r = 0.39	**r = 0.42**
Behavior	r = 0.36	r = 0.36	r = 0.41	r = 0.34	**r = 0.37**
Total	**r = 0.76***	**r = 0.73***	**r = 0.76***	**r = 0.72***	**r = 0.07***

* Significant at $P < 0.001$; VABS = Vineland Adaptive Behavior Scale.

Table 3. Spearman correlation coefficients for the areas and total of the Stanford-Binet with the domains and total of the VABS in the second evaluation

VABS	Stanford-Binet				
	Verbal Reasoning	Visual Abstract Reasoning	Quantitative Reasoning	Short Term Memory	Total
Communication	r = 0.91*	r = 0.72*	r = 0.89*	r = 0.93*	**r = 0.85***
Daily Living Skills	r = 0.78*	r = 0.68*	r = 0.79*	r = 0.82*	**r = 0.73***
Socialization	r = 0.80*	r = 0.61*	r = 0.87*	r = 0.82*	**r = 0.72***
Motor Skills	r = 0.70*	r = 0.71*	r = 0.66*	r = 0.71*	**r = 0.70***
Behavior	r = -0.37	r = 0.23	r = -0.31	r = 0.36	**r = 0.24**
Total	**r = 0.85***	**r = 0.68***	**r = 0.83***	**r = 0.88***	**r = 0.79***

* Significant at $P < 0.001$; VABS = Vineland Adaptive Behavior Scale.

Table 4. Spearman correlation coefficients for the areas of the Stanford-Binet with the domains of the VABS in both evaluations

VABS	Stanford-Binet				
	Verbal Reasoning	Visual Abstract Reasoning	Quantitative Reasoning	Short Term Memory	Total
Communication	r = 0.36	r = 0.16	r = 0.03	r = 0.36	**r = 0.55***
Daily Living Skills	r = 0.14	r = 0.14	r = 0.46*	r = 0.06	**r = 0.03**
Socialization	r = -0.24	r = -0.16	r = 0.41	r = 0.07	**r = -0.08**
Motor Skills	r = 0.22	r = 0.15	r = 0.10	r = 0.32	**r = 0.11**
Behavior	r = 0.31	r = 0.21	r = 0.17	r = 0.34	**r = 0.05**
Total	**r = 0.18**	**r = -0.44***	**r = 0.45***	**r = 0.54***	**r = 0.10**

* Significant at $P \leq 0.05$; VABS = Vineland Adaptive Behavior Scale.

DISCUSSION

In the present study, cognitive skills were highly correlated with adaptive skills in children with ASD. The Short-Term Memory area correlated with all VABS domains, except for motor skills. It may be presumed that the information processed and stored in memory is not used for motor aspects. Children likely need to use frequent, repeated practice to memorize and store motor sequences.

Regarding short-term memory, children are able to organize the information received from the environment by encoding active memory into long-term memory. The improvement in this specific skill allowed information to be transferred from long-term memory to active memory and the processes of trial, elaboration, interpretation, and re-codification used by the children to become more socially adapted. The development of memory involved changes in the skills of recognition, recall, strategies, problem solving, metacognition, and information content.[35]

Over the course of 12 months, logical-mathematical cognitive skills and memory promoted better social inclusion in children with ASD. General cognitive skills promote improvement in communication. The performance of cognitive, behavioral, and adaptive skills changed significantly over the course of 12 months, and specific cognitive skills promoted social inclusion.

The Visual-Abstract Reasoning area was inversely correlated with the total VABS over the course of 12 months. In terms of the average performance on the test in this area, there was no significant increase in the mean values of either evaluation, although Visual-Abstract Reasoning is often mentioned in the literature as the specific cognitive skill with the greatest emphasis in children with ASD.[36,37] This result indicates that greater use of visual-spatial skills denotes less social inclusion, regardless of the time of evaluation. Visual-Abstract Reasoning measures spatial skills; it is a prerequisite for environmental stimulation and is directly correlated with fluid intelligence. This is an innate biological skill that children perform to solve problems linked to visual-spatial-perceptive processes. Children do not require others to help or even teach them this skill. The Stanford-Binet tests are related to the visual-spatial process and are based on visual analysis and synthesis of geometric figures from the whole to the parts and vice versa. Children may have had difficulties with social adaptation because the tests were self-satisfying, interesting, and self-reinforcing. In other words, the visual stimuli contributed to social isolation.

The Quantitative Reasoning area correlated with Daily Living Skills and total VABS over the course of 12 months. Elementary logic operations involve the possibility of reconstituting the path taken by thought, that is, the reversibility of the reasoning carried out.[7] The solution of a mathematical problem, or logical quantitative reasoning, is divided into the representation and solving of the problem. According to the literature, individuals may differ in their ability to correctly translate sentences that make up the problem.[12] To represent the problem, a child needs to have linguistic knowledge for a verbal analysis of the mathematical problem solicited on the test and its quantitative relation with the response required. Knowledge of the world is necessary for a child to represent a quantity.

Children's linguistic knowledge increases with age. To solve mathematical problems, a child requires strategic knowledge or planning. Daily living skills are related to habits of self-sufficiency that allow children to actively participate in the environment in which they live. Children in this study exhibited improvements in elementary logic operations. It may be hypothesized that the improvement in the reversibility of thought, linguistic knowledge, and perception of the world enabled these children to translate the mathematical propositions solicited on the test as well as integrate, plan, and execute the activities. Corroborating these findings, the fact that they were able to perform an elementary mathematical operation facilitated organizing their desk, placing the correct number of plates solicited, handling money, telling time, and considering the possibility of a car approaching when they crossed the street.[12] No significant associations were found in the literature between attention, working memory, inhibitory control, thinking flexibility, and social skills; however, planning appeared to be associated with adaptive communication skills.[38]

The Short-Term Memory area was directly correlated with the total VABS over the course of 12 months. This finding corroborates a previous study,[22] which reported that memory promoted adaptive behavior in children with ASD. With the retention of knowledge and recognition of the information to be used correctly, more organized thought allowed the use of memory in a more coherent and adequate fashion. In the present study, attention was found to be a key factor in improving short-term memory. Attention is the means by which humans actively process a limited amount of information through the senses, memory, and cognitive processes. There appears to be a limit to the amount of information on which we can concentrate our mental resources at any given time. When we diminish our attention to sensations, thoughts, and memories, we may focus on stimuli that interest us. Our results corroborate the previous studies[27,28] that showed that attention probably opened paths for memory processes in children and adolescents with ASD and facilitated social adaptation.

The intellectual capability to use more general reasoning processes, relate to complex ideas, form abstract concepts, or perform mental operations when solving relatively new problems is directly correlated with improvements in the Communication domain. This indicates that the children with ASD in the present study used reasoning and mental operations to develop speech, diminish their difficulties in being with others, and pay attention to social cues. Such skills are necessary for the development of gestural and visual communication that precedes the manifestation of speech.[39]

CONCLUSION

In summary, the present study provided evidence of specific skills that promote the social inclusion of children with ASD over time. The identification of these skills assists the clinical and educational operations of multidisciplinary teams regarding the cognitive failures that hinder the social adaptation process and are common to individuals with these conditions.

REFERENCES

1. Bee H, Boyd D. A criança em desenvolvimento. 11ª ed. Porto Alegre: Artmed; 2011.
2. Papalia D, Martorell G. Desenvolvimento Humano. 14ª ed. Porto Alegre: AMGH; 2022.
3. Barros PM, Hazin I. Avaliação das funções executivas na infância: revisão dos conceitos e instrumentos. Psicol Pesq. 2013;7(1):13-22. https://doi.org/10.5327/z1982-1247201300010003.
4. CaballoVE. Manual de avaliação e treinamento das habilidades sociais. São Paulo: Santos; 2003.
5. Marturano EM, Loureiro SR. O desenvolvimento socioemocional e as queixas escolares. In: Del Prette A, Del Prette, ZAP. Habilidades sociais, desenvolvimento e aprendizagem. Campinas: Alínea; 2003. p. 259-91.
6. Klin, A. Autismo e Síndrome de Asperger: uma visão geral [Autism and Asperger syndrome: an overview]. Braz J Psychiatry. 2006;28(suppl 1):s3-11. PMID: 16791390; https://doi.org/10.1590/s1516-44462006000500002.
7. Sternberg RJ. Psicologia cognitiva. 4a ed. Porto Alegre: Artes Médicas; 2008.
8. Silva JA. Inteligência para o sucesso pessoal e profissional. Ribeirão Preto: Funpec; 2007.
9. Primi R. Inteligência: avanços nos modelos teóricos e nos instrumentos de medida. Aval Psicol. 2003;2(1):67-77. Available from: http://pepsic.bvsalud.org/scielo.php?script=sci_arttext&pid=S1677-04712003000100008. Accessed in 2023 (Ju. 7).
10. American Psychiatric Association. Manual diagnostico e estatístico de transtornos mentais (DSM-5). 5ª ed. Porto Alegre: Artmed; 2014.
11. Baghdadli A, Assouline B, Sonié S, et al. Developmental trajectories of adaptive behaviors from early childhood to adolescence in a cohort of 152 children with autism spectrum disorders. J Autism Dev Disord. 2012;42(7):1314-25. PMID: 21928042; https://doi.org/10.1007/s10803-011-1357-z.
12. Cardoso MP. Habilidades matemáticas em crianças com transtorno do espectro autista (TEA). [thesis]. Salvador: Postgraduate program in Education, Universidade Federal da Bahia (UFBA); 2016.
13. Happé F, Frith U. The weak coherence account: detail-focused cognitive style in autism spectrum disorders**.** J Autism Dev Disord. 2006;36(1):5-25. PMID: 16450045; https://doi.org/10.1007/s10803-005-0039-0.
14. Happe F. Autism as a neurodevelopmental disorder of mind-reading. J Br Acad. 2015;3:197-209. https://doi.org/10.5871/jba/003.197.
15. Diamond A. Executive functions. Annu Rev Psychol. 2013;64:135-68. PMID: 23020641; https://doi.org/10.1146/annurev-psych-113011-143750.
16. Tager-Flusberg H, Skwerer PD, Joseph RM, et al. Conducting research with minimally verbal participants with autism spectrum disorder. Autism. 2017;21(7):852-61. PMID: 27354431; https://doi.org/10.1177/1362361316654605.
17. Gökçen E, Frederickson N, Petrides KV. Theory of mind and executive control deficits in typically developing adults and adolescents with high levels of Autism traits. J Autism Dev Disord. 2016;46(6):2072-87. PMID: 26886468; https://doi.org/10.1007/s10803-016-2735-3.
18. Brignell A, Williams K, Jachno K, et al. Patterns and predictors of language development from 4 to 7 years in verbal children with and without autism spectrum disorder. J Autism Dev Disord. 2018;48(10):3282-95. PMID: 29705923; https://doi.org/10.1007/s10803-018-3565-2.
19. Pecukonis M, Plesa Skwerer D, Eggleston B, Meyer S, Tager-Flusberg H. Concurrent social communication predictors of expressive language in minimally verbal children and adolescents with autism spectrum disorder. J Autism Dev Disord. 2019;49(9):3767-85. PMID: 31187332; https://doi.org/10.1007/s10803-019-04089-8.
20. Fernell E, Hedvall A, Norrelgen F, et al. Developmental profiles in preschool children with autism spectrum disorders referred for intervention. Res Dev Disabil. 2010;31(3):790-9. PMID: 20207104; https://doi.org/10.1016/j.ridd.2010.02.003.

21. Maranhão SSA, Pires IAH. Funções executivas e habilidades sociais no espectro autista: um estudo multicasos. Cad Pós-Grad Disturb Desenvolv. 2017;17(1):100-13. Available from: http://pepsic.bvsalud.org/scielo.php?script=sci_arttext&pid=S1519-03072017000100011. Accessed in 2023 (Jun. 7).
22. Talli I. Verbal short-term memory as language predictor in children with autism spectrum disorder. J Behav Brain Sci. 2020;10(5):200-19. https://doi.org/10.4236/jbbs.2020.10513.
23. Williams D, Happé F, Jarrold C. Intact inner speech use in autism spectrum disorder: evidence from a short-term memory task. J Child Psychol Psychiatry. 2008;49(1):51-8. PMID: 18181880; https://doi.org/10.1111/j.1469-7610.2007.01836.x.
24. Gaigg SB, Bowler DM, Gardiner JM. Episodic but not semantic order memory difficulties in autism spectrum disorder: evidence from the historical figures task. Memory, 2014;22(6):669-78. PMID: 23815188; https://doi.org/10.1080/09658211.2013.811256.
25. Bowler DM, Poirier M, Martin JS, Gaigg SB. Nonverbal short-term serial order memory in autism spectrum disorder. J Abnorm Psychol. 2016;125(7):886-93. PMID: 27732024; https://doi.org/10.1037/abn0000203.
26. Chien YL, Gau SS, Shang CY, et al. Visual memory and sustained attention impairment in youths with autism spectrum disorders. Psychol Med. 2015;45(11):2263-73. PMID: 25902960; https://doi.org/10.1017/s0033291714003201;
27. Kenworthy L, Black DO, Harrison B, della Rosa A, Wallace GL. Are executive control functions related to autism symptoms in high-functioning children? Child Neuropsychol. 2009;15(5):425-40. PMID: 19173090; https://doi.org/10.1080/09297040802646983.
28. Freeman LM, Locke J, Rotheram-Fuller E, Mandell D. Brief Report: examining executive and social functioning in elementary-aged children with autism. J Autism Dev Disord. 2017;47(6):1890-5. PMID: 28260182; https://doi.org/10.1007/s10803-017-3079-3.
29. Baron-Cohen S, Lombardo MV. Autism and talent: the cognitive and neural basis of systemizing. Dialogues Clin Neurosci. 2017;19(4):345-53. PMID: 29398930; https://doi.org/10.31887/dcns.2017.19.4/sbaroncohen.
30. Stevenson RA, Siemann JK, Woynaroski TG, et al. Brief report: Arrested development of audiovisual speech perception in autism spectrum disorders. J Autism Dev Disord. 2014;44(6):1470-7. PMID: 24218241; https://doi.org/10.1007/s10803-013-1992-7.
31. World Health Organization. International Statistical Classification of Diseases and Related Health Problems (ICD-11). Geneva: WHO; 2022. Available from: https://icd.who.int/en. Accessed in 2023 (Jun. 7).
32. Thorndike RL, Hagen EP, Satler JM. Stanford-Binet Intelligence Scale. 4th ed. Chicago: Riverside; 1986.
33. Sparrow S, Balla D, Cichetti D. The Vineland Adaptive Behavior Scales. Circle Pines: American Guidance Service; 1984.
34. Van Belle G, Fisher LD, Heagerty PJ, Lumley T. Biostatistics: a methodology for the Health Sciences. 2nd ed. Hoboken: Wiley; 2004.
35. Izquierdo I. Memória. Porto Alegre: ArtMed; 2002.
36. Cardillo R, Lanfranchi S, Mammarella IC. A cross-task comparison on visuospatial processing in autism spectrum disorders. Autism. 2020;24(3):765-79. PMID: 31778069; https://doi.org/10.1177/1362361319888341.
37. Mammarella IC, Cardillo R, Zoccante L. Differences in visuospatial processing in individuals with nonverbal learning disability or autism spectrum disorder without intellectual disability. Neuropsychology. 2019;33(1):123-34. PMID: 30335415; https://doi.org/10.1037/neu0000492.
38. Ozonoff S, Cook I, Coon H, et al. Performance on Cambridge Neuropsychological Test Automated Battery subtests sensitive to frontal lobe function in people with autistic disorder: evidence from the Collaborative Programs of Excellence in Autism network. J Autism Dev Disord. 2004;34(2):139-50. PMID: 15162933; https://doi.org/10.1023/b:jadd.0000022605.81989.cc.
39. Perissinoto J. Conhecimentos essenciais para atender bem as crianças com Autismo. São José dos Campos: Pulso; 2003.

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Maternal and perinatal outcomes of minimally invasive fetal surgeries: experience from two reference centers in Rio de Janeiro, Brazil

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ABSTRACT

BACKGROUND: Concerns regarding high open surgery-related maternal morbidity have led to improvements in minimally invasive fetal surgeries.

OBJECTIVE: To analyze the perinatal and maternal outcomes of minimally invasive fetal surgery performed in Rio de Janeiro, Brazil.

DESIGN AND SETTING: Retrospective cohort study conducted in two tertiary reference centers.

METHODS: This retrospective descriptive study was conducted using medical records from 2011 to 2019. The outcomes included maternal and pregnancy complications, neonatal morbidity, and mortality from the intrauterine period to hospital discharge.

RESULTS: Fifty mothers and 70 fetuses were included in this study. The pathologies included twin-twin transfusion syndrome, congenital diaphragmatic hernia, myelomeningocele, lower urinary tract obstruction, pleural effusion, congenital upper airway obstruction syndrome, and amniotic band syndrome. Regarding maternal complications, 8% had anesthetic complications, 12% had infectious complications, and 6% required blood transfusions. The mean gestational age at surgery was 25 weeks, the mean gestational age at delivery was 33 weeks, 83% of fetuses undergoing surgery were born alive, and 69% were discharged from the neonatal intensive care unit.

CONCLUSION: Despite the small sample size, we demonstrated that minimally invasive fetal surgeries are safe for pregnant women. Perinatal mortality and prematurity rates in this study were comparable to those previously. Prematurity remains the most significant problem associated with fetal surgery.

INTRODUCTION

Fetal surgery involves heterogeneous interventions, varying from simple to complex, in which the primary goal is to improve the health of newborns diagnosed with abnormalities during prenatal period through intrauterine treatments that decrease the morbidity and mortality rates of potentially severe or lethal congenital anomalies.[1-3]

Fetal therapy has seen significant advancements in recent decades, and ultrasound has made the approach to fetal procedures safer owing to the availability of real-time guidance.[1,2,4] In the early 1980s, open surgical treatments were started [5,6], but concerns about the high maternal morbidity rates related to open surgeries have led to the search for less invasive alternatives.[7] The increasing popularity of videoendoscopic surgery in the 1990s, combined with recent experience in fetoscopy, introduced the concept of endoscopic or minimally invasive fetal surgery [4], which is under continuous development and improvement.[8]

In Brazil, one of the first fetal endoscopic surgeries was fetoscopy for the laser treatment of twin-twin transfusion syndrome (TTTS), which was performed in 2001.[9,10] Since then, several surgical techniques for fetal surgeries, both minimally invasive and open surgeries, specifically for myelomeningocele, have been performed.[10] Currently, few groups have performed percutaneous endoscopic fetal surgery for the treatment of myelomeningocele; Brazilian and German researchers have pioneered advances in performing this technique. The neurological results of this technique are similar to those of the open technique.[3,10-14]

OBJECTIVE

This article describes maternal and perinatal outcomes of minimally invasive fetal surgeries performed at two fetal medicine referral centers in Rio de Janeiro, Brazil.

METHODS

This retrospective study included all pregnant women who underwent delivery and minimally invasive fetal surgery between 2011 and 2019 at the Instituto Fernandes Figueira/Fiocruz (IFF/Fiocruz) and Clínica Perinatal, which are both referral centers for maternal-fetal medicine in Rio de Janeiro, Brazil. Clinical data and outcomes were exclusively assessed by reviewing medical records from the prenatal period to hospital discharge. This study was approved by the local institutional ethics committee under number 27452719.5.0000.5269, in accordance with the National Health Council resolution 466/12.

Outcomes included maternal and obstetric complications, neonatal morbidity, and fetal and neonatal mortality from the intrauterine period to hospital discharge. Maternal complications included anesthetic complications, infectious complications, need for blood transfusion, and admission to intensive care unit. Preterm labor, preterm delivery, chorioamnionitis, and preterm premature rupture of ovular membranes (PPROM) were considered pregnancy complications. Neonatal morbidities were defined as findings of brain injury on ultrasonography, retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), neonatal infection, need for ventilatory support, admission to the neonatal intensive care unit (NICU), or length of stay in the NICU.

Cerebral injuries were detected using cranial ultrasound in neonates, and they were classified as mild to severe intraventricular hemorrhages [15] or as mild to severe periventricular leukomalacia.[16] ROP was classified into five stages based on the International Classification of Retinopathy of Prematurity.[17] BPD was defined for newborns under 32 weeks of oxygen therapy > 21% for at least 28 days after 36 weeks of post-menstrual age or discharge to home, whichever came first, or for newborns aged ≥ 32 weeks, oxygen therapy for > 28 days but < 56 days postnatal age or discharge to home, whichever came first.[18] NEC diagnosis was based on clinical signs and symptoms and radiological findings, surgically confirmed in some cases.[19] Neonatal infections confirmed via laboratory testing were considered owing to the difficulty of classifying neonatal sepsis based on medical records.

Statistical analyses were performed using SPSS software version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Frequency measures were used for categorical variables and means and standard deviations were used for numerical variables.

RESULTS

Seventy-five surgeries were performed between 2011 and 2019. Patients who were followed up and gave birth in the research units were included, totaling 50 patients (8 at IFF/Fiocruz and 42 at Perinatal). Twenty patients had multiple pregnancies; the total of fetus was 70. Pathologies seen were as follows: 18 (36%) patients with TTTS, with or without fetal growth restriction; 12 (24%) with congenital diaphragmatic hernia (CDH); 9 (18%) with myelomeningocele (MMC); 4 (8%) with lower urinary tract obstruction; 4 (8%) with pleural effusion; 2 (4%) with congenital high airway obstruction syndrome (CHAOS); and 1 (2%) with amniotic band syndrome. The outcomes of all pathologies are described together, and for discussion purposes, the pathologies with the highest incidence were analyzed separately (TTTS, CDH, and MMC). One case each of CHAOS and CDH occurred in a woman with multiple pregnancies. **Table 1** presents the baseline characteristics of the study population.

Surgical variables

The mean gestational age on the day of surgery was 25 weeks (range, 16–32 weeks), being 21 weeks (17–25 weeks) in the TTTS

Table 1. Baseline characteristics of the study population

Maternal variables	Results (N = 50)
Mean age (years)	33 (20 to 42)
Comorbidities – no. (%)	
No	36 (72)
Yes	14 (28)
Hypothyroidism	5 (10)
Diabetes mellitus	1 (2)
Arterial hypertension	1 (2)
Thrombophilia	2 (4)
Others	5 (10)
Conception – no. (%)	
Spontaneous	46 (92)
Assisted Reproduction Techniques	4 (8)
Number of fetuses – no. (%)	
Singleton pregnancy	30 (60)
Multiple Pregnancy	20 (40)
Delivery – no. (%)	
Caesarean section	45 (90)
Vaginal delivery	5 (10)
Fetal Pathology – no. (%)	
Twin-twin Transfusion Syndrome*	18 (36)
Congenital Diaphragmatic Hernia‡	12 (24)
Myelomeningocele	9 (18)
Lower Urinary Tract Obstruction	4 (8)
Pleural Effusion	4 (8)
Congenital Upper Airway Obstruction Syndrome‡	2 (4)
Amniotic Band Syndrome	1 (2)
Location of placenta – no. (%)	
Anterior	21 (42)
Others	29 (58)

*with or without Fetal Growth Restriction; ‡one case in multiple pregnancy

treatment group; 28 weeks (23–30 weeks) in fetuses with CDH for fetoscopic endoluminal tracheal occlusion (FETO); and 27 weeks (25–28 weeks) in the MMC correction group. 21 (42%) patients received local anesthesia or sedation, 11 (22%) received general anesthesia, and 30 (60%) received spinal anesthesia. The mean surgical time was 80 min (63, 66, and 148 min for TTTS, FETO, and MMC corrections, respectively). 41 patients (82%) received antibiotic prophylaxis, 36 (72%) received tocolytic agents, and 24 (48%) received atosiban. In addition, 21 (42%) patients required more than one surgical procedure: five patients had TTTS; 11 patients had CDH; 6 other patients had other pathologies that were not described in this article. In patients with CDH, the second procedure involves balloon removal through fetoscopy at approximately 34 weeks of gestation. **Table 2** presents these data in detail.

Maternal complications

Concerning maternal complications, four (8%) patients had anesthetic complications, three (6%) had post-spinal anesthesia headaches, and one (2%) had decreased oxygen saturation and required macronebulization, which quickly improved their clinical condition. Six (12%) patients had infectious complications or sepsis: two (4%) were due to urinary tract infection treated with antibiotics, two (4%) were diagnosed with appendicitis, and two (4%) with chorioamnionitis. Three (6%) patients required blood transfusions and three (6%) had other complications, such as migraine, hypotension, and chest pain. **Table 3** lists the maternal variables according to pathology.

Antepartum complications

Complications before delivery were classified into intraoperative and postoperative categories based on timing. Among 11 patients (22%), intraoperative issues were noted, with bleeding being the most common (12%), followed by procedure failure (6%), placental abruption (2%), and amniotic detachment (2%). Notably, no intraoperative complications occurred in the TTTS group, while the FETO group experienced one case (8%) of placental abruption on the day of balloon removal, while at MMC group,

Table 2. Fetal surgical variables

Surgery variables	Total (N = 50)	TTTS (N = 18)	CDH (N = 12)	MMC (N = 9)
Anesthesia – no. (%)				
Local anesthesia or sedation	21 (42)	9 (50)	6 (50)	-
General anesthesia	11 (22)	1 (6)	-	9 (100)
Spinal anesthesia	30 (60)	14 (78)	12 (100)	-
Antibiotic prophylaxis – no. (%)	41 (82)	15 (83)	11 (92)	9 (100)
Tocolytics – no. (%)	36 (72)	14 (78)	9 (75)	9 (100)
Atosiban	24 (48)	12 (67)	5 (42)	3 (33)
Nifedipine	9 (18)	5 (28)	4 (33)	-
Indomethacin	7 (14)	-	-	7 (78)
Mean gestational age (weeks)	25 (16 to 32)	21 (17 to 25)	28 (23 to 30)	27 (25 to 28)
Surgery time (minutes)	80 (30 to 203)	63 (40 to 120)	66 (30 to 130)	148 (110 to 203)
More than one procedure – no. (%)	21 (42)	5 (28)	11 (92)]	

TTTS: twin-twin transfusion syndrome; CHD: congenital diaphragmatic hernia; MMC: myelomeningocele

Table 3. Maternal complications due to fetal surgery

Maternal Complications	Total (N = 50)	TTTS (N = 18)	CDH (N = 12)	MMC (N = 9)
Anesthetic – no. (%)	4 (8)	2 (11)	-	1 (11)
Post-spinal anesthesia headaches	3 (6)	2 (11)	-	-
Decreased oxygen saturation needing macronebulization	1 (2)	-	-	1 (11)
Infectious/sepsis – no. (%)	6 (12)	3 (17)	-	3 (33)
Urinary tract infection treated with antibiotics	2 (4)	2 (11)	-	-
Appendicitis	2 (4)	1 (6)	-	1 (11)
Chorioamnionitis	2 (4)	-		2 (22)
Required blood transfusion – no. (%)	3 (6)	2 (11)	-	1 (11)
Others – no. (%)	3 (6)	-	2[ǂ](17)	1[ϟ] (11)

[ı] hypotension, [ǂ] chest pain and [ϟ] migraine

TTTS: twin-twin transfusion syndrome; CHD: congenital diaphragmatic hernia; MMC: myelomeningocele

four cases (45%) of intraoperative bleeding and one case (11%) of amniotic detachment. Postoperative complications were prevalent, affecting 36 patients (72%), with the most frequent being PPROM (40%), followed by preterm labor (26%), intrauterine death (14%), and chorioamnionitis (6%). Antepartum complications varied across groups: the TTTS group had 15 cases (83%), including PPROM (17%), preterm labor (28%), and intrauterine complications (27%); the CDH group experienced 8 cases (67%), primarily PPROM (33%) and preterm labor (17%); and the MMC group saw 8 cases (89%) of antepartum complications, predominantly PPROM (89%). Additionally, chorioamnionitis affected 22% of MMC patients, while preterm labor and appendicitis each occurred in 11% of cases. **Table 4** describes the complications according to the frequency of each pathology.

Childbirth-related variables

The study encompassed neonatal data across various conditions. On average, gestational age at delivery was 33 weeks, with a range of 25 to 40 weeks, resulting in 83% live births. Most newborns were admitted to the NICU, with 50% requiring resuscitation at the delivery room. Antenatal corticosteroids were administered to 76% of pregnant women. Respirator use was necessary for 48% of newborns, and surfactants were required in 19% cases. Additionally, 24% of newborns needed additional oxygen support after 28 days of life. Notably, mortality was observed in 26% of cases. Patients with TTTS had a mean gestational age at delivery of 31 weeks, with 96% live births. Among CDH patients, the mean gestational age at delivery was 37 weeks, with all infants admitted to the NICU and experiencing respiratory issues. Finally, patients with MMC had a mean gestational age at delivery of 33 weeks, with 100% live births and relatively lower mortality rates. **Table 5** describes the baseline characteristics of the study population, while **Table 6** summarizes the outcomes of the individual characteristics of each pathology.

DISCUSSION

MMC

The results of the Management of Myelomeningocele Study (MOMS), a randomized controlled trial, seem to have changed the timing of open spina bifida repair from the postnatal to the prenatal period. The trial was interrupted due to better efficacy in patients who underwent prenatal repair than in those who underwent postnatal repair.[3,20] However, because of the open nature of this fetal surgery, these favorable outcomes occur at the expense of increased risks of uterine dehiscence and rupture, as well as other morbidities in mothers.[3] As open fetal surgery by hysterotomy is an invasive procedure, fetoscopic surgical techniques aim to minimize surgical trauma.[13] Meanwhile, following significant technical improvements and a steep learning curve for the surgical teams, fetoscopic fetal surgery is considered on par

Table 4. Antepartum complications due to fetal surgery

Antepartum Complications	Total (N = 50)	TTTS (N = 18)	CDH (N = 12)	MMC (N = 9)
Intraoperative complications – no. (%)	11 (22)	-	1 (8)	5 (56)
Bleeding	6 (12)	-	-	4 (45)
Amniotic detachment	1 (2)	-	-	1 (11)
Placental abruption	1 (2)	-	1 (8)	-
Intraoperative fetal death	-	-	-	-
Failure to perform the procedure	3 (6)	-	-	-
Antepartum complications – no. (%)				
Yes	36 (72)	15 (83)	8 (67)	8 (89)
Preterm PROM	20 (40)	3 (17)	4 (33)	8 (89)
Chorioamnionitis	3 (6)	-	-	2 (22)
Preterm labor	13 (26)	5 (28)	2 (17)	1 (11)
Intrauterine death	10/70[ᵎ] (14)	10/37[‡] (27)	-	-
Others*	7 (14)	3 (17)	2 (17)	1 (11)
Mean GA at PROM preterm (weeks)	31 (18 to 37)	30 (27 to 32)	35 (30 to 37)	29 (26 to 36)
Mean GA at Chorioamnionitis (weeks)	32 (18 to 32)	-	-	32 (32 to 32)
Mean GA at Preterm labor (weeks)	30 (22 to 36)	29 (22 to 36)	34 (33 to 35)	32 (32 to 32)
Mean GA at Intrauterine death (weeks)	22 (18 to 26)	22 (18 to 26)	-	-
Mean GA at Others* (weeks)	30 (23 to 35)	28 (23 to 31)	35 (35 to 35)	-

* Fetal distress (4), appendicitis (2), and fetal anemia (1).

ᵎ The number corresponds to the total number of fetuses, which is 70.

‡ The number corresponds to the total number of fetuses, which is 37.

GA: gestational age; TTTS: twin-twin transfusion syndrome; CHD: congenital diaphragmatic hernia; MMC: myelomeningocele; Preterm PROM: preterm premature rupture of ovular membranes

Table 5. Childbirth-related variables

Childbirth-related variables	Total (N = 70)	TTTS (N = 27)	CDH (N = 12)	MMC (N = 9)
Mean GA at delivery (weeks)	33 (25 to 40)	31 (25 to 40)	37 (33 to 39)	33 (28 to 37)
Born alive – no. (%)	58 (83)	26 (96)	12 (100)	9 (100)
Mean birth weight (grams)	2,045 (500 to 3790)	1,536 (500 to 2830)	2,560 (1700 to 3180)	1,976 (1130 to 3130)
Mortality	15 (26)	4 (15)	7 (58)	-
NICU discharge	40 (69)	20 (74)	5 (42)	9 (100)
ICU discharge without sequela no. (%)	13 (23)	9 (33)	2 (17)	1 (11)
Number of days in the NICU	61 (5 to 509)	37 (14 to 509)	45 (29 to 64)	37 (5 to 110)
Number of hospitalization out of NICU (days)	88 (2 to 343)	3 (2 to 3)	343 (343 to 343)	-

TTTS: twin-twin transfusion syndrome; CHD: congenital diaphragmatic hernia; MMC: myelomeningocele; GA: gestational age; NICU: neonatal intensive care unit

Table 6. Disease-specific variables

Disease-specific variables	Results
Twin-twin Transfusion Syndrome	
Weight discordance before surgery (%)	28 (SD ± 13)
Quintero Stage - **no. (%)**	
Stage I	2 (11)
Stage II	14 (78)
Stage III	2 (11)
Stage IV	
Weight discordance after surgery (%)	27 (SD ± 17)
Marginal or velamentous cord insertion - **no. (%)**	4 (22)
Number of anastomoses endoscopically detected (mean)	9 (SD ± 3)
Congenital Diaphragmatic Hernia	
Laterality - **no. (%)**	
Right	1 (8)
Left	11 (92)
Liver Herniation - **no. (%)**	7 (58)
Lung-head ratio before surgery	0.88 (SD ± 0.13)
Mean GA at balloon removal (weeks)	34 (33 to 32)
Need for ECMO **- no. (%)**	2 (17)
Fetoscopic balloon removal failure needing ultrasound-guided punctures to removal **- no. (%)**	2 (17)
Myelomeningocele - no. (%)	
Type 2 Arnold Chiari syndrome	6 (67)
Intact suture at birth	6 (67)
Foot deformity	2 (22)
Tetraventricular dilatation	4 (45)

GA: gestational age; ECMO: extracorporeal membrane oxygenation

with open techniques by some researchers, although controlled head-to-head comparisons remain lacking.[3,21,22]

There are few maternal complications related to fetoscopic surgeries for myelomeningocele correction, justifying the continued investment in studies focusing on this technique, which is expected to be disseminated more widely. Regarding maternal complications in our study, two (22%) patients were diagnosed with chorioamnionitis who were treated with intravenous antibiotics, and one patient (11%) required blood transfusion during pregnancy, which was not directly related to surgery but rather to the context of appendicitis during pregnancy.

In a study intended only to assess maternal complications published by Kohl et al.[23] there was no need for maternal blood transfusion, placental abruption, or spontaneous postoperative uterine contractions at immediate perioperative period; however, they described pulmonary edema in one (1.9%) patient. Nonetheless, the incidence of acute pulmonary edema described in MOMS is 6% [20], indicating a lower risk of this complication with fetoscopic surgery. There were no cases of acute pulmonary edema in our study; however, this could have been due to the low number of cases.

Kohl et al.[23] also described the use of tocolysis for 24 h after the procedure: in two (4%) cases of chorioamniotic detachment after the procedure and in four (7.8%) patients who developed chorioamnionitis.[23] In our study, all patients also underwent tocolysis for a short time, and we had one (11%) case of chorioamniotic detachment.

Despite the use of tocolysis, premature births remain problematic. Mean gestational age at delivery in our study was 33 weeks, with PPROM occurring in eight (89%) patients, which was the same gestational age described by Diehl et al.[13] in an observational study with data from 72 patients, and the same as described by Lapa et al.[3] Lapa et al.[3] described the rate of PPROM as 80%, like ours. However, in a study published in 2021, which analyzed 170 pregnant women in eight reference centers worldwide, mean gestational age at delivery was 34.5 weeks with a PPROM rate of 67%, which decreased to 38% after modifying the technique used during the study with CO_2 humidification during fetoscopy.[12] Furthermore, three neonatal deaths related to prematurity were also reported [12], whereas in our study, there were no neonatal or intrauterine deaths related to intrauterine treatment for MMC.

CDH

Prenatally diagnosed CDH is associated with a high postnatal mortality rate owing to the coexistence of other major defects or

various combinations of pulmonary hypoplasia and persistent pulmonary hypertension.[24-29] Several observational studies have shown that FETO is associated with increased survival among children with severe pulmonary hypoplasia due to isolated left CDH; however, randomized clinical trials have not yet been published.[30] The TOTAL trial was the first randomized to assess FETO, as this study was terminated early because of identification of benefits of surgery versus expectant management. From 80 patients analyzed, 40 underwent FETO and 40 maintained expectant management.[30]

At surgery group, median gestational age at randomization in the TOTAL trial was 27.7 weeks, and 36 (90%) patients had intrathoracic liver herniation.[30] In our study, mean gestational age on the day of surgery was 28 weeks, and seven (58%) patients had intrathoracic liver herniation.

Regarding complications described at TOTAL trial related to fetal surgeries, 19 (48%) newborns were diagnosed with PPROM with a median gestational age of 32.5 weeks, one (2%) patient was diagnosed with placental abruption, one (2%) with bleeding when introducing trocater for fetoscopy, and eight (22%) with chorioamniotic detachments.[30] In our study, four (33%) patients were diagnosed with PPROM, which occurred with a mean gestational age of 35 weeks. There were no cases of bleeding related to introduction of trocaters during fetoscopy or diagnoses of chorioamniotic detachment after fetoscopy, but one (8%) patient was diagnosed with placental abruption after fetoscopy was employed to attempt to remove the balloon. In this case, fetoscopy to remove the balloon was unsuccessful, and it was necessary to puncture the balloon guided by ultrasound after birth. We observed one (8%) case in which fetoscopy to remove the balloon was unsuccessful, and patient developed premature labor and fetal distress after having undergone a cesarean section, which showed the presence of a hemoamnion. In this case, balloon was removed postnatally using ultrasound-guided puncture without complications. At TOTAL trial, there was one (2%) death due to failure to remove the balloon in a patient who did not follow the recommendations and moved to a place far from the trial reference centers.[30] No fetal deaths were related to balloon removal.

Mean gestational age at delivery in our population was 37 weeks, and all fetuses who underwent the procedure were born alive, with a mean birth weight of 2,560 g. Two (17%) required extracorporeal membrane oxygenation and five (42%) were discharged from the NICU. At TOTAL trial, mean gestational age at delivery was 34.6 weeks, all fetuses who underwent the procedure were born alive, mean birth weight was 2,300 g, and two (5%) required extracorporeal membrane oxygenation. Thirty (75%) patients at TOTAL trial gave birth before 37 weeks, whereas in our study, only two (17%) patients had preterm labor.

Regarding neonatal complications, at TOTAL trial, 12 (75%) newborns were diagnosed with BPD, 1 (6%) had leukomalacia, and 10 (62%) sepsis.[30] In our study, two (17%) infants were diagnosed with BPD, although we had seven (58%) newborns who needed oxygen after 28 days of life, which suggests that there may have been underdiagnosed in this classification. We did not diagnose leukomalacia in our study, and nine (75%) newborns were diagnosed with neonatal infection. We also obtained two (17%) diagnoses of intracranial hemorrhage and did not have any cases of ROP or NEC.

A multicenter study evaluated 210 pregnancies with CDH treated with FETO performed at a median gestational age of 27.1 weeks, with a median duration of 10 min. PPROM occurred in 47.1% of the patients, and delivery occurred at a median gestational age of 35.3 weeks. In 97.1% of the cases, newborns were live born, and 48% were discharged from the hospital alive.[27]

TTTS

The first randomized trial conducted to evaluate TTTS' treatment with endoscopic laser surgery compared to serial amnioreduction's treatment was published in 2004 by the Eurofoetus group. The study was terminated early after demonstrating the benefit of the group that underwent laser coagulation of placental anastomoses. In total, 72 patients were included in the laser group. According to Quintero's classification, there were six (8%) patients with stage I, 31 (43%) with stage II, 34 (47%) with stage III, and one (1%) with stage IV.[31] In our study, two (11%) patients were at Quintero stage I, 14 (78%) in stage II, and two in stage III (11%). None of the patients were in stage IV.

At Eurofoetus study, mean gestational age at delivery at laser group was 33.3 weeks, with a mean birth weight of 1,757 g.[31] Compared to our study, mean gestational age at delivery was 31 weeks, with a mean birth weight of 1,536 g, which were similar to the results published by Gheorghe et al.[32], Malshe et al.[33], and Habli et al.[34]

Regarding complications, at Eurofoetus study, 10 (15%) patients were diagnosed with PPROM within 28 days of the procedure and 16 (12%) fetuses were diagnosed with intrauterine death within 7 days of the procedure; in 76% of patients, at least one fetus survived.[31] Malshe et al.[33] described PPROM in 32 (15.8%) cases and fetuses were born alive in 78.3% of cases. Complications in our study were observed in three (17%) patients with PPROM, and there were 10 (27%) intrauterine deaths during pregnancy, which is consistent with the results of the studies cited above.[31,33] We also had three (17%) patients who experienced other complications, including one case of fetal distress, one case of fetal anemia, as well as a pregnant woman with appendicitis a few weeks after fetoscopy.

Neonatal complications were also described by Eurofoetus group: a total of 12 (8%) newborns died during the neonatal period, intraventricular hemorrhage grade III or IV was noted in two (1%) newborns, and leukomalacia in eight (6%) newborns[31]. In our group, four (15%) newborns were diagnosed with intracranial hemorrhage, but we included mild cases, not just the most severe ones; 20 (74%) newborns were discharged from NICU, with four

(15%) deaths registered at neonatal period. Records of patients with leukomalacia were not available. NEC was noted in our study in four (15%) cases, which was a much higher incidence than that described by Gheorghe et al.[32] (1.8%). Malshe et al.[33] described 12 (18.5%) cases of placental abruption and four (6.2%) cases of chorioamnionitis[33]. We did not observe chorioamnionitis or placental abruption in pregnancies subjected to laser treatment for TTTS.

At Eurofoetus study, no pregnant woman died or required blood transfusion or hospitalization in the maternal ICU.[31] No deaths were observed in our study; however, three (17%) patients had infectious complications not directly related to fetoscopy, two (11%) had urinary tract infections, and one (6%) had abdominal sepsis due to appendicitis.

A retrospective study published by Habli et al.[34] evaluated 152 pregnant women who underwent laser fetoscopy to treat TTTS and the incidence of postoperative complications; 147 (97%) patients in this study underwent procedure using epidural anesthesia, while the most used anesthesia was spinal in 14 (78%). In the same study, it was impossible to complete the procedure in five patients: two cases due to peritoneal leaks and three cases due to intraamniotic bleeding from trocar introduction or laceration of the chorion plate by the laser.[34] No complications were observed in our surgeries.

CONCLUSION

Our study assessed fetal surgeries performed at two reference centers for fetal medicine in Rio de Janeiro, Brazil. Fetal surgeries in Brazil play an important role, mainly because there is no possibility of pregnancy termination due to abortion.

Our study has some limitations, such as its retrospective descriptive nature based on data from medical records and the small sample size when considering the time evaluated. Analysis of less common diseases, combined with a small sample size selected for convenience through patients referred directly to the two reference centers, suggests that there is a possible selection bias, which means that our results cannot be extrapolated to other populations.

Therefore, intrauterine surgery may improve the prognosis of these fetuses; however, we cannot ignore the fact that intrauterine fetal surgeries, even minimally invasive surgeries, can result in complications in pregnant women and are associated with a higher risk of prematurity. Nonetheless, based on our findings, we conclude that intrauterine fetal surgeries are safe for pregnant women, with low morbidity, perinatal mortality, and prematurity rates, comparable to those previously reported. Premature birth remains a major problem associated with fetal surgery.

REFERENCES

1. Moreira de Sá RA, Nassar de Carvalho PR, Kurjak A, et al. Is intrauterine surgery justified? Report from the working group on ultrasound in obstetrics of the World Association of Perinatal Medicine (WAPM). J Perinat Med. 2016;44(7):737-43. PMID: 26124046; https://doi.org/10.1515/jpm-2015-0132.
2. Graves CE, Harrison MR, Padilla BE. Minimally invasive fetal surgery. Clin Perinatol. 2017;44(4):729-51. PMID: 29127956; https://doi.org/10.1016/j.clp.2017.08.001.
3. Lapa DA. Endoscopic fetal surgery for neural tube defects. Best Pract Res Clin Obstet Gynaecol. 2019;58:133-41. PMID: 31350160; https://doi.org/10.1016/j.bpobgyn.2019.05.001.
4. Norton ME, Scoutt LM, Feldstein VA, editors. Callen's ultrasonography in obstetrics and gynecology. Philadelphia: Elsevier; 2017.
5. Harrison MR, Filly RA, Golbus MS, et al. Fetal treatment 1982. N Engl J Med. 1982;307(26):1651-2. PMID: 7144864; https://doi.org/10.1056/nejm198212233072623.
6. Golbus MS, Harrison MR, Filly RA, Callen PW, Katz M. In utero treatment of urinary tract obstruction. Am J Obstet Gynecol. 1982;142(4):383-8. PMID: 7199255; https://doi.org/10.1016/s0002-9378(16)32377-8.
7. Rocha LSN, Amorim Filho AG, Bunduki V, et al. Cirurgia fetal no contexto atual. Rev Med. 2018;97(2):216-25. https://doi.org/10.11606/issn.1679-9836.v97i2p216-225.
8. Cruz-Martínez R, Gratacos E. Endocopic fetal surgery. Ginecol Obstet Mex. 2014;82(5):325-36. PMID: 24937948.
9. Pedreira DAL, Acácio GL, Drummond CL, et al. Laser for the treatment of twin to twin transfusion syndrome. Acta Cirurg Bras. 2005;20(6):478-81. PMID: 16302086; https://doi.org/10.1590/s0102-86502005000600015.
10. Peralta CFA, Barini R. Cirurgia fetal no Brasil. Rev Bras Ginecol Obstet. 2011;33(4):153-6. PMID: 21845345.
11. Pedreira DAL. Advances in fetal surgery. Einstein. 2016;14(1):110-2. PMID: 27074241; https://doi.org/10.1590/s1679-45082016md3449.
12. Lapa DA, Chmait RH, Gielchinsky Y, et al. Percutaneous fetoscopic spina bifida repair: effect on ambulation and need for postnatal cerebrospinal fluid diversion and bladder catheterization. Ultrasound Obstet Gynecol. 2021;58(4):582-9. PMID: 33880811; https://doi.org/10.1002/uog.23658.
13. Diehl D, Belke F, Kohl T, et al. Fully percutaneous fetoscopic repair of myelomeningocele: 30-month follow-up data. Ultrasound Obstet Gynecol. 2021;57(1):113-8. PMID: 32510722; https://doi.org/10.1002/uog.22116.
14. Carrabba G, Macchini F, Fabietti I, et al. Minimally invasive fetal surgery for myelomeningocele: preliminary report from a single center. Neurosurg Focus. 2019;47(4):E12. PMID: 31574466; https://doi.org/10.3171/2019.8.focus19438.
15. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978;92(4):529-34. PMID: 305471; https://doi.org/10.1016/s0022-3476(78)80282-0.
16. de Vries LS, Eken P, Dubowitz LM. The spectrum of leukomalacia using cranial ultrasound. Behav Brain Res. 1992;49(1):1-6. PMID: 1388792; https://doi.org/10.1016/s0166-4328(05)80189-5.
17. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol. 2005;123(7):991-9. PMID: 16009843; https://doi.org/10.1001/archopht.123.7.991.

18. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163(7):1723-9. PMID: 11401896; https://doi.org/10.1164/ajrccm.163.7.2011060.
19. Vermont Oxford Network. Vermond Oxford manual of operations part 2: data definitions & infant data forms. Burlington: Vermont Oxford Network; 2019. Available from: https://vtoxford.zendesk.com/hc/en-us/articles/360013115393-2019-Manualof-Operations-Part-2-Release-23-2-PDF. Accessed in 2023 (May 19).
20. Adzick NS, Thom EA, Spong CY, A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med. 2011;364(11):993-1004. PMID: 21306277; https://doi.org/10.1056/nejmoa1014379.
21. Sanz Cortes M, Lapa DA, Acácio GL, et al. Proceedings of the First Annual Meeting of the International Fetoscopic Myelomeningocele Repair Consortium. Ultrasound Obstet Gynecol. 2019;53(6):855-63. PMID: 31169957; https://doi.org/10.1002/uog.20308.
22. Joyeux L, De Bie F, Danzer E, et al. Learning curves of open and endoscopic fetal spina bifida closure: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2020;55(6):730-9. PMID: 31273862; https://doi.org/10.1002/uog.20389.
23. Degenhardt J, Schürg R, Winarno A, et al. Percutaneous minimal-access fetoscopic surgery for spina bifida aperta. Part II: maternal management and outcome. Ultrasound Obstet Gynecol. 2014;44(5):525-31. PMID: 24753062; https://doi.org/10.1002/uog.13389.
24. Colvin J, Bower C, Dickinson JE, Sokol J. Outcomes of congenital diaphragmatic hernia: a population-based study in Western Australia. Pediatrics. 2005;116(3):e356-63. PMID: 16140678; https://doi.org/10.1542/peds.2004-2845.
25. Jani J, Keller RL, Benachi A, et al. Prenatal prediction of survival in isolated left-sided diaphragmatic hernia. Ultrasound Obstet Gynecol. 2006;27(1):18-22. PMID: 16374756; https://doi.org/10.1002/uog.2688.
26. Gallot D, Boda C, Ughetto S, et al. Prenatal detection and outcome of congenital diaphragmatic hernia: a French registry-based study. Ultrasound Obstet Gynecol. 2007;29(3):276-83. PMID: 17177265; https://doi.org/10.1002/uog.3863.
27. Jani JC, Nicolaides KH, Gratacós E, et al. Severe diaphragmatic hernia treated by fetal endoscopic tracheal occlusion. Ultrasound Obstet Gynecol. 2009;34(3):304-10. PMID: 19658113; https://doi.org/10.1002/uog.6450.
28. Stege G, Fenton A, Jaffray B. Nihilism in the 1990s: the true mortality of congenital diaphragmatic hernia. Pediatrics. 2003;112(3):532-5. PMID: 12949279; https://doi.org/10.1542/peds.112.3.532.
29. Witters I, Legius E, Moerman P, et al. Associated malformations and chromosomal anomalies in 42 cases of prenatally diagnosed diaphragmatic hernia. Am J Med Genet. 2001;103(4):278-82. PMID: 11746006.
30. Deprest JA, Benachi A, Gratacos E, et al. Randomized trial of fetal surgery for moderate left diaphragmatic hernia. N Engl J Med. 2021;385(2):119-29. PMID: 34106555; https://doi.org/10.1056/nejmoa2026983.
31. Senat MV, Deprest J, Boulvain M, et al. Endoscopic laser surgery versus serial amnioreduction for severe twin-to-twin transfusion syndrome. N Engl J Med. 2004;351(2):136-44. PMID: 15238624; https://doi.org/10.1056/nejmoa032597.
32. Gheorghe CP, Boring N, Mann L, et al. Neonatal outcomes and maternal characteristics in monochorionic diamniotic twin pregnancies: uncomplicated versus twin-to-twin transfusion syndrome survivors after fetoscopic laser surgery. Fetal Diagn Ther. 2020;47(2):165-70. PMID: 31434071; https://doi.org/10.1159/000500858.
33. Malshe A, Snowise S, Mann LK, et al. Preterm delivery after fetoscopic laser surgery for twin-twin transfusion syndrome: etiology and risk factors. Ultrasound Obstet Gynecol. 2017;49(5):612-6. PMID: 27222097; https://doi.org/10.1002/uog.15972.
34. Habli M, Bombrys A, Lewis D, et al. Incidence of complications in twin-twin transfusion syndrome after selective fetoscopic laser photocoagulation: a single-center experience. Am J Obstet Gynecol. 2009;201(4):417.e1-7. PMID: 19788973; https://doi.org/10.1016/j.ajog.2009.07.046.

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Smoking and consumption of ultra-processed foods — a combination of risky choices: A cross-sectional study using Vigitel 2018 data

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ABSTRACT

BACKGROUND: Smoking and unhealthy diet are important risk factors for cardiovascular and metabolic diseases, contributing to public health crises.

OBJECTIVE: To evaluate the consumption of natural/minimally processed and ultra-processed foods by Brazilian adults (18–59 years old) according to smoking status.

DESIGN AND SETTING: Cross-sectional study of a representative population sample from 26 state capitals and the Federal District (Brazil-2018).

METHODS: Data were obtained from Vigitel—Surveillance System for Risk and Protection Factors for Chronic Diseases by Telephone Survey. Participants were categorized as smokers, ex-smokers, and never smokers. Multinomial logistic regression was used for analyses.

RESULTS: Of the 30,800 adults evaluated, 9.4% (95%CI: 8.7-10.2) were smokers and 16.5% (95%CI: 15.8-17.3) were ex-smokers. Smokers were less likely to consume fruit and natural juice, and more likely to consume soda or artificial juice (≥ 5 days/week) than ex-smokers and never smokers. Regarding the daily frequency of consumption, smokers were observed to be less likely to eat fruit more than 1 time/day and more likely to drink ≥ 3 cups/cans of soda/day. Compared to never smokers, smokers had a 42% higher chance of consuming ≥ 3 glasses of natural juice/day. On the day before the interview, fruit, milk, tubers, squash, and okra consumption were lower among smokers than non-smokers. Smokers were more likely to report consuming soft drinks, fruit juice, sauces, ready-made dishes, margarine, and sausages.

CONCLUSION: Smokers had lower fruit consumption, and higher consumption of natural juices and ultra-processed foods. We highlight the need for strategies that encourage healthy eating and smoking cessation.

INTRODUCTION

Smoking is responsible for the deaths of more than eight million people annually worldwide as a result of both the direct consumption of tobacco and exposure to passive smoking. More than 80% of the 1.3 billion smokers live in countries with less economic development.[1] Regarding noncommunicable chronic diseases (NCDs), in the Americas, 16% of the deaths due to cardiovascular disease, 25% due to cancer, and 52% due to chronic respiratory diseases are attributed to tobacco use disorder.[2] In Brazil, 28% (n = 156,337) of premature deaths in 2015 were caused by smoking, with an estimated total cost of R$ 56.9 billion in terms of health care and loss of productivity.[3]

Another important modifiable risk factor that increases the probability of developing NCDs is unhealthy eating[4]—a habit often adopted by smokers. Indeed, a study that estimated the combination of risk factors based on data from the 2015 Surveillance System for Risk and Protection Factors for Chronic Diseases by Telephone Survey (Vigitel) reported a greater likelihood among smokers of having an inadequate diet.[5] The co-occurrence of smoking and an unhealthy diet was found in 8.6% of the adult population (18–59 years of age) residing in Brazilian state capitals and the Federal District, and 10.8% of men.[6] In Brazil, an inadequate diet remained at the top of the list of 17 main risk factors for the global burden of disease in both sexes between 1990 and 2015, whereas smoking dropped from the second to the fourth position among men and from the fourth to the fifth position among women.[7]

In the adult population (≥ 18 years) of Belo Horizonte, the capital of the state of Minas Gerais, Gomes et al.[8] found that the prevalence of inadequate eating habits was higher among smokers and was characterized by more frequent consumption of soda, red meat, and meat with excess fat as well as a lower consumption of fruits and vegetables. Analyzing data from three dietary records of adults (18–70 years old) from Minnesota, USA, Raatz et al.[9] found a lower intake of energy, polyunsaturated fatty acids, dietary fiber, and micronutrients, such as calcium, iron, potassium, folate, and vitamins A, C, and E, among smokers than non-smokers. Another study found that the dietary quality scores for five of the eight indices selected were significantly diminished with smoking.[10] Studies have also shown that smokers have an altered sense of taste, with less sensitivity to bitter, sour, and salty flavors.[11,12]

In a study of 358,218 American adults (≥ 18 years of age), Adams et al.[13] quantified the population-attributable risk for nine chronic diseases. Among the risk factors with confirmed causality, smoking and obesity contributed to the occurrence of five to six diseases, whereas low fruit and vegetable consumption contributed to the occurrence of two. The authors also confirmed their hypothesis of a dose-response gradient between each outcome and the increase in the number of risk factors, demonstrating the additive effect of separate risk factors. Furthermore, a case-control study (2010–2015) by Fliss-Isakov et al.[14] showed an association of high ultra-processed food intake (≥ 44.8% of total kcal) with cases of colorectal adenomas in smokers, mainly advanced (Odds ratio [OR] = 4.76) and proximal (OR = 6.23), and a significant interaction between smoking and high intake of these foods.

OBJECTIVES

This study aimed to investigate the consumption of ultra-processed foods, and natural and minimally processed foods in Brazilian adults aged 18–59 years according to their smoking status (current smoker, ex-smoker, and never smoker). This study innovates by using questions incorporated into Vigitel in 2018, which assesses food consumption according to the NOVA classification presented in the 2014 Food Guide for the Brazilian Population.

METHODS

Study design and population

A cross-sectional study was conducted using data from the Surveillance System for Risk and Protection Factors for Chronic Diseases by Telephone Survey (Vigitel, in Portuguese), administered to the adult population (≥ 18 years of age) residing in 26 state capitals and the Federal District of Brazil in 2018.

The sampling procedures for the Vigitel survey sought to obtain probabilistic samples of the adult population based on records of residential telephone lines (landlines) in the state capitals and Federal District that were made available annually by the main residential telephone operators in the country. In the first stage, at least 5000 telephone lines were randomly selected from each city. This selection was systematic and stratified by the postal code. The selected lines were then divided into replicates of 200 lines each for the identification of active residential lines (eligible for the system). After confirming the eligibility of the line, the second sampling step was the selection of one of the adults (≥ 18 years of age) residing in the selected home.[15]

Measures

In 2018, the Vigitel survey identified 73,648 eligible lines for the 26 capital cities and the Federal District, and conducted 52,395 interviews. Post-stratification weights were assigned to each interviewee to obtain reliable estimates of the adult population having a residential telephone line in each city. The weights equated the sociodemographic distribution of the Vigitel sample to the distribution estimated for the total adult population of the same city, considering the following variables: sex (female, male), age group (18–24, 25–34, 35–44, 45–54, 55–64, and ≥ 65 years) and schooling (without instruction/incomplete primary school, complete primary/incomplete high school, complete high school/incomplete higher education and complete higher education).[15]

In the present study, the questions "Do you currently smoke?" and "Did you ever smoke in the past?" were used to compose the dependent variable, with individuals categorized as smokers, ex-smokers, and non-smoker (never smoked).

The sociodemographic variables of interest were sex, age group (18 to 29, 30 to 39 and 40 to 59 years of age), schooling (0 to 8, 9 to 11 and 12 or more years of study), skin color/ethnicity (White, Black or Brown), marital status (with or without a spouse), possession of a private health insurance plan (yes or no), and region of residence (Central West, Northeast, North, Southeast, South). Individuals of yellow skin color and indigenous individuals were excluded from the study on consideration of the absolute number of respondents in the smoker category (n = 49), which impeded the acquiring of estimates with acceptable precision.

Food consumption was evaluated through questions on the weekly frequency of consumption of raw and cooked vegetables, natural fruit juices and fruits, and soda or artificial juice, which were classified as 0 to 2, 3 to 4 or ≥ 5 days (regular consumption) per week. Questions were also posed on the daily frequency of consumption of raw and cooked vegetables (once or twice per day), natural juice (1, 2 or ≥ 3 glasses), fruits (1, 2 or ≥ 3 times) and soda/artificial juice (1, 2 or ≥ 3 glasses/cans per day).

The NOVA classification of foods was used to categorize foods and beverages consumed the day prior to the interview (yes or no) according to their degree of processing:[16]

- Natural or minimally processed foods: vegetables, fruits, meats, eggs, grains, tubers, legumes, nuts, and milk;
- Ultra-processed foods: soda, fruit drinks (juice in a box or can and powdered soft drinks), sweetened milk-based drinks, sweets, chips/crisps/crackers, sauces, ready-to-eat/semi-ready-to-eat products, margarine, processed meats, sandwich bread, hotdog/hamburger buns.

Statistical analysis

The distribution of smokers, ex-smokers, and non-smokers was determined according to sociodemographic characteristics, followed by an estimation of the proportion of food intake according to smoking status. Differences between groups were determined using Pearson's chi-squared test with the second-order (Rao and Scott) correction, and by odds ratios (OR) adjusted for age, sex, schooling, region of residence, and alcohol abuse or binge drinking (≥ 5 drinks for men, ≥ 4 drinks for women, on a single occasion, at least once in the last 30 days). Alcohol abuse was selected as an adjustment variable owing to the high prevalence observed among smokers (43.5%; 95%CI: 39.3-47.8) and former smokers (24.0%; 95%CI: 21, 8-26.3). Multinomial logistic regression was used to estimate the ORs for food intake among smokers compared to non-smokers and ex-smokers. Associations were determined using Wald's test, with a value of $P < 0.05$. Analyses were conducted using the survey module of Stata 15.1 (StataCorp LLC, College Station, Texas, United States), which considers the complex sampling of the study.

All participants received clarifications regarding the study objectives at the time of telephone contact. Written informed consent was replaced with verbal informed consent. This study was approved by the National Human Research Ethics Committee of the Health Ministry (report n. 355,590, 06/26/2013).

RESULTS

Data from 30,800 individuals aged 18–59 years were analyzed. The mean age was 36.7 years (95%CI: 36.5-36.9). The prevalence of smokers was 9.4% (95%CI: 8.7-10.2) in the total population, 12.4% among men and 6.7% among women. The prevalence of ex-smokers was 16.5% (95%CI: 15.8-17.3) and was higher among men than women (19.1% vs. 14.2%, respectively).

Most smokers were men aged between 40 and 59 years, with less than 12 years of schooling, without a spouse, without a private health insurance plan, and resided in the southeastern region of the country ($P < 0.0001$). Similar results were found for ex-smokers, except that the majority had a spouse (**Table 1**).

Regarding the weekly frequency of consumption (number of days in the week), compared to non-smokers, smokers were less likely to regularly consume (five or more days/week) natural fruit juice and fruits, and more likely to consume soda or artificial juice. The same pattern was observed in smokers compared to ex-smokers (**Table 2**).

In the analyses about the daily (number of times a day) frequency of consumption, the smokers were less likely to consume fruits more than once per day and more likely to ingest three or more glasses/cans of soda per day than non-smokers and ex-smokers. Paradoxically, smokers were 42% more likely than non-smokers to consume three or more glasses of natural fruit juice per day (**Table 3**).

Regarding natural and minimally processed foods, smokers were less likely to have consumed fruits and milk on the day prior to the interview compared to non-smokers and ex-smokers, and less likely to have consumed tubers and vegetables, such as pumpkin and okra, compared to non-smokers (**Table 4**). Regarding ultra-processed foods consumed the day prior to the interview, smokers were more likely to have consumed soda, fruit drinks, sauces, ready-to-eat, or semi-ready-to-eat products, margarine, and processed meats than ex-smokers and non-smokers (**Table 5**).

DISCUSSION

The results of the present study enabled identification of the dietary habits of smokers in comparison to those of ex-smokers and individuals who have never smoked. Smoking and a dietary pattern marked by high consumption of ultra-processed foods are among the modifiable risk factors that have an evident impact on health outcomes. Smokers had lower fruit intake and greater consumption of soda or artificial juice in both the weekly and daily frequency analysis. Daily consumption of three or more glasses of natural juice was higher among smokers than among non-smokers. On the day prior to the interview, smokers showed lower consumption of fruits, milk, and tubers, as well as greater consumption of ultra-processed foods such as soda, fruit drinks, sauces, ready-to-eat products, margarine, and processed meats.

The prevalence of smokers and ex-smokers in the population aged between 18 and 59 years residing in the Brazilian state capitals and Federal District was 9.4% and 16.5%, respectively. Data from the Vigitel survey on the trend of smoking indicators in adults (18 years of age or older) reveal a reduction in the prevalence of smokers (from 15.6% to 10.8%) and ex-smokers (22.2% to 21.2%) from 2006 to 2014.[17] According to the National Health Survey (Pesquisa Nacional de Saúde - PNS), the prevalence of all tobacco use indicators diminished between 2013 and 2019, and the prevalence of ex-smokers increased from 17.5% to 26.6% (prevalence ratio: 1.52; 95%CI: 1.46-1.58).[18] Brazil is recognized for combating tobacco use. In 2005, with the issuance of the guidelines of the World Health Organization Framework Convention on Tobacco Control, which consolidated the National Tobacco Control Policy, Brazil successfully implemented anti-smoking measures, such as the prohibition of advertising for tobacco products, an increase in

Table 1. Sociodemographic characteristics of adults residing in Brazilian state capitals and the Federal District according to smoking status. Vigitel, Brazil, 2018

Variable	% (95% CI)			P value*
	Never smoked	Ex-smoker	Smoker	
Sex				
Male	43.54 (42.29-44.80)	54.45 (51.86-57.00)	62.03 (57.99-65.90)	**< 0.0001**
Female	56.46 (55.20-57.71)	45.55 (43.00-48.14)	37.97 (34.10-42.01)	
Age group (in years)				
18 to 29	35.40 (34.17-36.65)	19.32 (17.27-21.55)	25.49 (21.73-29.65)	
30 to 39	27.82 (26.67-29.00)	22.77 (20.53-25.18)	26.55 (22.50-31.03)	**< 0.0001**
40 to 59	36.78 (35.67-37.91)	57.91 (55.27-60.50)	47.96 (43.77-52.18)	
Schooling (years of study)				
0 to 8	17.63 (16.62-18.68)	37.43 (34.85-40.07)	39.36 (35.25-43.62)	
9 to 11	43.26 (42.05-44.48)	37.21 (34.80-39.69)	38.72 (34.53-43.08)	**< 0.0001**
12 or more	39.11 (37.91-40.33)	25.36 (23.26-27.59)	21.92 (18.95-25.22)	
Ethnicity/skin color				
White	43.28 (42.00-44.56)	43.85 (41.19-46.54)	44.61 (40.56-48.74)	
Black	12.22 (11.35-13.16)	9.94 (8.45-11.66)	12.15 (9.59-15.28)	0.2596
Brown	44.50 (43.25-45.75)	46.21 (43.54-48.90)	43.24 (39.12-47.45)	
Marital status				
Without spouse	56.72 (55.49-57.93)	43.63 (41.10-46.20)	59.99 (55.86-63.97)	**< 0.0001**
With spouse	43.28 (42.07-44.51)	56.37 (53.80-58.90)	40.01 (36.03-44.14)	
Health insurance				
No	51.65 (50.41-52.89)	60.72 (58.19-63.20)	67.69 (63.79-71.36)	**< 0.0001**
Yes	48.35 (47.11-49.59)	39.28 (36.80-41.81)	32.31 (28.64-36.21)	
Region of residence				
Central West	12.36 (11.79-12.95)	11.26 (10.13-12.51)	11.28 (9.69-13.09)	
Northeast	27.63 (26.75-28.53)	23.69 (22.00-25.47)	16.56 (14.47-18.88)	
North	11.09 (10.59-11.61)	12.23 (10.96-13.62)	7.48 (6.17-9.04)	**< 0.0001**
Southeast	41.82 (40.46-43.18)	43.68 (40.93-46.46)	53.79 (49.72-57.82)	
South	7.10 (6.68-7.55)	9.14 (8.17-10.2)	10.90 (9.31-12.72)	

* P value from Pearson's chi-square test (Rao-Scott). CI = confidence interval.

Table 2. Weekly frequency and odds ratios of food intake in adults residing in Brazilian state capitals and the Federal District according to smoking status. Vigitel, Brazil, 2018

Weekly food frequency	Never smoked (0)	Ex-smoker (1)	Smoker (2)	OR[a] (2/1)	P[b]	OR[a] (2/0)	P[b]
Raw vegetables	P = 0.1644[c]						
< 5 times	60.81	60.75	64.87	1		1	
≥ 5 times	39.19	39.25	35.13	0.87	0.254	1.02	0.848
Cooked vegetables	**P = 0.0001**[c]						
< 5 times	73.88	77.63	80.18	1		1	
≥ 5 times	26.12	22.37	19.82	0.93	0.520	0.87	0.210
Natural juice	**P < 0.0001**[c]						
< 5 times	70.08	74.60	78.79	1		1	
≥ 5 times	29.92	25.40	21.21	0.80	**0.046**	0.69	**< 0.001**
Fruits	**P < 0.0001**[c]						
< 5 times	52.70	52.18	71.06	1		1	
≥ 5 times	47.30	47.82	28.94	0.49	**< 0.001**	0.51	**< 0.001**
Soda/artificial juice	**P < 0.0001**[c]						
< 3 times	73.14	73.08	57.27	1		1	
≥ 3 times	26.86	26.92	42.73	1.72	**< 0.001**	1.90	**< 0.001**

[a] Odds ratio (OR) controlled for age, sex, schooling, region of residence, and alcohol abuse; [b] P value from Wald's test; [c] P value from Pearson's chi-square test (Rao-Scott).

Table 3. Frequency and odds ratios of daily food intake in adults residing in Brazilian state capitals and the Federal District according to smoking status. Vigitel, Brazil, 2018

Daily food intake	Never smoked (0)	Ex-smoker (1)	Smoker (2)	OR[a] (2/1)	P[b]	OR[a] (2/0)	P[b]
Raw vegetables		P = 0.7487[c]					
1 time	72.67	73.80	72.93	1		1	
2 times	27.33	26.20	27.07	1.05	0.659	1.02	0.854
Cooked vegetables		P = 0.7826[c]					
1 time	67.10	66.02	66.37	1		1	
2 times	32.90	33.98	33.63	0.96	0.754	1.04	0.720
Natural juice		**P = 0.0087**[c]					
1 glass	42.97	40.97	35.28	1		1	
2 glasses	35.47	35.29	36.26	1.10	0.481	1.18	0.174
≥ 3 glasses	21.56	23.74	28.47	1.21	0.252	1.42	**0.028**
Fruits		**P = 0.0001**[c]					
1	47.65	49.63	57.52	1		1	
2	35.04	31.56	27.46	0.77	**0.043**	0.67	**0.001**
≥ 3 times	17.31	18.81	15.03	0.72	**0.031**	0.70	**0.012**
Soda/artificial juice		**P < 0.0001**[c]					
1 glass/can	42.13	38.64	30.59	1		1	
2 glasses/cans	37.20	35.37	33.30	1.12	0.438	1.13	0.355
≥ 3 glasses/cans	20.67	25.99	36.10	1.46	**0.022**	2.00	**< 0.001**

[a] Odds ratio (OR) controlled for age, sex, schooling, region of residence, and alcohol abuse; [b] P value from Wald's test. [c] P value from Pearson's chi-square test (Rao-Scott).

Table 4. Frequency and odds ratios of consumption of natural/minimally processed foods on the day prior to the interview among adults residing in Brazilian state capitals and the Federal District according to smoking status. Vigitel, Brazil, 2018

Food groups Natural or minimally processed foods	Never smoked (0)	Ex-smoker (1)	Smoker (2)	OR[a] (2/1)	P[b]	OR[a] (2/0)	P[b]
Vegetables		P = 0.0562[c]					
No	21.10	22.72	25.13	1		1	
Yes	78.90	77.28	74.87	0.92	0.491	0.94	0.583
Fruits		**P < 0.0001**[c]					
No	21.94	23.74	37.68	1		1	
Yes	78.06	76.26	62.32	0.57	**< 0.001**	0.53	**< 0.001**
Milk		**P = 0.0001**[c]					
No	43.68	43.82	52.56	1		1	
Yes	56.32	56.18	47.44	0.77	**0.011**	0.77	**0.006**
Legumes		P = 0.9330[c]					
No	26.87	26.49	26.38	1		1	
Yes	73.13	73.51	73.62	0.98	0.878	0.93	0.444
Grains		P = 0.1368[c]					
No	13.82	16.11	14.67				
Yes	86.18	83.89	85.33	1.06	0.681	0.83	0.139
Meats		P = 0.7443[c]					
No	10.26	10.46	11.27	1		1	
Yes	89.74	89.54	88.73	0.94	0.712	0.93	0.647
Eggs		P = 0.5870[c]					
No	58.53	58.12	56.44	1		1	
Yes	41.47	41.88	43.56	1.05	0.619	1.08	0.402
Tubers, pumpkin or okra		**P < 0.0001**[c]					
No	36.32	42.46	44.02	1		1	
Yes	63.68	57.54	55.98	0.98	0.859	0.81	**0.025**
Nuts		P = 0.0833[c]					
No	83.85	83.98	87.04	1		1	
Yes	16.15	16.02	12.96	0.81	0.117	0.84	0.149

[a] Odds ratio (OR) controlled for age, sex, schooling, region of residence, and alcohol abuse; [b] P value from Wald's test; [c] P value from Pearson's chi-square test (Rao-Scott).

Table 5. Frequency and odds ratios of consumption of ultra-processed foods on the day prior to the interview among adults residing in Brazilian state capitals and the Federal District according to smoking status. Vigitel, Brazil, 2018

Food groups Ultra-processed foods	Never smoked (0)	Ex-smoker (1)	Smoker (2)	OR[a] (2/1)	P[b]	OR[a] (2/0)	P[b]
Soda		**P < 0.0001**[c]					
No	73.40	73.49	57.96	1		1	
Yes	26.60	26.51	42.04	1.77	**< 0.001**	2.00	**< 0.001**
Other sweetened beverages		**P < 0.0001**[c]					
No	75.16	72.79	66.04	1		1	
Yes	24.84	27.21	33.96	1.26	**0.047**	1.46	**< 0.001**
Sweetened milk-based beverages		**P = 0.0020**[c]					
No	72.55	75.48	78.52	1		1	
Yes	27.45	24.52	21.48	0.82	0.118	0.87	0.220
Chips/crisps/crackers		P = 0.4035[c]					
No	77.63	76.97	75.20	1		1	
Yes	22.37	23.03	24.80	1.01	0.905	1.02	0.866
Sauces/ready-semi-ready-to-eat products		**P < 0.0001**[c]					
No	77.71	76.82	69.21	1		1	
Yes	22.29	23.18	30.79	1.27	**0.046**	1.54	**< 0.001**
Margarine		**P = 0.0020**[c]					
No	55.63	55.33	48.29	1		1	
Yes	44.37	44.67	51.71	1.27	**0.019**	1.23	**0.027**
Sweets		P = 0.1890[c]					
No	56.87	59.80	58.52	1		1	
Yes	43.13	40.20	41.48	1.01	0.904	1.09	0.387
Processed meats		**P < 0.0001**[c]					
No	74.17	71.01	62.11	1		1	
Yes	25.83	28.99	37.89	1.31	**0.017**	1.63	**< 0.001**
Sandwich bread/hotdog or hamburger buns		P = 0.9532[c]					
No	64.50	64.56	65.11	1		1	
Yes	35.50	35.44	34.89	0.89	0.326	1.00	0.963

[a] Odds ratio (OR) controlled for age, sex, schooling, region of residence, and alcohol abuse; [b] P value from Wald's test; [c] P value from Pearson's chi-square test (Rao-Scott).

the price of cigarettes, the use of warning images on cigarette packs, and the banning of smoking in closed group environments.[19,20]

The prevalence of smokers was higher among men, individuals aged 40–59 years, those without a spouse, those with a lower level of schooling, those who did not possess a private health insurance plan, and those who resided in the southeastern region of Brazil. Similar findings have been reported in previous studies.[17,21] The 2019 National Health Survey also found that tobacco use was greater among men, individuals between 40 and 59 years of age, those with less schooling and a low income, Black and Brown individuals, and residents of the southern, central western, and southeastern regions.[18] Using data from the 2008–2009 Family Budget Survey (Pesquisa de Orçamentos Familiares - POF), Bazotti et al.[21] found that approximately 10% of the Brazilian population reported spending on tobacco products, substantially impacting the family budget.

Smokers reported lower consumption of fruits and natural fruit juices, and greater consumption of soda and artificial juice. Using data from the 2015 Vigitel survey, Francisco et al.[5] found that smokers had a greater likelihood (OR = 1.50; 95%CI: 1.20-1.87) of having an inadequate diet, which was evaluated using an indicator comprising foods considered to be protectors from chronic disease (fruits, raw and cooked vegetables, milk and beans) and risk foods (sweets, red meat, soda and other sweetened beverages). In the city of Belo Horizonte, Brazil, 24.8% of non-smokers and 36.9% of smokers had an unhealthy diet (OR = 1.82; 95%CI: 1.49-2.22) characterized by the frequent consumption of soda or artificial juice, red meat, and meat with excess fat as well less frequent consumption of fruits and vegetables.[8] Notably, no studies were found in the literature that explore the consumption of specific foods and beverages according to smoking status. The present investigation is also the first to determine a greater likelihood of consumption of ultra-processed foods among smokers.

Some studies have investigated nutrient intake and overall diet quality according to the smoking habit. Raatz et al.[9] compared the usual nutrient intake of smokers and non-smokers aged 18–70 years

in the United States and found a lower intake of energy, polyunsaturated fatty acids, linoleic acid, dietary fiber, calcium, iron, magnesium, potassium, phosphorus, vitamins A, C and E, riboflavin, niacin, pantothenic acid, pyridoxin and folate among smokers. In addition, studies have shown that smokers have higher levels of oxidative stress, which increases the importance of consuming healthy antioxidant foods.[22,23]

A population-based cross-sectional study conducted in Luxemburg with individuals aged 18–64 years detected a significant inverse association between overall diet quality and smoking intensity, measured by the quantity of cigarettes smoked per day. Lower diet quality scores were found for five of the eight indices evaluated in the study, revealing poorer diet quality among moderate and heavy smokers compared to non-smokers after controlling for age, sex, schooling, cardiovascular health indicators, physical activity, adiposity, and alcohol intake.[10] Compared to those who had never smoked, ex-smokers had lower intake of processed meats, refined grains, solid fats, added sugars, and alcohol.[10] In a study conducted in the city of São Paulo, Brazil, Andrade et al.[24] found poorer dietary quality in smokers based on an indicator composed of 12 components (nine food groups, two nutrients, and a component corresponding to the percentage of energy obtained from solid fats, alcohol, and added sugars).

The consumption of three or more glasses of natural fruit juice per day by smokers merits further attention. Evidence from a systematic review and meta-analysis indicated a statistically significant association between the consumption of fruit juice (without added sugars) and a greater risk of weight gain and insulin resistance detected using the HOMA-IR index.[25] Furthermore, international guidelines establish a maximum of 240 ml/day for adults.[26] Data from the individual food intake module of the 2008–2009 Family Budgets Survey revealed that 5.49% of total energy from the diet of the Brazilian population came from fruits, with an important part of this energy derived from juices (2.45%).[27] The consumption of fruit juices does not offer the same health benefits as consuming the whole fruit, since the extraction process reduces the fiber content, leads to loss of nutrients that are sensitive to light, oxygen, and heat, and generates a lower sensation of satiety.[27,28]

Robust evidence from a set of observational studies indicate a direct association between the consumption of ultra-processed foods and adverse health outcomes.[29] A randomized clinical trial showed that a diet rich in ultra-processed foods promotes gain in body weight.[30] The concomitance of smoking and consumption of ultra-processed foods is a risky combination, especially among men with a low level of schooling. These findings are consistent with those of other studies on poor dietary quality in this population.

To our knowledge, no existing study has specifically analyzed the consumption of different foods according to smoking status (smokers, ex-smokers, and non-smokers). Thus, the present results can contribute to future studies along this line. The Vigitel telephone survey involves a variety of questions on the frequency of consumption of foods considered markers of healthy and unhealthy diets, and on the use of cigarettes. Among the limitations related to the methods adopted by the Vigitel survey, the information reported by the participants regarding food consumption may have been subject to recall bias. Therefore, it was impossible to establish causal relationships because of the cross-sectional design of the study. Moreover, the sample of the Vigitel survey is restricted to individuals with a residential telephone line (landline) who reside in state capitals and the Federal District, which limits the representativeness of the findings. However, the use of weighting factors reduced this problem by equating the demographic characteristics of the sample with those of the adult population in Brazil.

CONCLUSION

The present study enabled us to outline the food consumption profile of smokers, who were found to have a lower weekly and daily frequency of fruit consumption and a greater frequency of soda or artificial juices consumption compared to ex-smokers and non-smokers. Attention is to be drawn to the high consumption of natural fruit juices (three or more glasses per day) among smokers. On the day prior to the interview, smokers reported a lower frequency of consumption of natural and minimally processed foods, such as fruits, milk, and tubers, as well as a greater frequency of ultra-processed foods, such as soda, fruit drinks, sauces, ready-to-eat products, margarine, and processed meats. These findings underscore the importance of promoting a healthy diet, especially among smokers, through strategies that consider concomitance of these risk behaviors.

REFERENCES

1. World Health Organization. Tobacco. Key facts. Genebra: World Health Organization; 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/tobacco. Accessed in 2022 (Nov. 26).
2. Pan American Health Organization. Strategy and Plan of Action to Strengthen Tobacco Control in the Region of the Americas 2018-2022. Washington, D.C: Pan American Health Organization; 2017. Available from: https://iris.paho.org/handle/10665.2/34441. Accessed in 2023 (May 17).
3. Pinto M, Bardach A, Palacios A, et al. Burden of smoking in Brazil and potential benefit of increasing taxes on cigarettes for the economy and for reducing morbidity and mortality. Cad Saude Pública. 2019;35(8):e00129118. PMID: 31483047; https://doi.org/10.1590/0102-311x00129118.
4. World Health Organization. Global status report on noncommunicable diseases 2010. Geneva: World Health Organization; 2011. Available from: https://apps.who.int/iris/handle/10665/44579. Accessed in 2023 (May 17).

5. Francisco PMSB, Assumpção D, Borim FSA, Senicato C, Malta DC. Prevalence and co-occurrence of modifiable risk factors in adults and older people. Rev Saúde Pública. 2019;53:86. PMID: 31644769; https://doi.org/10.11606/s1518-8787.2019053001142.
6. Francisco PMSB, Assumpção D, Malta DC. Co-occurrence of Smoking and Unhealthy Diet in the Brazilian Adult Population. Arq Bras Cardiol. 2019;113(4):699-709. PMID: 31691752; https://doi.org/10.5935/abc.20190222.
7. Malta DC, Felisbino-Mendes MS, Machado IE, et al. Risk factors related to the global burden of disease in Brazil and its Federated Units, 2015. Rev Bras Epidemiol. 2017;20(Suppl 1):217-32. PMID: 28658385; https://doi.org/10.1590/1980-5497201700050018.
8. Gomes CS, Silveira EA, Velasquez-Melendez G. Neighborhood environment is associated with unhealthy food intake in a Brazilian urban area. Appetite. 2022;172:105972. PMID: 35176434; https://doi.org/10.1016/j.appet.2022.105972.
9. Raatz SK, Jahns L, Johnson LK, et al. Smokers report lower intake of key nutrients than nonsmokers yet both fall short of meeting recommended intakes. Nutr Res. 2017;45:30-7. PMID: 29037329; https://doi.org/10.1016/j.nutres.2017.07.010.
10. Alkerwi A, Baydarlioglu B, Sauvageot N, et al. Smoking status is inversely associated with overall diet quality: Findings from the ORISCAV-LUX study. Clin Nutr. 2017;36(5):1275-82. PMID: 27595637; https://doi.org/10.1016/j.clnu.2016.08.013.
11. Doty RL, Chen JH, Overend J. Taste Quality Confusions: Influences of Age, Smoking, PTC Taster Status, and other Subject Characteristics. Perception. 2017;46(3-4):257-67. PMID: 28056649; https://doi.org/10.1177/0301006616685577.
12. Berube L, Duffy VB, Hayes JE, Hoffman HJ, Rawal S. Associations between chronic cigarette smoking and taste function: Results from the 2013-2014 national health and nutrition examination survey. Physiol Behav. 2021;240:113554. PMID: 34375623; https://doi.org/10.1016/j.physbeh.2021.113554.
13. Adams ML, Grandpre J, Katz DL, Shenson D. The impact of key modifiable risk factors on leading chronic conditions. Prev Med. 2019;120:113-8. PMID: 30658065; https://doi.org/10.1016/j.ypmed.2019.01.006.
14. Fliss-Isakov N, Zelber-Sagi S, Ivancovsky-Wajcman D, Shibolet O, Kariv R. Ultra-processed food intake and smoking interact in relation with colorectal adenomas. Nutrients. 2020;12(11):3507. PMID: 33202603; https://doi.org/10.3390/nu12113507.
15. Brasil. Vigitel Brasil 2018: vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico: estimativas sobre frequência e distribuição sociodemográfica de fatores de risco e proteção para doenças crônicas nas capitais dos 26 estados brasileiros e no Distrito Federal em 2018. Brasília: Ministério da Saúde, 2019. Available from: https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/svsa/vigitel/vigitel-brasil-2018.pdf/view. Accessed in 2023 (May 17).
16. Monteiro CA, Cannon G, Moubarac JC, et al. The UN Decade of Nutrition, the NOVA food classification and the trouble with ultra-processing. Public Health Nutr. 2018;21(1):5-17. PMID: 28322183; https://doi.org/10.1017/s1368980017000234.
17. Malta DC, Stopa SR, Santos MAS, et al. Evolution of tobacco use indicators according to telephone surveys, 2006-2014. Cad Saúde Pública. 2017;33(Suppl 3):e00134915. PMID: 28954056; https://doi.org/10.1590/0102-311x00134915.
18. Malta DC, Gomes CS, Andrade FMD, et al. Tobacco use, cessation, secondhand smoke and exposure to media about tobacco in Brazil: results of the National Health Survey 2013 and 2019. Rev Bras Epidemiol. 2021;24(suppl 2):e210006. PMID: 34910060; https://doi.org/10.1590/1980-549720210006.supl.2.
19. Portes LH, Machado CV, Turci SRB, et al. Tobacco control policies in brazil: a 30-year assessment. Ciên Saude Colet. 2018;23(6):1837-48. PMID: 29972492; https://doi.org/10.1590/1413-81232018236.05202018.
20. Instituto Nacional de Câncer José Alencar Gomes da Silva. Convenção-Quadro para Controle do Tabaco: texto oficial. Rio de Janeiro: INCA, 2015. Available from: https://www.inca.gov.br/publicacoes/livros/convencao-quadro-para-o-controle-do-tabaco-texto-oficial. Accessed in 2023 (May 17).
21. Bazotti A, Finokiet M, Conti IL, França MTA, Waquil PD. Smoking and poverty in Brazil: an analysis of the profile of the smoking population based on the 2008-09 Brazilian government Family Budget Survey. Cien Saude Colet. 2016;21(1):45-52. PMID: 26816162; https://doi.org/10.1590/1413-81232015211.16802014.
22. Karademirci M, Kutlu R, Kilinc I. Relationship between smoking and total antioxidant status, total oxidant status, oxidative stress index, vit C, vit E. Clin Respir J. 2018;12(6):2006-12. PMID: 29247592; https://doi.org/10.1111/crj.12757.
23. Ahmadkhaniha R, Yousefian F, Rastkari N. Impact of smoking on oxidant/antioxidant status and oxidative stress index levels in serum of the university students. J Environ Health Sci Eng. 2021;19(1):1043-6. PMID: 34150292; https://doi.org/10.1007/s40201-021-00669-y.
24. Andrade SC, Previdelli NA, Cesar CLG, Marchioni DML, Fisberg RM. Trends in diet quality among adolescents, adults and older adults: A population-based study. Prev Med Rep. 2016;4:391-6. PMID: 27547722; https://doi.org/10.1016/j.pmedr.2016.07.010.
25. Fardet A, Richonnet C, Mazur A. Association between consumption of fruit or processed fruit and chronic diseases and their risk factors: a systematic review of meta-analyses. Nutr Rev. 2019;77(6):376-87. PMID: 30995309; https://doi.org/10.1093/nutrit/nuz004.
26. Auerbach BJ, Dibey S, Vallila-Buchman P, Kratz M, Krieger J. Review of 100% fruit juice and chronic health conditions: implications for Sugar-Sweetened Beverage Policy. Adv Nutr. 2018;9(2):78-85. PMID: 29659683; https://doi.org/10.1093/advances/nmx006.
27. Costa JC, Canella DS, Martins APB, et al. Consumption of fruits and the association with ultra-processed food intake in Brazil in 2008-2009. Cien Saude Colet. 2021;26(4):1233-44. PMID: 33886753; https://doi.org/10.1590/1413-81232021264.07712019.

28. Brasil. Ministério da Saúde. Guia Alimentar para a População Brasileira. 2 Ed. Brasília-DF: Ministério da Saúde; 2014. Available from: https://bvsms.saude.gov.br/bvs/publicacoes/guia_alimentar_populacao_brasileira_2ed.pdf. Accessed in 2023 (May 17).
29. Pagliai G, Dinu M, Madarena MP, et al. Consumption of ultra-processed foods and health status: a systematic review and meta-analysis. Br J Nutr. 2021;125(3):308-18. PMID: 32792031; https://doi.org/10.1017/s0007114520002688.
30. Hall KD, Ayuketah A, Brychta R, et al. Ultra-processed diets cause excess calorie intake and weight gain: an inpatient randomized controlled trial of ad libitum food intake. Cell Metab. 2019;30(1):67-77.e3. PMID: 31105044; https://doi.org/10.1016/j.cmet.2019.05.008.

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Long-term complications and outcomes of therapeutic embolization of cerebral arteriovenous malformations: a systematic review

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ABSTRACT

BACKGROUND: Embolization is a promising treatment strategy for cerebral arteriovenous malformations (AVMs). However, consensus regarding the main complications or long-term outcomes of embolization in AVMs remains lacking.

OBJECTIVE: To characterize the most prevalent complications and long-term outcomes in patients with AVM undergoing therapeutic embolization.

DESIGN AND SETTING: This systematic review was conducted at the Federal University of Alagoas, Arapiraca, Brazil.

METHODS: This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria. Data were obtained from MEDLINE, PubMed, LILACS, and SciELO databases, which included the epidemiological profile of the population, characteristics of the proposed therapy, complications (hemorrhagic events and neurological deficits), and long-term outcomes (modified Rankin scale pre- and post-treatment, AVM recanalization, complete obliteration, and deaths).

RESULTS: Overall, the analysis included 34 articles (2,799 patients). Grade III Spetzler–Martin AVMs were observed in 34.2% of cases. Notably, 39.3% of patients underwent embolization combined with radiosurgery. The most frequently reported long-term complication was hemorrhage, which occurred in 8.7% of patients at a mean follow-up period of 58.6 months. Further, 6.3% of patients exhibited neurological deficits after an average of 34.7 months. Complete obliteration was achieved in 51.4% of the cases after a mean period of 36 months. Recanalization of AVMs was observed in 3.5% of patients. Long-term death occurred in 4.0% of patients.

CONCLUSION: Embolization of AVMs is an increasingly safe strategy with low long-term complications and satisfactory outcomes, especially in patients who have undergone combination therapies.

SYSTEMATIC REVIEW REGISTRATION: https://www.crd.york.ac.uk/prospero/ Registration number CRD42020204867.

NTRODUCTION

Cerebral arteriovenous malformations (AVMs) are anomalous communications between cerebral arteries and veins, a complex capillary network, resulting in an increased risk of intraparenchymal hemorrhage.[1] Other hemodynamic changes include venous hypertension, reversal of venous flow, and hypoperfusion of areas adjacent to the AVM.[2,3]

AVM is a rare condition, with an incidence of approximately one case per year per 100,000 people and 2–4% of the annual risk of hemorrhage, accounting for 5–25% of the mortality rate.[2-4] Neurological deficits occur in 10–50% of cases following the hemorrhage.[2-4] Notably, the risk of cerebral bleeding is higher in patients with previous bleeding and AVMs deeply located in the brain.[4]

Four therapeutic strategies are employed for AVMs. In some cases, conservative management can be adopted, with doctors and patients aware of the risk of bleeding and the appearance of other symptoms. The intervention options include microsurgical resection, radiosurgery, and therapeutic embolization, which can be used alone or in combination. Nevertheless, the risks and benefits of each therapeutic alternative must be assessed individually during patient assessment.[5-7]

Embolization stands out among treatment options. Currently, embolization can be used as a single therapeutic modality or as an adjunctive therapy to microsurgery or radiosurgery to block arterial blood flow in AVMs, thus reducing their size and high-risk characteristics.[8,9] However, this type of intervention can cause long-term complications, and outcomes vary among patients. The characterization of complications and outcomes can facilitate the selection of the best therapeutic intervention to achieve higher rates of complete obliteration and cure.

OBJECTIVE

This systematic review was aimed at analyzing the literature on the most prevalent long-term complications and outcomes in patients with AVMs undergoing therapeutic endovascular embolization.

METHODS

Articles search

This systematic review was performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and was registered in the PROSPERO—International Prospective Register of Systematic Reviews—under the registration number CRD42020204867. Two independent researchers searched for articles published from February to July 2020 in the electronic databases MEDLINE, PubMed, LILACS, and SciELO.

The keywords used for the research were "Intracranial Arteriovenous Malformations" and "Therapeutic Embolization" in conjunction with the Boolean operators AND and OR. Combinations were made using the same keywords, such as "Embolization, Therapeutic/Adverse Effects," "Embolization, Therapeutic/Epidemiology," "Embolization, Therapeutic/Rehabilitation," "Embolization, Therapeutic/Statistics and Numerical Data," "Intracranial Arteriovenous Malformations/Therapy," and "Intracranial Arteriovenous Malformations/Surgery." The following filters were used for the type of study: "Clinical Study," "Clinical Trial," "Observational Study," and "Randomized Controlled Trial." All keywords and filters were written in English, Spanish, and Portuguese. Notably, we did not identify any previous reviews on this topic.

Articles selection

Articles with an evaluation of at least one long-term outcome or complication in patients diagnosed with AVMs and treated with therapeutic embolization in isolation or combined with other therapeutic strategies (radiosurgery and/or microsurgery) were included in this review. The exclusion criteria were as follows: 1) studies describing other intracranial AVMs, such as cavernomas, developmental venous anomalies, Galen's vein malformations, and dural fistulas; 2) studies with no therapeutic embolization; 3) studies with a lack of evidence for long-term follow-up of patients; 4) studies that referred to short-term complications/outcomes (up to 30 days after treatment); 5) technical notes, experience reports, and literature reviews; and 6) publications in languages other than English, Portuguese, and Spanish.

The initial inclusion eligibility of identified studies was assessed by two independent authors based on the titles and abstracts. Subsequently, articles with titles and abstracts meeting the inclusion criteria were selected for further review. Thereafter, the same two authors read the full texts and selected eligible articles based on the inclusion and exclusion criteria. Any disagreements between the two authors were analyzed and resolved by a third or fourth author. The reference lists of the selected articles were revised to identify potentially relevant articles that were lost during online searches.

Data extraction

The data were initially extracted and typed on a spreadsheet by one author and confirmed by another author to ensure accuracy. The extracted data included: 1) population profile of each study (number of participants, age, sex, initial presentation, presence of aneurysms, and Spetzler–Martin scale); 2) characterization of the proposed therapy (type of embolizing material, number of embolizations, and approach used for embolization); 3) follow-up time and number of participants lost; 4) long-term complications and outcomes (intracranial hemorrhages, neurological deficits, recanalization of AVMs, effects of radiosurgery, complete obliteration, death, and other outcomes); 5) modified Rankin scale (mRs) score pre- and post-treatment.

Data synthesis and evaluation of study quality

Outcomes that occurred within and after 30 days following the therapeutic intervention were considered short- and long-term outcomes and complications, respectively. Descriptive statistics were employed to calculate the rates and averages for each study. Quality analysis of the selected studies was performed using the Newcastle–Ottawa Scale.[10] This scale has three domains: selection (maximum of four stars), comparability (maximum of two stars), and results (maximum of three stars). A study is considered to have strong evidence if it receives three or four, one or two, and two or three stars in the selection, comparability, and results domains, respectively. Moderate evidence is considered if a study receives two, one or two, and two or three stars in the selection, comparability, and results domains, respectively. Limited evidence is considered if a study receives zero or one, zero, and zero or one stars in the selection, comparability, and results domains, respectively.

RESULTS

We obtained 601 studies from the database searches (PubMed, 507; MEDLINE, 42; LILACS, 24; SciELO, 28). Another 22 articles were selected from the reference lists of the pre-selected studies. A total of 412 articles remained after eliminating the duplicates. Further, 338 articles were excluded based on titles and abstracts, leaving 93 articles for full-text reading. Of these, 58 articles that did not meet the inclusion criteria were excluded. Finally, 34 articles were included in this systematic review (5 case-control studies, 15 retrospective cohorts, and 14 prospective cohorts) (**Figure 1**). The quality analysis of each study included in this review is summarized in **Figure 2**.

The data of 2,799 patients with AVMs treated using embolization therapy alone or in combination with other treatments were assessed in this review. The mean age of patients was 32.3 years (range 9.7–44.2 years), and 52.2% were male and 47.8% were female (**Table 1**). The most prevalent clinical presentation was hemorrhage (42.6%), followed by headaches (32.4%), seizures (30.6%), and neurological deficits (12%). Notably, 116 (4.4%) asymptomatic patients at the time of admission were also identified from the selected studies. Patients also presented with more than one clinical presentation on admission. Additionally, other symptoms such as visual disturbances, weakness, speech disorders, and imbalance are also possible, as reported by Yang et al.[11] and Yang et al.[12]

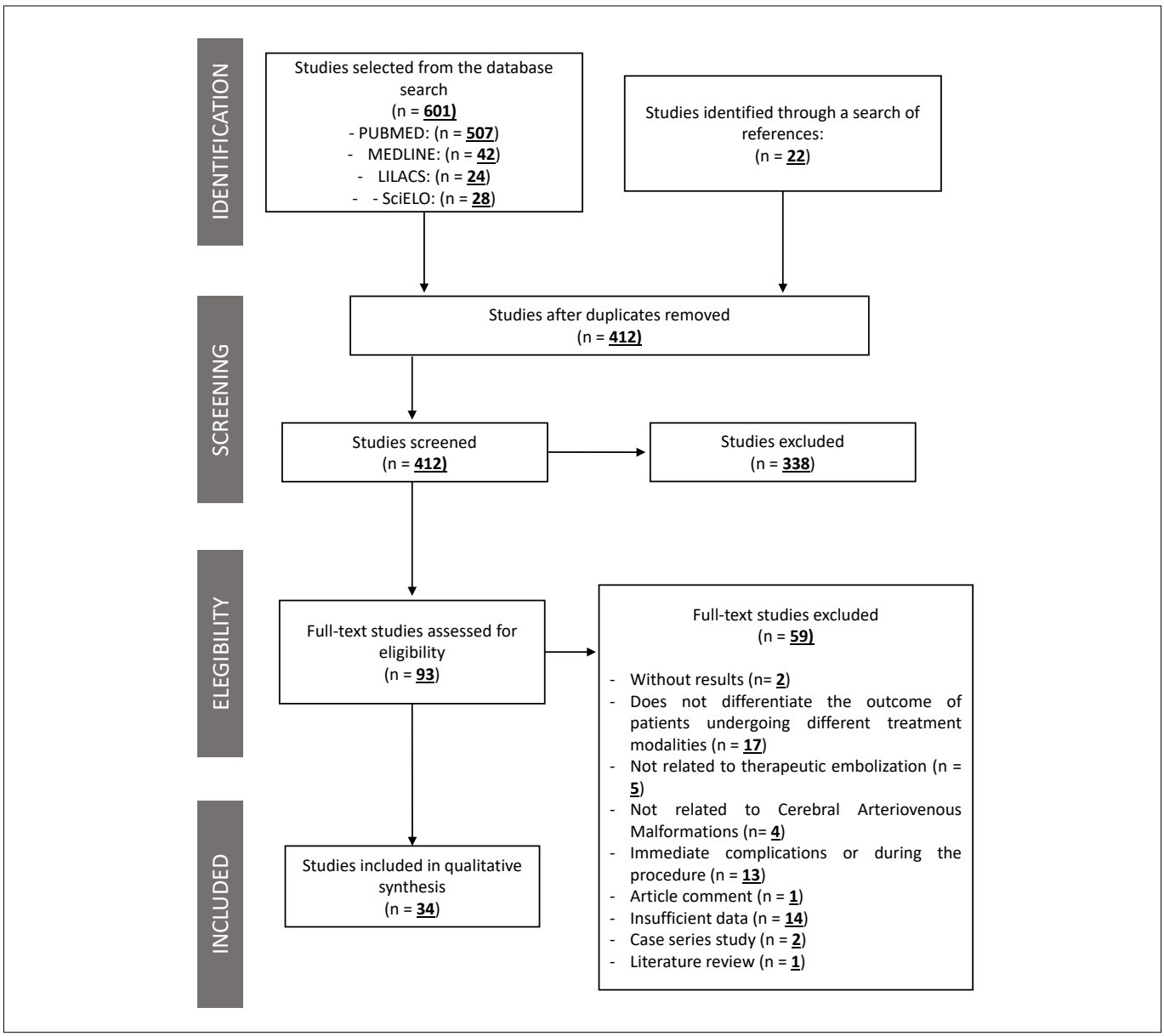

Figure 1. Flowchart from studies selection.

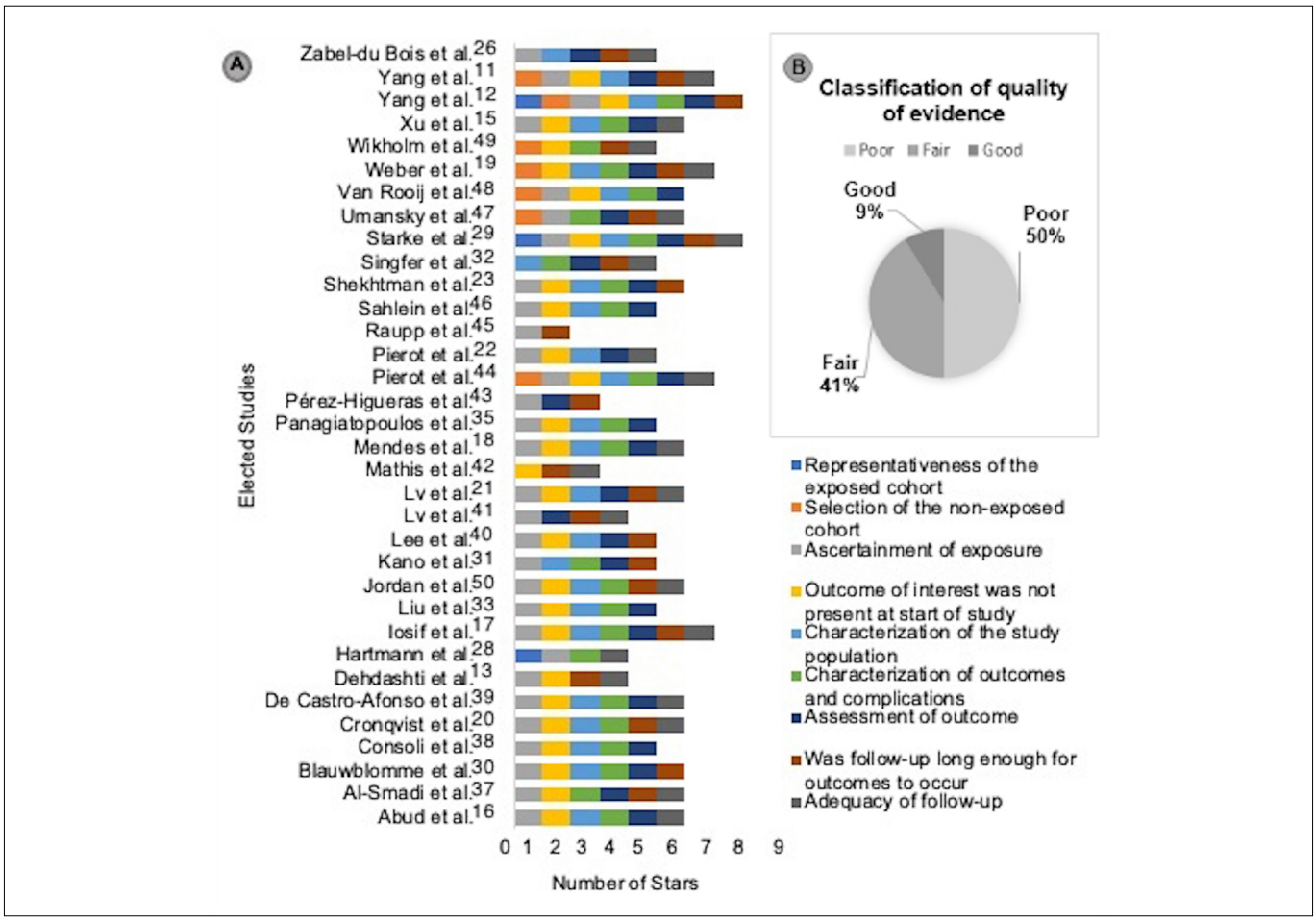

Figure 2. Assessment of methodological quality of studies using the Newcastle Ottawa Scale.

Of the selected articles, 13 provided information about the mRs score before treatment. Of the 1002 patients, 90.2% (n = 908) had a mRs score of 0–2. Further, 25 studies classified AVMs according to the Spetzler–Martin scale, with a total of 2,130 cases. Of these, 16.1% (n = 343), 30.8% (n = 656), 34.2% (n = 728), 15.5% (n = 331), 2.7% (n = 58), and 0.7% (n = 14) were grade I, II, III, IV, V, and VI Spetzler–Martin AVMs, respectively. Additionally, 16 studies (1,731 patients) reported the presence of aneurysms associated with AVMs, with a prevalence rate of 26.2% (n = 454). No information was collected regarding aneurysm characteristics (**Table 2**).

A total of 2,589 patients were treated in the reviewed studies. Of these, 37.1% (n = 961) underwent embolization alone, 39.3% (n = 1,017) underwent embolization and radiosurgery, and 23% (n = 594) underwent embolization and microsurgery. Only 17 patients (0.6%) underwent three combined strategies (embolization, radiosurgery, and microsurgery). Data of patients who were treated with the three therapies were presented only by Dehdashti et al.,[13] Singfer et al.,[14] Xu et al.,[15] and Yang et al.[12](**Table 2**).

The approach used for vascular access in therapeutic embolization was not specified in most studies. Of the studies that specified the approach, Abud et al.[16] and Iosif et al.[17] used an arterial approach, whereas Mendes et al.[18] and Weber et al.[19] used a combined arterial and venous approach. Twenty studies reported the use of Onyx as an embolic material, and seven studies used it in combination with other materials. Other embolic materials include N-butyl-2-cyanoacrylate, synthetic glue based on cyanoacrylate (Glubran), polyvinyl alcohol, and springs. Dehdashti et al.,[13] Yang et al.,[11] and Yang et al.[12] did not specify the type of material used for embolization. The average number of embolization sessions per patient was approximately two.

Analyzing long-term complications, 12 studies reported bleeding events with a prevalence of 8.7% (112/1,291 patients). The mean follow-up period in these 12 studies was 58.6 months. Cronqvist et al.,[20] Lv et al.,[21] and Pierot et al.[22] reported the variations in long-term complications during the follow-up period (**Table 3**). Fourteen studies reported neurological deficits as a long-term complication, and six did not specify the nature of the deficits. A total

Table 1. Characteristics of studies included in the systematic review and patients with cerebral arteriovenous malformations

Reference	Type of study	Characteristics of the patients			
		Number	Age (Years, mean)	Sex	
				M	F
Yang et al.[11]	Cohort (retrospective)	31	26.4	15	16
Yang et al.[12]	Cohort (retrospective)	420	35.0	180	240
Dehdashti et al.[13]	Case-control	135	36.0	70	65
Singfer et al.[14]	Cohort (retrospective)	61	38.0	32	29
Xu et al.[15]	Cohort (prospective)	86	30.3	51	35
Abud et al.[16]	Cohort (retrospective)	17	32.7	8	9
Iosif et al.[17]	Cohort (prospective)	73	40.5	45	28
Mendes et al.[18]	Cohort (prospective)	7	13.5	3	4
Weber et al.[19]	Cohort (retrospective)	47	36.0	31	16
Cronqvist et al.[20]	Cohort (prospective)	21	40.7	15	6
Lv et al.[21]	Cohort (retrospective)	144	27.9	92	52
Pierot et al.[22]	Cohort (retrospective)	20	33.2	9	11
Shekhtman et al.[23]	Case-control	40	32.1	24	16
Zabel-du Bois et al.[26]	Cohort (retrospective)	50	37.2	27	23
Hartmann et al.[28]	Cohort (prospective)	233	36.0	109	124
Starke et al.[29]	Cohort (prospective)	202	35.0	84	118
Blauwblomme et al.[30]	Cohort (prospective)	106	9.7	62	44
Kano et al.[31]	Case-control	120	33.0	61	59
Liu et al.[33]	Cohort (prospective)	31	32.6	19	12
Panagiatopoulos et al.[35]	Cohort (retrospective)	82	44.2	41	41
Al-Smadi et al.[37]	Cohort (retrospective)	34	10.6	22	12
Consoli et al.[38]	Cohort (prospective)	84	38.2	52	32
de Castro-Afonso et al.[39]	Cohort (retrospective)	23	11.7	11	12
Lee et al.[40]	Case-control	25	42.0	15	10
Lv et al.[41]	Cohort (retrospective)	30	31.0	22	8
Mathis et al.[42]	Cohort (prospective)	24	N/S	N/S	N/S
Pérez-Higueras et al.[43]	Cohort (prospective)	45	35.0	22	23
Pierot et al.[44]	Cohort (prospective)	117	42.6	72	45
Raupp et al.[45]	Cohort (prospective)	104	30.0	59	45
Sahlein et al.[46]	Cohort (retrospective)	130	34.2	64	66
Umansky et al.[47]	Cohort (retrospective)	12	N/S	N/S	N/S
van Rooij et al.[48]	Cohort (retrospective)	24	41.0	17	7
Wikholm et al.[49]	Cohort (prospective)	150	35.5	67	83
Jordan et al.[50]	Cohort (prospective)	71	N/S	41	30
Total		2,799	32.3	1,442 (52.2%)	1,321 (47.8%)

N/S = not specified; M = Male; F = Female.

of 81 neurological deficits were reported in 1,291 patients (6.3%). The mean follow-up period was 34.7 months. The most common deficits were hemiparesis, speech disorders (aphasia and dysarthria), visual disturbances (hemianopia and diplopia), ataxia, paresthesia, facial paralysis, permanent weakness in the right hand, and unilateral deafness (one case) (**Table 3**).

Twenty-three studies provided information on long-term obliteration/cure rates. Notably, 552 complete obliterations were reported in 1,071 patients (51.4%), with a mean duration of 36 months. Additionally, nine studies reported 36 long-term deaths in a population of 889 patients (4%). Of these, three studies reported that deaths occurred due to hemorrhagic events. The shortest follow-up time until death was 30 days, and the longest was 56.04 months (**Table 3**).

Data on long-term recanalization of AVMs were only described in five studies. A total of 231 patients were followed up, of whom eight cases of recanalization (3.5%) were identified. Of these, one was identified after 1 year of follow-up, whereas four were identified

Table 2. Clinical and angiographic profiles of patients with cerebral arteriovenous malformations

Variable	Subgroup	Number of studies	Total number of patients	Number of patients per subgroup	%
Initial clinical presentation	Asymptomatic	32	2,609	116	4.4%
	Hemorrhage	32	2,609	1,113	42.6%
	Neurological deficit	32	2,609	313	12.0%
	Headache	32	2,609	845	32.4%
	Seizure	32	2,609	799	30.6%
	Others	2	451	257*	57.0%
Modified Rankin scale score (mRs; pre-treatment)	mRs 0–2	13	1,002	908	90.6%
	mRs >2	13	1,002	94	9.4%
Angiographic presentation	Spetzler–Martin Grade I	25	2,130	343	16.1%
	Spetzler–Martin Grade II	25	2,130	656	30.8%
	Spetzler–Martin Grade III	25	2,130	728	34.2%
	Spetzler–Martin Grade IV	25	2,130	331	15.5%
	Spetzler–Martin Grade V	25	2,130	58	2.7%
	Presence of brain aneurysms	16	1,731	454	26.2%
Proposed treatment	Isolated embolization	34	2,589	961	37.1%
	Embolization + Radiosurgery	34	2,589	1017	39.3%
	Embolization + Microsurgery	34	2,589	594	23%
	Embolization + Radiosurgery + Microsurgery	34	2,589	17	0.6%

*Visual disturbances (82 cases), weakness (73 cases), speech disorders (67 cases), and imbalance (35 cases).

at an interval of 2.5–4 months. Additionally, other outcomes that did not fit our study variables, such as the long-term effects of radiosurgery, acute myocardial infarction, and memory impairment (eight patients), were also reported (**Table 3**).

DISCUSSION

Our study showed that AVMs generally affect young adults (30–40 years old) and are more prevalent in males. The most common clinical presentation was hemorrhage, followed by headaches, seizures, and focal neurological deficits. The patients selected for endovascular treatment, either alone or in combination, mostly had Spetzler–Martin grade II or III AVMs. The most frequent long-term complications were hemorrhagic events (8.7%) and neurological deficits (6.3%). In most studies, the follow-up time until the onset of these complications was >2 years. Notably, 51.4% of patients (552 of 1,071) achieved complete AVM obliteration after an average of 36 months of follow-up, whereas recanalization was identified in 3.5% patients (8 of 231). Finally, 4% of patients (36 of 889) died, mostly due to hemorrhagic events.

Long-term hemorrhagic events

The risk of long-term bleeding varies according to treatment type. Procedures that have a direct effect on AVMs, such as microsurgery and embolization, have a relatively short post-treatment bleeding latency period, varying from days to months. However, in radiosurgery, the latency period between the end of the procedure and hemorrhage can vary from 2 to 3 years.[12,23] The clinical presentation (with or without initial bleeding) also affects the risk of long-term bleeding. The risk of new hemorrhage in the first year is 6.5–32.9% in patients with a clinical presentation of hemorrhagic events (ruptured AVMs), whereas a lower risk of 0–3.6% is observed for patients without hemorrhage in the initial clinical presentation.[23,21,24,25]

Lv et al.[21] analyzed the bleeding rates in patients with AVMs after embolization alone or in combination and reported 20 long-term bleeding events, 11 of which involved hemorrhage at initial clinical presentation. Further, the mean follow-up time until the appearance of a bleeding event in the groups without and with bleeding at the initial presentation was 3.5 and 7.3 years, respectively.

Table 3. Long-term complications and outcomes of included patients in the systematic review

Complications and outcomes	Number of studies	Total number of patients	Patients per complications and outcome	%	Follow-up (months, mean)
Hemorrhagic events	12	1,291	112	8.7%	58.6
Neurological deficits	14	1,291	81*	6.3%	34.7
Complete obliteration/ cure	23	1,071	552	51.4%	36.0
Recanalization	5	231	8	3.5%	18.1
Death	9	889	36	4%	N/S
Modified Rankin scale (mRs) score 0–2 (post-treatment)	12	636	589	92.6%	N/S
Modified Rankin scale (mRs) score > 2 (post-treatment)	12	636	47	7.4%	N/S
Reference	**Other complications and outcomes**				
Dehdashti et al.[13]	Total improvement of headache after treatment: C = 28 patients (67%); CT = 8 patients (20%)				
Hartmann et al.[28]	Acute myocardial infarction (1 patient)				
Kano et al.[31]	Effects of radiosurgery (10 patients), approximately 7 months after treatment				
Lee et al.[40]	Effects of radiosurgery (11 patients), approximately 6 months after treatment				
Lv et al.[41]	Seizure control: excellent (21 patients), good (4 patients), fair (2 patients), and poor (3 patients)				
Wikholm et al.[49]	Impaired memory (8 patients), with a later improvement (4 patients)				
Zabel-du Bois et al.[26]	15/50 had visual deterioration or visual field changes before radiosurgery. Deficits were maintained in 87% of the cases, 1 patient resolved completely and 1 improved partially. Asymptomatic focal edema developed in 42% of patients 7.5 months after radiosurgery				
Shekhtman et al.[23]	Glasgow Outcome Scale score: 1 (2 patients), 2 (0), 3 (1 patient), 4 (12 patients) and 5 (15 patients)				

N/S = not specified; C = cases; CT = controls.

*Hemiparesis (15 cases), speech disorder (11 cases, including 4 aphasia, 3 dysarthria, and 4 unspecified cases), visual disturbance (10 cases, including 5 hemianopia, 2 diplopia, and 3 unspecified cases), ataxia (2 cases), paresthesia (2 cases), facial paralysis (2 cases), permanent weakness in the right hand (1 case), and unilateral deafness (1 case).

Zabel-du Bois et al.[26] identified six hemorrhagic events in a group of 50 patients who underwent embolization and radiosurgery, with an average time of 8.5 months. Further, they reported the lowest rate of obliteration after embolization in patients with hemorrhagic events.

Long-term neurological deficits

The literature indicates a 4–18% risk of permanent neurological deficit, which may vary according to the embolizing material, technique used, and AVM characteristics.[27] Hartmann et al.[28] reported a 14% permanent neurological deficit rate in a series of 233 cases and a total of 545 embolizations.

Pierot et al.,[22] in their retrospective cohort study, analyzed 20 patients who underwent 77 embolizations followed by radiosurgery, with Onyx as the embolizing material. Worsening of the neurological clinical presentation was reported in only one patient, with a pre-mRs score of 1 evolving to 2, and the overall neurological clinical results were classified as satisfactory.

Starke et al.[29] identified 19 patients with post-embolization neurological deficits (9 with a mRs score ≤ 2 and 10 with a mRs score > 2) among 202 patients who underwent embolization. After a mean follow-up of 43.4 months, five persistent neurological deficits were identified, which were equivalent to 1% of the procedures and 2% of the patients. The authors concluded that most neurological deficits were transient and that even moderate and severe deficits were likely to improve over time.

Complete obliteration and death

Recently, the role of endovascular therapy in the treatment of AVMs has improved. However, low cure rates (16–32.8%) have been reported using endovascular embolization as a single treatment modality, with mortality rates ranging from 0% to 7.5%. More recently, some studies reported an obliteration rate of ≥ 51% using Onyx, indicating advancement in the role of endovascular therapy in the treatment of AVMs.[30,28,23] Iosif et al.[17] reported a high cure rate (95%) in 73 patients with low-grade AVMs using Onyx as an embolizing agent within an

angiographic follow-up time of 12–18 months, indicating the superiority of therapeutic embolization to small-sized AVMs. However, randomized clinical trials are required to confirm the superiority of this therapeutic approach.

The factors that determine the success of endovascular therapy depend on the selection of AVM characteristics. Abud et al.,[16] in a series of 17 patients undergoing embolization to cure AVMs using Onyx as an embolizing agent, concluded that the success of embolization was dependent on small AVM size (1–3 cm), location other than in the brainstem or deep brain structures, with renal arteries easily accessible by a microcatheter with the possibility of reflux of 2–3 cm, and a clear location of the proximal parts of the drainage veins such that the operator recognizes the venous filling with Onyx in time.

The role of embolization in radiosurgery varies from occlusion of aneurysms to decreasing the volume of AVMs, decreasing the radiation doses to which the nidus needs to be exposed, and decreasing the amount of cerebral blood flow. However, the obliteration is slow to achieve. Kano et al.[31] described cure rates of 35%, 53%, 55%, and 59% at 3, 4, 5, and 10 years, respectively. Singfer et al.[32] reported a 77.2% cure rate after an average of 5 years of follow-up.

The cure rate also varies according to the embolization agent used. Liu et al.[33] evaluated the results of AVM embolization using Glubran 2 as an embolizing agent. Of the 31 patients who underwent embolization, 27 had an obliteration rate of 100%, whereas 4 had an obliteration rate of 90%–99%. The duration of clinical and angiographic follow-ups ranged from 3 to 6 months.

Recanalization of AVMs

Recanalization (or recurrence) of AVMs is defined as new radiological evidence or a new event, commonly hemorrhage, in a patient who underwent angiographic examination after treatment, indicating complete obliteration of the AVM nidus. The use of new treatment techniques has enabled lower recanalization rates and, consequently, less AVM recurrence.[34]

Panagiatopoulos et al.[35] reported complete obliteration in 20 patients and four AVM recurrences 2.5–4 months after embolization through angiographic examination among 80 patients (average of 1.45 embolizations per patient), using Onyx as an embolizing agent. Of the four recurrences, two were identified as minimal.

Other complications and long-term outcomes

Kano et al.[31] reported adverse effects related to radiosurgery, which were unrelated to previous embolization, in an average follow-up period of 7 months in 10 patients (8.3%). One patient required a surgical procedure because of cyst formation and cerebral edema 8 months after radiosurgery. Postoperatively, the same patient developed persistent aphasia and hemiparesis.

Valavanis et al.,[36] in their study including 1,114 patients, reported the development of amyotrophic lateral sclerosis (ALS) in seven patients after an average follow-up of 132 months. Notably, the low production of vascular endothelial growth factors by AVMs with significant angiogenesis, possibly due to several embolization procedures, may contribute to the development of ALS.

Shekhtman et al.,[23] in their case-control study, compared the outcomes of patients who underwent embolization and microsurgery (n = 40) with those who underwent microsurgery alone (n = 40). Long-term outcomes were assessed in 30 patients who underwent embolization and microsurgery using the Glasgow Outcome Score (GOS), with an average follow-up time of 27.6 months. Of these, 2, 0, 1, 12, and 15 patients had GOS 1, 2, 3, 4, and 5, respectively. Of the 40 patients that underwent microsurgery only, 1, 2, 0, 19, and 18 had GOS 1, 2, 4, and 5, respectively.

Study limitations

All studies included in this review were cohort or case-control studies with inherent limitations of observational studies, such as selection bias, sample size, and losses during follow-up. Most of the studies included in this review were hospital-based studies in single centers, increasing the risk of bias and limiting the representativeness of the data. In addition, the generalizability of the results was limited owing to the limitations in the selection of cases and controls. Notably, only a few studies selected for this review had a control group, and the follow-up period was small.

Although most of the included studies used current techniques, studies conducted in the 1990s and early 2000s were limited by the lack of technological advances in endovascular therapy, introduction of catheters, and development of new embolic agents. Finally, the outcomes may be influenced by the heterogeneity of the studies in terms of evaluation methods and follow-up protocols. Consequently, multicenter and randomized studies involving a larger sample size, with sufficiently long follow-up periods are crucial to overcome these limitations.

CONCLUSIONS

Embolization of AVMs is a therapeutic strategy exhibiting greater safety in microsurgical or radiosurgical treatment, with high cure rates depending on the characteristics of the AVMs, technique, and resources used during the endovascular procedure. Further, long-term complications are low, and outcomes are considered positive, especially in patients who undergo combination therapies.

REFERENCES

1. Finby N, Begg CF. Arteriovenous malformation of the brain. N Y State J Med. 1965;65:554-8. PMID: 14276301.
2. Mast H, Young WL, Koennecke HC, et al. Risk of spontaneous haemorrhage after diagnosis of cerebral arteriovenous malformation. Lancet.

1997;350(9084):1065-8. PMID: 10213548; https://doi.org/10.1016/s0140-6736(97)05390-7.

3. Laakso A, Hernesniemi J. Arteriovenous malformations: epidemiology and clinical presentation. Neurosurg Clin N Am. 2012;23(1):1-6. PMID: 2210785; https://doi.org/10.1016/j.nec.2011.09.012.
4. Galaktionov DM, Dubovoy AV, Kiselev VS, et al. Kombinirovannoe lechenie arteriovenoznykh mal'formatsiĭ golovnogo mozga s ispol'zovaniem éndovaskuliarnogo i mikrokhirurgicheskogo metodov [Combination treatment of cerebral arteriovenous malformations using endovascular and microsurgical techniques]. Zh Vopr Neirokhir Im N N Burdenko. 2017;81(4):26-32. PMID: 28914868; https://doi.org/10.17116/neiro201781426-32.
5. van Beijnum J, van der Worp HB, Buis DR, et al. Treatment of brain arteriovenous malformations: a systematic review and meta-analysis. JAMA. 2011;306(18):2011-9. PMID: 22068993; https://doi.org/10.1001/jama.2011.1632.
6. Zuurbier SM, Al-Shahi Salman R. Interventions for treating brain arteriovenous malformations in adults. Cochrane Database Syst Rev. 2019;9(9):CD003436. PMID: 31503327; https://doi.org/10.1002/14651858.CD003436.pub4.
7. Mohr JP, Parides MK, Stapf C, et al. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. Lancet. 2014;383(9917):614-21. PMID: 24268105; https://doi.org/10.1016/S0140-6736(13)62302-8.
8. Ogilvy CS, Stieg PE, Awad I, et al. Recommendations for the management of intracranial arteriovenous malformations: a statement for healthcare professionals from a special writing group of the Stroke Council, American Stroke Association. Circulation. 2001;103(21):2644-57. PMID: 11382737; https://doi.org/10.1161/01.cir.103.21.2644.
9. Bendok BR, El Tecle NE, El Ahmadieh TY, et al. Advances and innovations in brain arteriovenous malformation surgery. Neurosurgery. 2014;74 Suppl 1:S60-73. PMID: 24402494; https://doi.org/10.1227/NEU.0000000000000230.
10. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. 2013. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed in 2022 (Nov 16).
11. Yang W, Wei Z, Wang JY, et al. Long-term Outcomes of Patients With Giant Intracranial Arteriovenous Malformations. Neurosurgery. 2016;79(1):116-24. PMID: 26695091; https://doi.org/10.1227/NEU.0000000000001189.
12. Yang W, Hung AL, Caplan JM, et al. Delayed Hemorrhage After Treatment of Brain Arteriovenous Malformations (AVMs). World Neurosurg. 2016;87:98-109. PMID: 26704216; https://doi.org/10.1016/j.wneu.2015.11.057.
13. Dehdashti AR, Thines L, Willinsky RA, et al. Multidisciplinary care of occipital arteriovenous malformations: effect on nonhemorrhagic headache, vision, and outcome in a series of 135 patients. J Neurosurg. 2010;113(4):742-8. PMID: 20059323; https://doi.org/10.3171/2009.11.JNS09884.
14. Singfer U, Hemelsoet D, Vanlangenhove P, et al. Unruptured Brain Arteriovenous Malformations: Primary ONYX Embolization in ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations)-Eligible Patients. Stroke. 2017;48(12):3393-6. PMID: 29114088; https://doi.org/10.1161/STROKEAHA.117.018605.
15. Xu F, Ni W, Liao Y, et al. Onyx embolization for the treatment of brain arteriovenous malformations. Acta Neurochir (Wien). 2011;153(4):869-78. PMID: 21046174; https://doi.org/10.1007/s00701-010-0848-6.
16. Abud DG, Riva R, Nakiri GS, et al. Treatment of brain arteriovenous malformations by double arterial catheterization with simultaneous injection of Onyx: retrospective series of 17 patients. AJNR Am J Neuroradiol. 2011;32(1):152-8. PMID: 20966066; https://doi.org/10.3174/ajnr.A2247.
17. Iosif C, de Lucena AF, Abreu-Mattos LG, et al. Curative endovascular treatment for low-grade Spetzler-Martin brain arteriovenous malformations: a single-center prospective study. J Neurointerv Surg. 2019;11(7):699-705. PMID: 30602485; https://doi.org/10.1136/neurintsurg-2018-014390.
18. Mendes GA, Iosif C, Silveira EP, et al. Transvenous Embolization in Pediatric Plexiform Arteriovenous Malformations. Neurosurgery. 2016;78(3):458-65. PMID: 26457485; https://doi.org/10.1227/NEU.0000000000001057.
19. Weber W, Kis B, Siekmann R, et al. Preoperative embolization of intracranial arteriovenous malformations with Onyx. Neurosurgery. 2007;61(2):244-52; discussion 252-4 PMID: 17762736; https://doi.org/10.1227/01.NEU.0000255473.60505.84.
20. Cronqvist M, Wirestam R, Ramgren B, et al. Endovascular treatment of intracerebral arteriovenous malformations: procedural safety, complications, and results evaluated by MR imaging, including diffusion and perfusion imaging. AJNR Am J Neuroradiol. 2006;27(1):162-76. PMID: 16418378.
21. Lv X, Wu Z, Jiang C, et al. Endovascular treatment accounts for a change in brain arteriovenous malformation natural history risk. Interv Neuroradiol. 2010;16(2):127-32. PMID: 20642886; https://doi.org/10.1177/159101991001600203.
22. Pierot L, Kadziolka K, Litré F, Rousseaux P. Combined treatment of brain AVMs with use of Onyx embolization followed by radiosurgery. AJNR Am J Neuroradiol. 2013;34(7):1395-400. PMID: 23391837; https://doi.org/10.3174/ajnr.A3409.
23. Shekhtman OD, Maryashev SA, Eliava SS, et al. Combined treatment of cerebral arteriovenous malformations. Experience of the Burdenko Neurosurgical Institute. Zh Vopr Neirokhir Im N N Burdenko. 2015;79(4):4-18. PMID: 26529618; https://doi.org/10.17116/neiro20157944-18.
24. da Costa L, Wallace MC, Ter Brugge KG, et al. The natural history and predictive features of hemorrhage from brain arteriovenous malformations. Stroke. 2009;40(1):100-5. PMID: 19008469; https://doi.org/10.1161/STROKEAHA.108.524678.
25. Halim AX, Johnston SC, Singh V, et al. Longitudinal risk of intracranial hemorrhage in patients with arteriovenous malformation of the brain within a defined population. Stroke. 2004;35(7):1697-702. PMID: 15166396; https://doi.org/10.1161/01.STR.0000130988.44824.29.

26. Zabel-du Bois A, Milker-Zabel S, Huber P, Schlegel W, Debus J. Risk of hemorrhage and obliteration rates of LINAC-based radiosurgery for cerebral arteriovenous malformations treated after prior partial embolization. Int J Radiat Oncol Biol Phys. 2007;68(4):999-1003. PMID: 17398029; https://doi.org/10.1016/j.ijrobp.2007.01.027.
27. Choi JH, Mohr JP. Brain arteriovenous malformations in adults. Lancet Neurol. 2005;4(5):299-308. PMID: 15847843; https://doi.org/10.1016/S1474-4422(05)70073-9.
28. Hartmann A, Pile-Spellman J, Stapf C, et al. Risk of endovascular treatment of brain arteriovenous malformations. Stroke. 2002;33(7):1816-20. PMID: 12105359; https://doi.org/10.1161/01.str.0000020123.80940.b2.
29. Starke RM, Komotar RJ, Otten ML, et al. Adjuvant embolization with N-butyl cyanoacrylate in the treatment of cerebral arteriovenous malformations: outcomes, complications, and predictors of neurologic deficits. Stroke. 2009;40(8):2783-90. PMID: 19478232; https://doi.org/10.1161/STROKEAHA.108.539775. 24
30. Blauwblomme T, Bourgeois M, Meyer P, et al. Long-term outcome of 106 consecutive pediatric ruptured brain arteriovenous malformations after combined treatment. Stroke. 2014;45(6):1664-71. PMID: 24788975; https://doi.org/10.1161/STROKEAHA.113.004292.
31. Kano H, Kondziolka D, Flickinger JC, et al. Stereotactic radiosurgery for arteriovenous malformations after embolization: a case-control study. J Neurosurg. 2012;117(2):265-75. PMID: 22631689; https://doi.org/10.3171/2012.4.JNS111935.
32. Singfer U, Hemelsoet D, Vanlangenhove P, et al. Unruptured Brain Arteriovenous Malformations: Primary ONYX Embolization in ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations)-Eligible Patients. Stroke. 2017;48(12):3393-6. PMID: 29114088; https://doi.org/10.1161/STROKEAHA.117.018605.
33. Liu J, Lv M, Lv X, et al. Curative glubran 2 embolization of cerebral arteriovenous malformations patient selection and initial results. Interv Neuroradiol. 2014;20(6):722-8. PMID: 25496682; https://doi.org/10.15274/INR-2014-10063.
34. Aboukaïs R, Vinchon M, Quidet M, et al. Reappearance of arteriovenous malformations after complete resection of ruptured arteriovenous malformations: true recurrence or false-negative early postoperative imaging result? J Neurosurg. 2017;126(4):1088-93. PMID: 27231973; https://doi.org/10.3171/2016.3.JNS152846.
35. Panagiotopoulos V, Gizewski E, Asgari S, et al. Embolization of intracranial arteriovenous malformations with ethylene-vinyl alcohol copolymer (Onyx). AJNR Am J Neuroradiol. 2009;30(1):99-106. PMID: 18842759; https://doi.org/10.3174/ajnr.A1314.
36. Valavanis A, Schwarz U, Baumann CR, Weller M, Linnebank M. Amyotrophic lateral sclerosis after embolization of cerebral arterioveneous malformations. J Neurol. 2014;261(4):732-7. PMID: 24509642; https://doi.org/10.1007/s00415-014-7260-8.
37. Al-Smadi AS, Ansari SA, Shokuhfar T, et al. Safety and outcome of combined endovascular and surgical management of low grade cerebral arteriovenous malformations in children compared to surgery alone. Eur J Radiol. 2019;116:8-13. PMID: 31153578; https://doi.org/10.1016/j.ejrad.2019.02.016.
38. Consoli A, Scarpini G, Rosi A, et al. Endovascular treatment of unruptured and ruptured brain arteriovenous malformations with Onyx18: a monocentric series of 84 patients. J Neurointerv Surg. 2014;6(8):600-6. PMID: 24126640; https://doi.org/10.1136/neurintsurg-2013-010869.
39. de Castro-Afonso LH, Nakiri GS, Oliveira RS, et al. Curative embolization of pediatric intracranial arteriovenous malformations using Onyx: the role of new embolization techniques on patient outcomes. Neuroradiology. 2016;58(6):585-94. PMID: 26909692; https://doi.org/10.1007/s00234-016-1666-1.
40. Lee CC, Chen CJ, Ball B, et al. Stereotactic radiosurgery for arteriovenous malformations after Onyx embolization: a case-control study. J Neurosurg. 2015;123(1):126-35. PMID: 25658780; https://doi.org/10.3171/2014.12.JNS141437.
41. Lv X, Li Y, Jiang C, Yang X, Wu Z. Brain arteriovenous malformations and endovascular treatment: effect on seizures. Interv Neuroradiol. 2010;16(1):39-45. PMID: 20377978; https://doi.org/10.1177/159101991001600105.
42. Mathis JA, Barr JD, Horton JA, et al. The efficacy of particulate embolization combined with stereotactic radiosurgery for treatment of large arteriovenous malformations of the brain. AJNR Am J Neuroradiol. 1995;16(2):299-306. PMID: 7726076.
43. Pérez-Higueras A, López RR, Tapia DQ. Endovascular Treatment of Cerebral AVM: Our Experience with Onyx. Interv Neuroradiol. 2005;11(Suppl 1):141-57. PMID: 20584469; https://doi.org/10.1177/15910199050110S118.
44. Pierot L, Cognard C, Herbreteau D, et al. Endovascular treatment of brain arteriovenous malformations using a liquid embolic agent: results of a prospective, multicentre study (BRAVO). Eur Radiol. 2013;23(10):2838-45. PMID: 23652849; https://doi.org/10.1007/s00330-013-2870-6.
45. Raupp EF, Fernandes J. Does treatment with N-butyl cyanoacrylate embolization protect against hemorrhage in cerebral arteriovenous malformations? Arq Neuropsiquiatr. 2005;63(1):34-9. PMID: 15830062; https://doi.org/10.1590/s0004-282x2005000100007.
46. Sahlein DH, Mora P, Becske T, Nelson PK. Nidal embolization of brain arteriovenous malformations: rates of cure, partial embolization, and clinical outcome. J Neurosurg. 2012;117(1):65-77. PMID: 22540403; https://doi.org/10.3171/2012.3.JNS111405.
47. Umansky D, Corn BW, Strauss I, et al. Combined treatment approach to cerebral arteriovenous malformation in pediatric patients: stereotactic radiosurgery to partially Onyx-embolized AVM. Childs Nerv Syst. 2018;34(11):2269-74. PMID: 29882061; https://doi.org/10.1007/s00381-018-3854-2.
48. van Rooij WJ, Jacobs S, Sluzewski M, et al. Curative embolization of brain arteriovenous malformations with onyx: patient selection, embolization technique, and results. AJNR Am J Neuroradiol. 2012;33(7):1299-304. PMID: 22383233; https://doi.org/10.3174/ajnr.A2947.

49. Wikholm G, Lundqvist C, Svendsen P. The Göteborg cohort of embolized cerebral arteriovenous malformations: a 6-year follow-up. Neurosurgery. 2001;49(4):799-805; discussion 805-6. PMID: 11564239; https://doi.org/10.1097/00006123-200110000-00004.
50. Jordan J, Llibre JC, Vazquez F. Predictors of neurological deficit after endovascular treatment of cerebral arteriovenous malformations and functional repercussions in prospective follow-up. Neuroradiol J. 2014;27(6):718-24. PMID: 25489896; https://doi.org/10.15274/NRJ-2014-10095.

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Emicizumab prophylaxis in people with hemophilia A and inhibitors: a systematic review and meta-analysis

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ABSTRACT

BACKGROUND: Until recently, the treatment of people with hemophilia A and inhibitors (PwHAi) was based on the use of bypassing agents (BPA). However, the advent of emicizumab as prophylaxis has demonstrated promising results.

OBJECTIVES: We aimed to compare the bleeding endpoints between PwHAi on BPA and those on emicizumab prophylaxis.

DESIGN AND SETTING: Systematic review of interventions and meta-analysis conducted at the Universidade Federal de Goiás, Goiânia, Goiás, Brazil.

METHODS: The CENTRAL, MEDLINE, Scopus, and LILACS databases were searched on February 21, 2023. Two authors conducted the literature search, publication selection, and data extraction. The selected publications evaluated the bleeding endpoints between PwHAi on emicizumab prophylaxis and those on BPA prophylaxis. The risk of bias was evaluated according to the Joanna Briggs Institute criteria. A meta-analysis was performed to determine the annualized bleeding rate (ABR) for treated bleeds.

RESULTS: Five publications (56 PwHAi) were selected from the 543 retrieved records. Overall, bleeding endpoints were lower during emicizumab prophylaxis than during BPA prophylaxis. All the publications had at least one risk of bias. The only common parameter for the meta-analysis was the ABR for treated bleeds. During emicizumab prophylaxis, the ABR for treated bleeds was lower than during BPA prophylaxis (standard mean difference: −1.58; 95% confidence interval −2.50, −0.66, P = 0.0008; I^2 = 68.4%, P = 0.0031).

CONCLUSION: Emicizumab was superior to BPA in bleeding prophylaxis in PwHAi. However, both the small population size and potential risk of bias should be considered when evaluating these results.

SYSTEMATIC REVIEW REGISTRATION: CRD42021278726, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=278726.

INTRODUCTION

Hemophilia A (HA) is an X-linked recessive bleeding disorder characterized by reduced or absent coagulation factor (F) VIII activity.[1] The clinical presentation depends on residual FVIII activity. Mild HA (FVIII 5%–40%) is characterized by increased bleeds mainly during surgery or after trauma, whereas severe HA (FVIII < 1%) is characterized by both spontaneous and provoked bleeds.[1] Moderate HA (1%–5%) has a wide phenotype, depending on the residual FVIII activity.[1] Bleeds occur mainly in joints, although they may also occur in vital organs.[1] Consequently, joint bleeds lead to arthropathy and worsen quality of life.[1]

The most effective therapy to prevent bleeds among people with HA (PwHA) is the regular use (prophylaxis) of FVIII replacement, although episodic infusions may still be required to treat breakthrough bleeds (episodic treatment).[2] However, some PwHA develop FVIII inhibitors, which are alloantibodies that neutralize the clotting activity of FVIII.[2,3] This occurs in approximately 20%–30% of severe and 5%–10% of moderate/mild PwHA.[1] Consequently, as PwHA and inhibitors (PwHAi) present higher mortality and morbidity than PwHA without inhibitors,[4,5] they experience decreased social and emotional functioning, physical pain/discomfort, and arthropathy.[6]

To revert these outcomes, immune tolerance induction (ITI) is indicated.[7] ITI comprises the administration of repeated doses of FVIII to eradicate inhibitors.[7] Nonetheless, this treatment is unsuccessful in approximately 30%–40% of PwHAi, who will ultimately require bypassing agents (BPA) for both prophylactic and episodic treatments.[7] The current available BPA are activated prothrombin

complex concentrate (aPCC) and recombinant activated FVII (rFVIIa).[8] They have similar effectiveness as prophylactic or episodic therapeutics.[9]

However, this scenario has changed since the advent of emicizumab, a humanized, bispecific monoclonal antibody. Emicizumab acts as a FVIII-mimetic agent, linking to the activated FIX (FIXa) and FX to reestablish the coagulation process.[10] In addition, since the structure of emicizumab has no homology with FVIII, it is not neutralized by the anti-FVIII inhibitors.[11] Finally, compared with BPA prophylaxis, emicizumab prophylaxis has demonstrated promising results in some publications.[12-15] Further potential benefits are its bioavailability after subcutaneous administration and its increased half-life, which demands weekly or even monthly infusions.[10] Despite the apparent advantages, no systematic review has analyzed its actual benefits as prophylaxis for PwHAi compared with BPA prophylaxis.

OBJECTIVE

We conducted a systematic review and meta-analysis to compare bleeding endpoints between PwHAi on emicizumab and those on BPA prophylaxis.

METHODS

Protocol and registration

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021278726). We conducted the systematic review according to the Cochrane recommendations[16] and reported it according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (**Supplementary Table 1**).[17] The research question was "Is emicizumab prophylaxis effective at reducing the bleeding endpoints among PwHAi when compared with BPA prophylaxis?".

Literature search

A literature search was performed by two authors on February 21, 2023. Specific search strategies were used for each of the following databases: Cochrane Central Register of Controlled Trials (CENTRAL); Medical Literature Analysis and Retrieval System Online (MEDLINE) via PubMed; Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS; in English, Latin-American, and Caribbean Center on Health Sciences Information); and Scopus (**Table 1**). In addition, we manually searched the reference lists of published reviews retrieved from MEDLINE to obtain additional publications that met the eligibility criteria. We also accessed the ClinicalTrials platform (www.clinicaltrials.gov) on February 21, 2023, using "hemophilia A with inhibitor" in the "condition or disease" section and "emicizumab" in the "other terms" section, to detect registered studies and used their identification numbers to search for potential missing publications.

Inclusion and exclusion criteria

The included publications presented information on the bleeding endpoints among PwHAi on emicizumab prophylaxis compared to those on BPA prophylaxis. Randomized and nonrandomized controlled trials, as well as observational studies were included. No restrictions on the publication date or language were applied. Publications were excluded for the following reasons: absence of bleeding evaluation; lack of data on emicizumab prophylaxis; publication type other than original article (for example, reviews or posters); absence of discrimination between data on PwHAi and PwHA without inhibitors; existence of a more recent publication with the same population; or absence of PwHAi on BPA prophylaxis.

Publication selection

The web-based app Rayyan (https://www.rayyan.ai/) was used in the screening process.[18] After the exclusion of duplicates, titles and abstracts were independently screened according to the inclusion criteria by two authors. Subsequently, publications that potentially fit the inclusion criteria were read entirely by the two authors to decide on inclusion in the systematic review. Discussions on contrasting selection results were conducted by

Table 1. Search strategies in each platform (February 21, 2023)

Platform	Search strategy	Number of publications
CENTRAL	(((((hemophilia) OR (haemophilia)) OR (factor VIII)) OR (FVIII)) AND (((inhibitor) OR (anti-factor VIII)) OR (anti-FVIII))) AND (((emicizumab) OR (ACE910)) OR (hemlibra))	30
MEDLINE	("hemophilia A") OR ("haemophilia A") AND (emicizumab OR hemlibra OR ACE910) AND (inhibitor OR anti-FVIII OR anti-factor VIII)	318
LILACS	"hemophilia A" OR "haemophilia A" [Words] and emicizumab OR hemlibra OR ACE910 [Words] and inhibitor OR anti-FVIII OR anti-factor VIII [Words]	01
Scopus	((hemophilia OR haemophilia OR factor AND viii OR fviii) AND (inhibitor OR "anti-factor viii" OR "anti-fviii") AND (emicizumab OR ace910 OR hemlibra)) AND (LIMIT-TO (DOCTYPE , "ar"))	194

Table legend: CENTRAL = Cochrane Central Register of Controlled Trials; MEDLINE = Medical Literature Analysis and Retrieval System Online; LILACS = Literatura Latino-Americana e do Caribe em Ciências da Saúde.

the coordinators. We contacted the authors of publications that did not contain the information required for inclusion, specifically requesting lacking data. If such data were not provided, the publication was excluded.

Data extraction

Data were extracted from the publications selected for the systematic review by two authors using a standardized form. This file contains information on the authors of the publication, study design, country(ies) where the studies were conducted, population size, population characteristics (age, sex, disease severity, and inhibitor titer), emicizumab/BPA regimens, and adverse events (AEs). Moreover, we collected information on bleeding endpoints as the main outcome of this systematic review.

Risk of bias assessment

The risk of bias was assessed by two authors using the Joanna Briggs Institute (JBI) critical appraisal checklists for quasi-experimental trials, randomized controlled trials, and cohort studies.[19] Following the JBI guidelines, we did not define cut-off values for categorizing the publications as having low, moderate, or high risk of bias[19]. Conversely, we presented the overall risk of bias for each domain.

Publication bias was not assessed owing to the small number of publications included in this systematic review.

Meta-analysis

The main outcome analyzed was the annualized bleeding rate (ABR) for treated bleeds. Initially, we calculated the mean and standard deviation (SD) of the study samples based on the median and range according to the methodology described by Hozo et al.[20] Heterogeneity between studies was evaluated using the I^2 statistic. I^2 values of 60%–100%, 40%–59%, and 0%–39% indicated high, moderate, and low heterogeneity, respectively.[21] We also used the Cochran's *Q* test was used to verify the heterogeneity between the selected studies.[22] The null hypothesis was that all studies were identical. Next, random- or fixed-effects models were used to analyze the magnitude of effect on ABR for treated bleeds after intervention implementation, when study heterogeneity was high (≥ 50%). A meta-analysis was conducted for all pooled studies that evaluated the emicizumab maintenance regimen of 1.5 mg/kg weekly according to the type of study (controlled trials and cohort) as subgroups. Statistical inference was performed using the Student's *t* test. The effect size was presented as the standardized mean difference for the pre-post studies with the respective 95% confidence interval (95%CI). Forest plots were generated to visualize the results. Analyses were conducted using the R software version 4.1.3 (R Core Team, Vienna, Austria).[23]

RESULTS

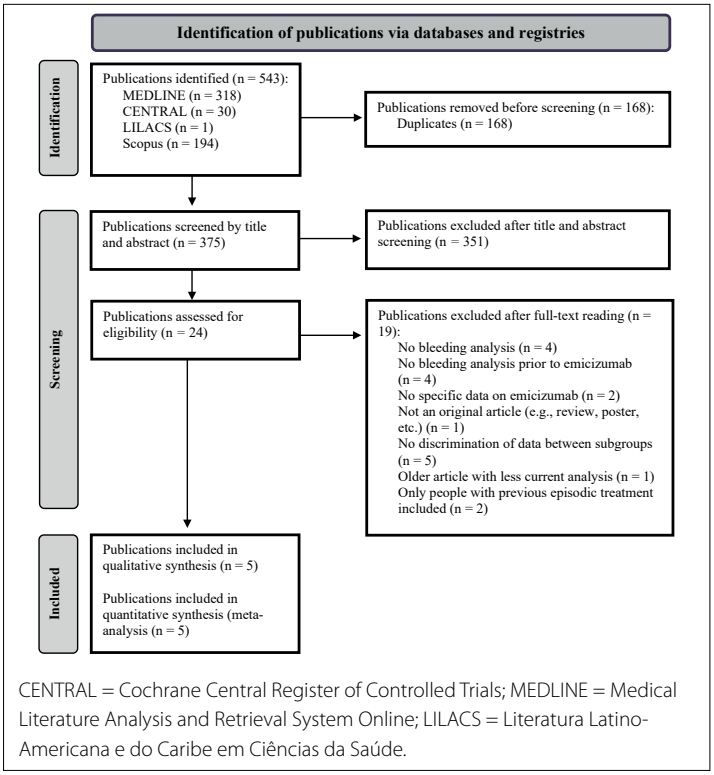
Publication selection

The literature search retrieved 543 publications. After duplicate removal and title/abstract screening, 24 publications were evaluated (**Supplementary Table 2**). Subsequently, 19 publications were excluded because they did not completely fulfill the inclusion criteria. Thus, five publications were included in the final version: one randomized controlled trial,[12] two non-randomized controlled trials,[13,24] and two cohort studies.[25,26] A PRISMA diagram of the selection process is presented in **Figure 1**. A search of the reference lists did not yield any new publications.

In the ClinicalTrials database, 20 registered studies were identified. Among these, we excluded two trials that did not use emicizumab as the main investigated drug, four trials that did not include PwHAi cases, and one trial that had been revised to include two protocols. The analysis of the remaining 12 studies did not identify any new publications.

Study characteristics

Among the selected publications, two controlled trials presented limited information regarding the specific subgroup of PwHAi that received previous prophylactic BPA (**Table 2**).[12,13] However, the data of PwHAi who received episodic and prophylactic BPA are mixed in the tables and comparisons. Both



CENTRAL = Cochrane Central Register of Controlled Trials; MEDLINE = Medical Literature Analysis and Retrieval System Online; LILACS = Literatura Latino-Americana e do Caribe em Ciências da Saúde.

Figure 1. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart for study selection.

Table 2. Characteristics of the populations in the included publications

First author, year	Study design	Sponsor	Country (ies)	N	Age	Sex	HA severity	Inhibitor titer (BU/mL)	BPA prophylaxis regimen	Emicizumab prophylaxis regimen: loading dose	Emicizumab prophylaxis regimen: maintenance dose	ABR for treated bleeds during BPA prophylaxis	ABR for treated bleeds during emicizumab prophylaxis	Adverse events*
Oldenburg, 2017[12]	Controlled RCT	Roche and Chugai Pharmaceutical	Spain, Costa Rica, USA, Italy, United Kingdom, Germany, Japan, Poland, Australia, Republic of Korea, France, South Africa, New Zealand, Taiwan	24	17#	M	NR	NR	NR	3.0 mg/kg QW × 4	1.5 mg/kg QW	Med: 11.5 Mean: 17.1 SD: 13.2	Med: 0 Mean: 9.7 SD: 11.1	Yes#
Young, 2019[13]	Controlled NRCT	Roche and Chugai Pharmaceutical	United Kingdom, USA, Spain, Germany, Italy, South Africa, Japan, Turkey, France, Costa Rica	15	<12	M	NR	>5	NR	3.0 mg/kg QW × 4	1.5 mg/kg QW	Med: 17.9 Mean: 20.4 SD: 13.3	Med: 0 Mean: 0.3 SD: 0.4	No 2 neutralizing ADA
Shima, 2021[24]	Controlled NRCT	Chugai Pharmaceutical	Japan	3	>12	M	Severe	NR	NR	3.0 mg/kg QW × 4	3.0 mg/kg QW	Med: 24.3 Mean: 25.4 SD: 3.5	Med: 0 Mean: 0.6 SD: 0.6	No
Misgav, 2021[25]	Cohort	None	Israel	2	62.9 (mean)	NR	Severe	35.6	>2 times/ week	3.0 mg/kg QW × 4	1.5 mg/kg QW	Med: 15.5, Mean: 15.5 SD: 6.1	Med: 2.2 Mean: 2.2 SD: 0.6	No
McCary, 2020[26]	Cohort	None	USA	12	8.05 (median)	M	Severe	NR	4 times/ week	3.0 mg/kg QW × 4	Not informed	Med: 2 Mean: 7.3 SD: 7.3	Med: 0 Mean: 0 SD: 0.2	No

Table legend: *Related to emicizumab only; # People with hemophilia A without and with inhibitors; ABR = annualized bleeding rate; ADA = anti-drug antibodies; BPA = bypassing agents; BU = Bethesda units; HA = hemophilia A; QW = weekly; M = male; Med = median; NR = not reported/not possible to be inferred; NRCT = non-randomized controlled trial; RCT = randomized controlled trial; SD = standard deviation; USA = United States of America.

studies included only some of the participants in the intra-individual analysis of ABR, thus presenting partial results of emicizumab prophylaxis *versus* BPA prophylaxis. In Shima et al.,[24] Misgav et al.,[25] and McCary et al.,[26] comparisons involved only PwHAi on prophylaxis.

Overall, data of 56 European, Asian, and Central American male PwHAi were analyzed. We could not characterize the overall age range, HA severity, or inhibitor titer because some publications did not discriminate the data.

Treatment regimens

The treatment regimens with emicizumab in the included publications consisted of loading doses of 3.0 mg/kg weekly for a month.[12,13,24-26] The maintenance regimens consisted of weekly 1.5 mg/kg injections in most of the publications.[12,13,24,25] McCary et al.[26] did not specifically describe this information, mentioning that the regimens were either weekly, every 2 weeks, or every 4 weeks. The BPA prophylaxis regimen before study entry was partially detailed in two publications, in which 14 PwHAi received prophylactic BPA four times/week,[26] or at least two times/week.[25]

Risk of bias assessment

The evaluation of the risk of bias is described in **Supplementary Figure 1**. In two controlled trials, PwHAi on episodic treatment with BPA were evaluated together with PwHAi on BPA prophylaxis.[12,13] In addition, in the study by Oldenburg et al.,[12] the randomization method was not explained, and the assessors were not blinded. None of the publications adjusted the outcomes for potential confounding factors, such as target joints and disease severity.[12,13,24-26]

Bleeding endpoints

Several methods have been used for bleed evaluation[12,13] (**Supplementary Table 3**). ABR for treated bleeds was the only

common method used in all the publications (**Table 2**). However, while the randomized controlled trial, one non-randomized controlled trial, and cohort studies performed inferential statistics,[12,13,25,26] only a descriptive analysis was performed by Shima et al.[24]

Oldenburg et al.[12] have reported that 80% of PwHAi on emicizumab prophylaxis experienced a reduced median ABR for treated bleeds compared to those on BPA prophylaxis. Young et al.[13] described that emicizumab prophylaxis prevented more bleeding than BPA prophylaxis. Shima et al.[24] have reported a higher efficacy of emicizumab prophylaxis than BPA prophylaxis, with the median ABR for treated bleeds reduced to zero. Additionally, all PwHAi in cohort studies experienced reduced bleeding rates.[25,26]

ABR for treated bleeds

For the subgroup of PwHAi analyzed by Oldenburg et al.,[12] the median ABR for treated bleeds was 11.5, during BPA prophylaxis and decreased to zero during emicizumab prophylaxis. In a study by Young et al.,[13] the ABR for treated bleed was reduced from 17.9 during BPA prophylaxis to zero during emicizumab prophylaxis. In addition, while the overall median ABR for treated bleeds in Shima et al.[24] was 24.3 among PwHAi on BPA prophylaxis, it decreased to zero during emicizumab prophylaxis. Lastly, in cohort studies,[25,26] the median ABR for treated bleeds was reduced from 2 and 15.5 during BPA prophylaxis to 0 and 2.2 during emicizumab prophylaxis, respectively.

The results of the meta-analysis are presented in **Figure 2**. Altogether, all publications[12,13,24–26] reported decreased ABR for treated bleeds with emicizumab prophylaxis compared to those treated with BPA prophylaxis (P = 0.0008), with severe heterogeneity (I^2 = 68.4%) (**Figure 2A**). A decrease in ABR for treated bleeds with emicizumab prophylaxis in comparison with those treated with BPA prophylaxis was also observed when only the PwHAi on the 1.5 mg/kg weekly emicizumab regimen was analyzed (P = 0.0173),[12,13,25]

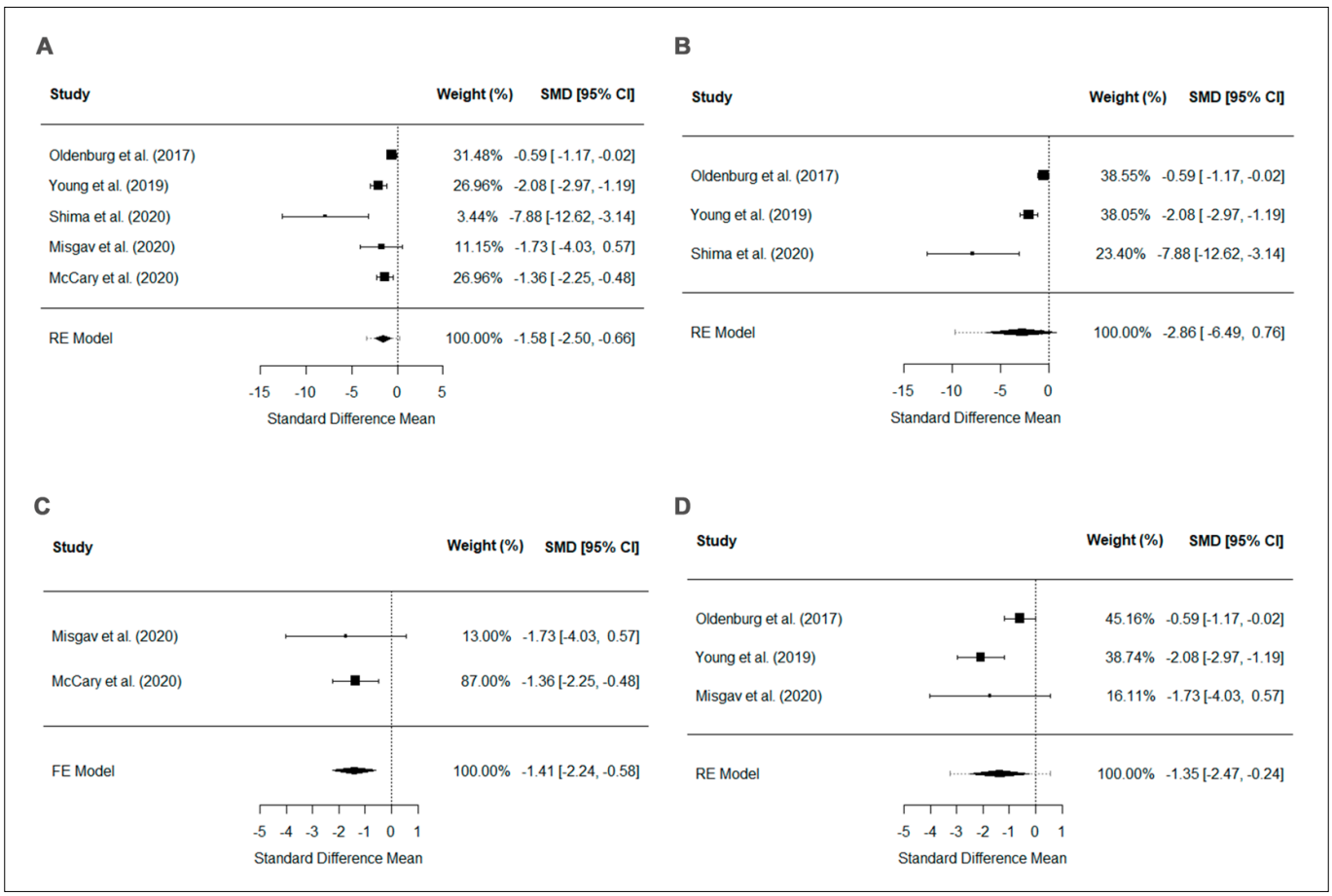


Figure 2. Forest plot comparing the annualized bleeding rate for treated bleeds among people with hemophilia A and inhibitors on emicizumab prophylaxis versus bypassing agents prophylaxis in A) all the included publications; B) publications that used the 1.5 mg/kg weekly regimen for emicizumab prophylaxis; C) cohort studies; and D) controlled trials. FE = fixed effect; RE = randomized effect; SMD = standard mean deviation; 95%CI = 95% confidence interval.

with severe heterogeneity (I^2 = 71,4%) (**Figure 2B**), and when only the cohort studies were evaluated (P = 0.0008),[25,26] with mild heterogeneity (I^2 = 0.0%) (**Figure 2C**). Regarding the separate analysis of controlled trials,[12,13,24] no difference in the ABR for treated bleeds between the treatments was noted (P = 0.1220) (**Figure 2D**).

Safety

All the publications reported on safety issues regarding emicizumab prophylaxis.[12,13,24-26] In one trial, five reported thrombotic events associated with the concomitant use of emicizumab and high daily doses of aPCC for > 1 day.[12] All the cases resolved after aPCC was interrupted, and two participants resumed emicizumab prophylaxis. Despite the resolution, one participant died because of bleeding. No other thrombotic events have been reported in other publications.[13,24-26]

Only one publication reported the development of neutralizing anti-drug antibodies (ADA) in two PwHAi,[13] one of which presented a loss of efficacy, leading to discontinuation. The other individual remained in the trial because his neutralizing ADA levels were undetectable after 2 months. Moreover, although no participant in the study by Oldenburg et al.[12] tested positive for ADA, two of them presented with decreased emicizumab plasma concentrations over time. However, no increase in bleeding was observed until the end of the study. Other AEs, such as nasopharyngitis, infection-site reactions, headaches, and rhabdomyolysis, were either mild, moderate, or deemed unrelated to emicizumab.[12,13,24-26]

DISCUSSION

Meta-analysis of the pooled data from this systematic review confirmed that emicizumab prophylaxis is superior to BPA prophylaxis in reducing the ABR for treated bleeds in PwHAi. Interestingly, meta-analysis of controlled trials sponsored by pharmaceutical industries did not indicate differences between emicizumab and BPA as prophylaxis for PwHAi. Differences were only detected when cohort studies were included in the pooled data.

Several publications were not included in this review because we could not separate results from PwHA without and with inhibitors, and those receiving episodic and prophylactic treatments with BPA.[27,28] They have demonstrated that emicizumab prophylaxis indeed reduced bleeds in comparison to both previous prophylactic and episodic treatment with factors.[27,28] In an Israeli publication, ABR for treated bleeds decreased from 2 (0–30) during BPA treatment to 1 (0–3) in PwHAi on emicizumab prophylaxis compared with previous prophylactic and episodic treatments.[27] In addition, although Barg et al.[28] did not analyze ABR, they have reported that almost 65% of PwHAi did not need additional hemostatic treatment other than emicizumab.

However, some publications still present conflicting information, demonstrating a variable response to emicizumab prophylaxis and a considerable persistent amount of breakthrough bleeds.[29,30] In a prospective study, half of the patients, including PwHAi, still had bleeds while on emicizumab prophylaxis.[29] In addition, Warren et al.[30] described a wide variability in bleeding rates in PwHAi on emicizumab prophylaxis, ranging from 0 to 6.1, although the majority of events were related to trauma.

Conflicts are not only related to bleeding but also to the safety of emicizumab. Thrombotic events, some of which are fatal, have been reported in three publications.[12,29,31] The HAVEN 1 controlled trial detected these events in association with the use of aPCC, including three thrombotic microangiopathies (TMA), which led researchers to change treatment protocols for breakthrough bleeds.[12] Since then, no more events have been reported in controlled trials. By contrast, in real-world evaluations, other thrombotic events continue to be detected, one of them associated with the use of aPCC 30 days after emicizumab was discontinued.[29,31] This may be a consequence of the persistence of emicizumab in the blood for approximately 6 months.[32] Postmarketing evaluations have also revealed venous thrombosis and one additional case of TMA in PwHA, although inhibitor status was not provided.[33] Moreover, one PwHAi on emicizumab prophylaxis developed myocardial infarction 36 h after administered with rFVIIa for a bleeding episode.[34] These situations expose the need for continuous monitoring of thrombotic events in order to clarify their relationship with this new drug.

Another safety issue involves the development of neutralizing ADA. They were first detected in two PwHAi enrolled in a publication that included this systematic review.[12,13] A case report of a pediatric PwHAi has also been published, resulting in emicizumab discontinuation.[35] Furthermore, the development of non-neutralizing ADA was also noted in 11 PwHAi of the HAVEN trials.[36] This is an important issue because in case emicizumab no longer prevents bleeds, BPA prophylaxis needs to be resumed.[7]

One important aspect of the meta-analysis results was the high heterogeneity among publications. This finding may be attributed to differences in study designs,[37] variations in intervention methods (dosage and duration),[37] and publication bias, which could not be assessed.[38]

This systematic review had some limitations. First, the small number of publications included revealed that few studies were conducted to allow for a more thorough evaluation of PwHAi. In addition, the number of PwHAi who received BPA prophylaxis and then switched to emicizumab prophylaxis was small. Second, the fact that not all publications discriminated data based on inhibitor status and prior BPA prophylaxis limited the potential inclusion of comparisons in the meta-analysis. The meta-analysis also presents limitations. Because of the small number of publications,

we merged data from controlled trials and cohort studies to integrate the results, which may influence the interpretability of the findings considering the heterogeneous study designs and quality of evidence. Additionally, the different dosages, age ranges, and small populations across studies warrant careful evaluation of the results. Finally, the difficulty regarding the analysis of AEs was also an issue, as we were unable to identify which events occurred specifically in the population of PwHAi under BPA prophylaxis who switched to emicizumab prophylaxis.

PwHAi have more bleeds and more difficult-to-treat bleeds than their non-inhibitor counterparts.[39,40] Hence, morbidity, including hemophilic arthropathy and worse quality of life, and mortality secondary to hemorrhage are more frequent among PwHAi than those PwHA without inhibitors.[4,5,41] The BPA prophylaxis has an effectiveness of approximately 60%–72%,[42,43] implying that bleeding events may still occur.[44] In addition, up to 20% of the bleeding events in PwHAi may not be controlled with any BPA on usual recommended regimens.[40,45] Therefore, the reduction of ABR due to BPA prophylaxis for PwHAi may not be followed by significant joint health and quality of life improvements and reduced mortality compared with those PwHAi exclusively treated on-demand.[43,44] The introduction of more effective prophylactic therapeutic (i.e., emicizumab) in the armamentarium for treating PwHAi may result in better avoidance of hemophilic arthropathy,[46,47] assurance of an adequate quality of life,[48,49] and maintenance of mortality similar to the people without hemophilia. Hence, future research should focus on separate analyses of PwHAi from those without inhibitors, specially evaluating concurrent (head-to-head) emicizumab and BPA prophylaxes in a pre-calculated population size, as well as a better description of prior BPA prophylaxis and AEs.

CONCLUSION

This systematic review and meta-analysis demonstrated that emicizumab prophylaxis was superior to BPA prophylaxis in preventing ABR for treated bleeds in PwHAi. However, the results should be interpreted with caution because of the small population size and potential risk of bias.

REFERENCES

1. Mehta P, Reddivari AKR. Hemophilia. In: Mehta P, Reddivari AKR. StatPearls. Treasure Island: StatPearls Publishing; 2023. PMID: 31869071. Available at: https://www.ncbi.nlm.nih.gov/books/NBK551607/. Accessed in 2023 (March 30).
2. Ljung R, Auerswald G, Benson G, et al. Inhibitors in haemophilia A and B: Management of bleeds, inhibitor eradication and strategies for difficult-to-treat patients. Eur J Haematol. 2019;102(2):111-22. PMID: 30411401; https://doi.org/10.1111/ejh.13193.
3. Witmer C, Young G. Factor VIII inhibitors in hemophilia A: rationale and latest evidence. Ther Adv Hematol. 2013;4(1):59-72. PMID: 23610614; https://doi.org/10.1177/2040620712464509.
4. Morfini M, Haya S, Tagariello G, et al. European Study on Orthopaedic Status of haemophilia patients with inhibitors. Haemophilia. 2007;13(6):606-12. PMID: 17880451; https://doi.org/10.1111/j.1365-2516.2007.01518.x.
5. Soucie JM, Ciafrini C, Janco RL, et al. Joint range-of-motion limitations among young males with hemophilia: prevalence and risk factors. Blood. 2004;103(7):2467-73. PMID: 14615381; https://doi.org/10.1182/blood-2003-05-1457.
6. Kreuz W, Ettingshausen CE. Inhibitors in patients with haemophilia A. Thromb Res. 2014;134(s1):s22-6. PMID: 24745722; https://doi.org/10.1016/j.thromres.2013.10.016.
7. Carcao M, Escuriola-Ettingshausen C, Santagostino E, et al. The changing face of immune tolerance induction in haemophilia A with the advent of emicizumab. Haemophilia. 2019;25(4):676-84. MID: 31033112; https://doi.org/10.1111/hae.13762.
8. Shapiro AD, Mitchell IS, Nasr S. The future of bypassing agents for hemophilia with inhibitors in the era of novel agents. J Thromb Haemost. 2018;16(12):2362-74. PMID: 30264916; https://doi.org/10.1111/jth.14296.
9. Astermark J, Donfield SM, DiMichele DM, et al. A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: the FEIBA NovoSeven Comparative (FENOC) Study. Blood. 2007;109(2):546-51. PMID: 16990605; https://doi.org/10.1182/blood-2006-04-017988.
10. Knight T, Callaghan MU. The role of emicizumab, a bispecific factor IXa- and factor X-directed antibody, for the prevention of bleeding episodes in patients with hemophilia A. Ther Adv Hematol. 2018;9(10):319-34. PMID: 30344994; https://doi.org/10.1177/2040620718799997.
11. Kitazawa T, Igawa T, Sampei Z, et al. A bispecific antibody to factors IXa and X restores factor VIII hemostatic activity in a hemophilia A model. Nat Med. 2012;18(10):1570-4. PMID: 23023498; https://doi.org/10.1038/nm.2942.
12. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. N Engl J Med. 2017;377(9):809-18. PMID: 28691557; https://doi.org/10.1056/nejmoa1703068.
13. Young G, Liesner R, Chang T, et al. A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. Blood. 2019;134(24):2127-38. PMID: 31697801; https://doi.org/10.1182/blood.2019001869.
14. Shima M, Hanabusa H, Taki M, et al. Long-term safety and efficacy of emicizumab in a phase 1/2 study in patients with hemophilia A with or without inhibitors. Blood Adv. 2017;1(22):1891-9. PMID: 29296836; https://doi.org/10.1182/bloodadvances.2017006684.
15. Pipe SW, Shima M, Lehle M, et al. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised

phase 3 study. Lancet Haematol. 2019;6(6):e295-305. PMID: 31003963; https://doi.org/10.1016/s2352-3026(19)30054-7.

16. Higgins JPT, Thomas J, Chandler J, et al., eds. Cochrane Handbook for Systematic Reviews of Interventions. Wiley; 2019. http://doi.org/10.1002/9781119536604.
17. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. J Clin Epidemiol. 2021;134:178-89. PMID: 33789819; https://doi.org/10.1016/j.jclinepi.2021.03.001.
18. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210. PMID: 27919275; https://doi.org/10.1186/s13643-016-0384-4.
19. Aromataris E, Munn Z, edits. JBI Manual for Evidence Synthesis. JBI, 2020. https://doi.org/10.46658/JBIMES-20-01.
20. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13. PMID: 15840177; https://doi.org/10.1186/1471-2288-5-13.
21. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60. PMID: 12958120; https://doi.org/10.1136/bmj.327.7414.557.
22. Cochran WG. The Combination of Estimates from Different Experiments. Biometrics. 1954;10(1):101-29. https://doi.org/10.2307/3001666.
23. The R Foundation. R: A language and environment for statistical computing. 2021. Available at: https://www.r-project.org/. Accessed in 2023 (March 30).
24. Shima M, Nagao A, Taki M, et al. Long-term safety and efficacy of emicizumab for up to 5.8 years and patients' perceptions of symptoms and daily life: A phase 1/2 study in patients with severe haemophilia A. Haemophilia. 2021;27(1):81-9. PMID: 33236410; https://doi.org/10.1111/hae.14205.
25. Misgav M, Brutman-Barazani T, Budnik I, et al. Emicizumab prophylaxis in haemophilia patients older than 50 years with cardiovascular risk factors: real-world data. Haemophilia. 2021;27(2):253-60. PMID: 33595174; https://doi.org/10.1111/hae.14261.
26. McCary I, Guelcher C, Kuhn J, et al. Real-world use of emicizumab in patients with haemophilia A: Bleeding outcomes and surgical procedures. Haemophilia. 2020;26(4):631-6. PMID: 32311809; https://doi.org/10.1111/hae.14005.
27. Barg AA, Livnat T, Budnik I, et al. Emicizumab treatment and monitoring in a paediatric cohort: real-world data. Br J Haematol. 2020;191(2):282-90. PMID: 32656767; https://doi.org/10.1111/bjh.16964.
28. Barg AA, Avishai E, Budnik I, et al. Emicizumab prophylaxis among infants and toddlers with severe hemophilia A and inhibitors—a single-center cohort. Pediatr Blood Cancer. 2019;66(11):e27886. PMID: 31348595; https://doi.org/10.1002/pbc.27886.
29. Barg AA, Budnik I, Avishai E, et al. Emicizumab prophylaxis: Prospective longitudinal real-world follow-up and monitoring. Haemophilia. 2021;27:383-91. PMID: 33892524; https://doi.org/10.1111/hae.14318.
30. Warren BB, Chan A, Manco-Johnson M, et al. Emicizumab initiation and bleeding outcomes in people with hemophilia A with and without inhibitors: a single-center report. Res Pract Thromb Haemost. 2021;5(5):e12571. PMID: 34377887; https://doi.org/10.1002/rth2.12571.
31. Ebbert PT, Xavier F, Seaman CD, Ragni MV. Emicizumab prophylaxis in patients with haemophilia A with and without inhibitors. Haemophilia. 2020;26(1):41-6. PMID: 31746522; https://doi.org/10.1111/hae.13877.
32. Cafuir L, Kruse-Jarres R, Mancuso ME, Kempton CL. Emicizumab for hemophilia A without inhibitors. Expert Rev Hematol. 2019;12(7):515-24. PMID: 31130012; https://doi.org/10.1080/17474086.2019.1624519.
33. Makris M, Iorio A, Lenting PJ. Emicizumab and thrombosis: the story so far. J Thromb Haemost. 2019;17(8):1269-72. PMID: 31368220; https://doi.org/10.1111/jth.14556.
34. Gundabolu K, Goldsweig A, Bhatt VR, Koepsell SA, Harper JL. ST-segment elevation myocardial infarction (STEMI) and pulmonary embolism in a hemophilia A patient receiving emicizumab and recombinant activated factor VII. Haemophilia. 2020;26(1):e5-e8. PMID: 31694063; https://doi.org/10.1111/hae.13871.
35. Harkins Druzgal C, Kizilocak H, Brown J, Sennett M, Young G. Neutralizing antidrug antibody to emicizumab in a patient with severe hemophilia A with inhibitors: new case with detailed laboratory evaluation. J Thromb Haemost. 2020;18(9):2205-8. PMID: 32544268; https://doi.org/10.1111/jth.14957.
36. Paz-Priel I, Chang T, Asikanius E, et al. Immunogenicity of emicizumab in people with hemophilia A (PwHA): results from the HAVEN 1-4 studies. Blood. 2018;132(suppl. 1):633. https://doi.org/10.1182/blood-2018-99-118492.
37. Gagnier JJ, Moher D, Boon H, Beyene J, Bombardier C. Investigating clinical heterogeneity in systematic reviews: a methodologic review of guidance in the literature. BMC Med Res Methodol. 2012;12:111. PMID: 22846171; https://doi.org/10.1186/1471-2288-12-111.
38. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L, Moreno SG. Assessing Publication Bias in Meta-Analyses in the Presence of Between-Study Heterogeneity. J R Stat Soc Ser A Stat Soc. 2010;173(3):575-91. https://doi.org/10.1111/j.1467-985X.2009.00629.x.
39. van Velzen AS, Eckhardt CL, Streefkerk N, et al. The incidence and treatment of bleeding episodes in non-severe haemophilia A patients with inhibitors. Thromb Haemost. 2016;115(3):543-50. PMID: 26582077; https://doi.org/10.1160/th15-03-0212.
40. Teitel J, Berntorp E, Collins P, et al. A systematic approach to controlling problem bleeds in patients with severe congenital haemophilia A and high-titre inhibitors. Haemophilia. 2007;13(3):256-63. PMID: 17498074; https://doi.org/10.1111/j.1365-2516.2007.01449.x.
41. duTreil S. Physical and psychosocial challenges in adult hemophilia patients with inhibitors. J Blood Med. 2014;5:115-22. PMID: 25093002; https://doi.org/10.2147/jbm.s63265.
42. López-Fernández MF, Roca CA, Álvarez-Román MT, et al. Spanish Consensus Guidelines on prophylaxis with bypassing agents in patients

with haemophilia and inhibitors. Thromb Haemost. 2016;115(5):872-95. PMID: 26842562; https://doi.org/10.1160/th15-07-0568.

43. Chai-Adisaksopha C, Nevitt SJ, Simpson ML, Janbain M, Konkle BA. Bypassing agent prophylaxis in people with hemophilia A or B with inhibitors. Cochrane Database Syst Rev. 2017;9(9):CD011441. PMID: 28944952; https://doi.org/10.1002/14651858.cd011441.pub2.
44. Mahlangu J, Oldenburg J, Callaghan MU, et al. Bleeding events and safety outcomes in persons with haemophilia A with inhibitors: a prospective, multi-centre, non-interventional study. Haemophilia. 2018;24(6):921-9. PMID: 30295389; https://doi.org/10.1111/hae.13612.
45. Berntorp E. Differential response to bypassing agents complicates treatment in patients with haemophilia and inhibitors. Haemophilia. 2009;15(1):3-10. PMID: 19016901; https://doi.org/10.1111/j.1365-2516.2008.01931.x.
46. Shima M, Takedani H, Kitsukawa K, et al. AOZORA: long-term safety and joint health in paediatric persons with haemophilia A without factor VIII inhibitors receiving emicizumab – protocol for a multicentre, open-label, phase IV clinical study. BMJ Open. 2022;12(6):e059667. PMID: 35697445; https://doi.org/10.1136/bmjopen-2021-059667.
47. Kiialainen A, Niggli M, Kempton CL, et al. Effect of emicizumab prophylaxis on bone and joint health markers in people with haemophilia A without factor VIII inhibitors in the HAVEN 3 study. Haemophilia. 2022;28(6):1033-43. PMID: 35905294; https://doi.org/10.1111/hae.14642.
48. Oldenburg J, Mahlangu JN, Bujan W, et al. The effect of emicizumab prophylaxis on health-related outcomes in persons with haemophilia A with inhibitors: HAVEN 1 study. Haemophilia. 2019;25(1):33-44. PMID: 30427582; https://doi.org/10.1111/hae.13618.
49. Mahlangu J, Oldenburg J, Callaghan MU, et al. Health-related quality of life and health status in persons with haemophilia A with inhibitors: A prospective, multicentre, non-interventional study (NIS). Haemophilia. 2019;25(3):382-91. PMID: 31016855; https://doi.org/10.1111/hae.13731.

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Treatment of Parkinson's disease by deep brain stimulation: a bibliometric analysis

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ABSTRACT

BACKGROUND: For more than 30 years, deep brain stimulation (DBS) has been a therapeutic tool for Parkinson's disease (PD) treatment. DBS can ameliorate several motor and non-motor symptoms and improve the patients' quality of life.

OBJECTIVES: To analyze the global scientific production of original and review articles on Parkinson's disease treatment using deep brain stimulation.

DESIGN AND SETTING: Descriptive, bibliometric study with a quantitative approach.

METHOD: The research protocol was conducted in March 2023 using the Web of Science database. Six hundred eighty-four articles were included in the analysis. Data were imported into RStudio Desktop Software, linked to R Software. The Bibliometrix R package, its Biblioshiny web interface, and VOSviewer software were used for the analysis.

RESULTS: The international production began in 1998. Movement Disorders is the journal with the largest number of published articles and the most cited. Michael Okun and Andres Lozano are the authors who produced the most in this area. The University of Florida is the most active affiliated institution in Brazil. The United States has the largest number of collaborations and is mainly published by local researchers. In contrast, countries such as the United Kingdom and Canada have a high number of multi-country publications. The 15 most cited studies predominantly investigated subthalamic nucleus stimulation.

CONCLUSION: DBS for Parkinson's disease is a relatively novel therapeutic approach, with studies that have expanded over the last twenty-five years. Most scientific production was quantitative and restricted to specialized journals. The United States, Europe, and China held the most articles.

INTRODUCTION

Parkinson's disease (PD) is a chronic neurological disorder that affects motor function and causes tremors, rigidity, and bradykinesia.[1] Deep brain stimulation (DBS) is a surgical treatment for PD, especially for patients or those who experience significant side effects. It improves both motor and non-motor symptoms as well as the patient's quality of life.[2]

Research on the use of DBS in the treatment of PD has evolved exponentially over the years. In the 1990s, stimulation of the subthalamic nucleus (STN) was effective in reducing motor symptoms in patients with advanced disease.[3,4] Studies have focused on establishing the best parameters for DBS therapy and analyzing its long-term effects.[5,6]

Bibliometric studies are used to assess the impact of research topics, identify research trends, evaluate researchers and institutions, and inform research policies. Thus, bibliometric studies provide a way to objectively measure the impact and productivity of research and can help inform decision-making regarding research policies and funding.

OBJECTIVE

To analyze the worldwide scientific production of original and review articles on Parkinson's disease treatment by deep brain stimulation.

METHODS

Research design

This article is a descriptive bibliometric study with a quantitative approach guided by the five recommended steps in bibliometric research.[7] Since this is a bibliometric study, no ethics committee approval was required.

The use of bibliometric analyses has been growing in the field of health, particularly in neurology. The literature points to bibliometric analyses on various topics, such as movement disorders,[8] dystonia,[9] Parkinson's disease stem cells,[10] and deep brain stimulation.[11] Notably, this type of analysis allows the investigation of more data than systematic literature reviews, while maintaining high rigor, scientific soundness, transparency, and replicability.[12,13]

Data-gathering period

Scientific articles were searched using an advanced query in the Web of Science™ (WoS) database on March 19, 2023. WoS was used in this study because of its international academic recognition. It is considered one of the most comprehensive scientific bases, that pioneered the aggregation of journals from more than 100 areas of knowledge.[14]

Selection criteria

Original and review articles published before March 19, 2023, were included in the study. In addition, documents that deviated from the scope of the research, opinion articles, reflection articles, editorials, and case studies were excluded.

Data-gathering

To formulate the search strategy, both controlled and uncontrolled descriptors from Medical Subject Headings (MeSH) were used, along with search operators and wildcard characters. In WoS, the search included only the titles of the documents, following the approach used in other studies, to increase the search accuracy of the search and reduce false-positive results.[15,12]

Thus, the search first resulted in 3434 articles, after filtering and applying the previously described criteria, 1,698 articles remained, which had all available information downloaded in text file format for analysis. **Figure 1** shows both the search strategy and the selection process of the included articles.

Data processing and analysis

The recovered data were imported into RStudio Desktop Software, version 2023.03.0+368 (©Posit Software, Massachusetts, United States, 2023), linked to R Software, version 4.2.3 (The R Foundation, Vienna, Austria, 2023). For the analysis, we used the Bibliometrix R package (© K-Synth Srl, Academic Spin-Off of the University of Naples Federico II, Naples, Italy, 2023) and the Biblioshiny application, which provides a web interface for Bibliometrix.[16]

In this study, we sought to elucidate on: the number of articles published per year, the scientific journals that published the most and those that were most cited, the productivity of authors according to Lotka's Law,[17] and according to time, the most productive institutions and countries, collaboration rate, the most cited articles, the conceptual structure, and thematic evolution using KeyWords Plus™.

RESULTS

As described previously, 1,698 articles were analyzed in the present study. The search was carried out for the period of 1945 to 2023 and identified the first result of an article published in 1998; for this reason, the period considered was from 1998 to 2023.

The evolution of scientific production on PD and DBS is shown in **Figure 2**, which graphically displays the annual number of publications in the period studied, demonstrating that international interest in the subject has been constantly growing, reaching its peak in 2020 and despite a reduction in 2021, remains high.

When analyzing the articles, 358 scientific journals were identified. **Figure 3A** shows a list of the most representative journals regarding the number of publications. In contrast, **Figure 3B** shows

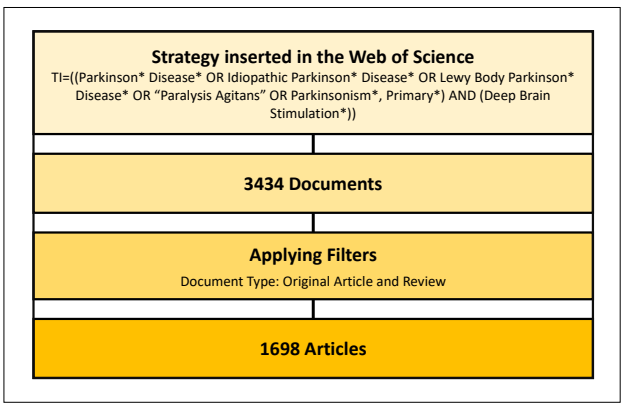


Figure 1. Search strategy used and selection of articles included.

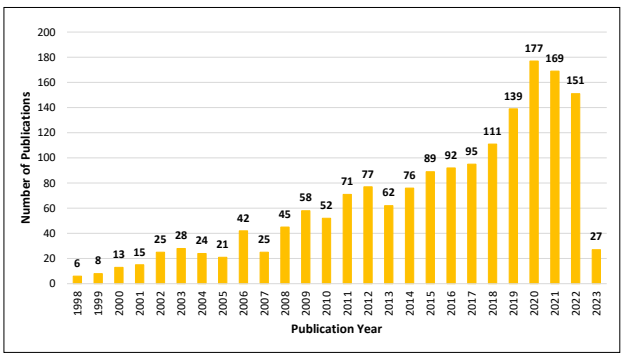


Figure 2. Annual distribution of articles according to year of publication.

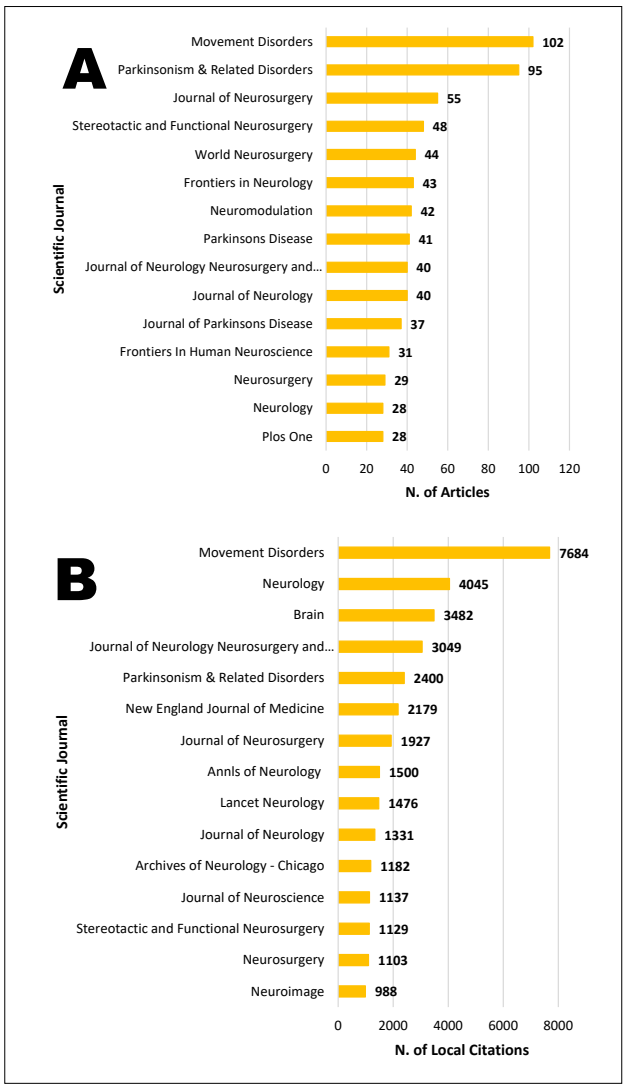


Figure 3. Scientific journals that published the most articles and most cited scientific journals.

the most cited journals in the references of the evaluated articles. The scientific journal Movement Disorders stood out for publishing the most articles on the subject and being the most cited.

Lotka's Law (**Figure 4**) describes the publication frequency of the authors on a given topic. According to this law, a large proportion of scientific literature is produced by a small number of authors and the production of many small producers is equal to a small number of large producers. In this study, the articles evaluated were produced by 5,923 authors. Among them, 65% published only one article, 32% published two to eight articles, and 3% published 9 to 52 articles, demonstrating compliance with Lotka's law.

Figure 5 shows the production (article publications) of the 15 principal authors over time. In this figure, the size of the bubble is proportional to the number of articles (larger bubbles indicate a more significant number of articles) and the intensity of the color is proportional to the total citations (TC) per year (dark blue indicates a more significant number of citations). In terms of the number of articles, Michael Okun (n = 52) was the most productive author, followed by Andres Lozano (n = 50), Jens Volkmann

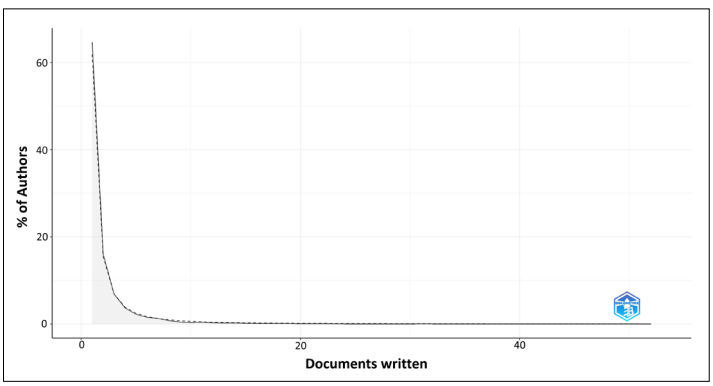


Figure 4. Productivity of scientists according to Lotka's Law.

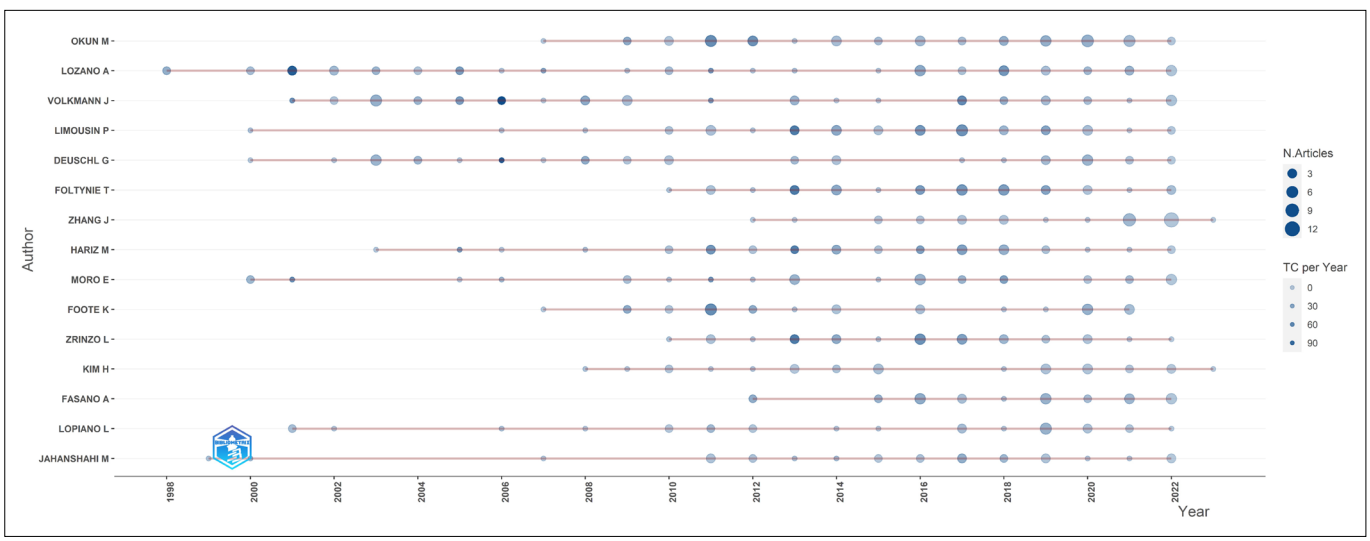


Figure 5. Top - Authors' production over time.

(n = 45), Patricia Limousin (n = 43), and Guenther Deuschl (n = 38). Consequently, the most cited were Andres Lozano (n = 98), Jens Volkmann (n = 112), and Guenther Deuschl (n = 99), with more than 90 citations.

When evaluating the authors' affiliations, 1,863 institutions were identified. Therefore, **Figure 6** presents the institutions most involved in research on the subject according to the co-occurrence of these institutions at the authors' addresses. Notably, the same institution can be present more than once in each article. The results showed that 1,021 (54.8%) institutions appeared only once. Authors from the University of Florida were the most active on this research topic, appearing 150 times.

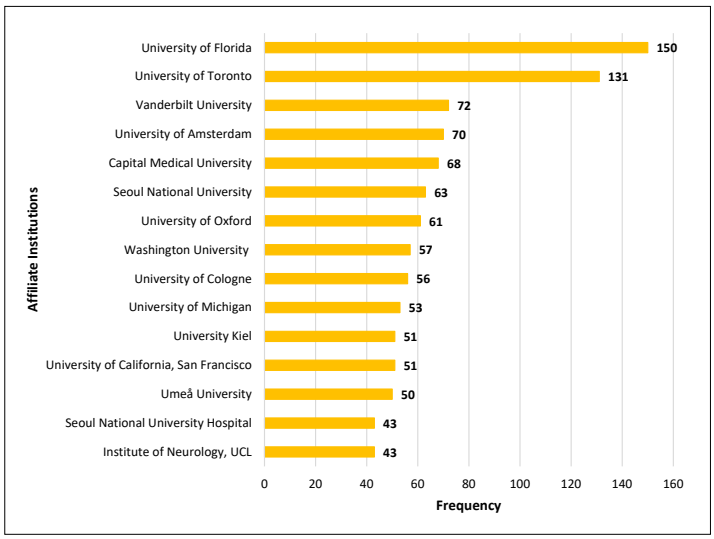
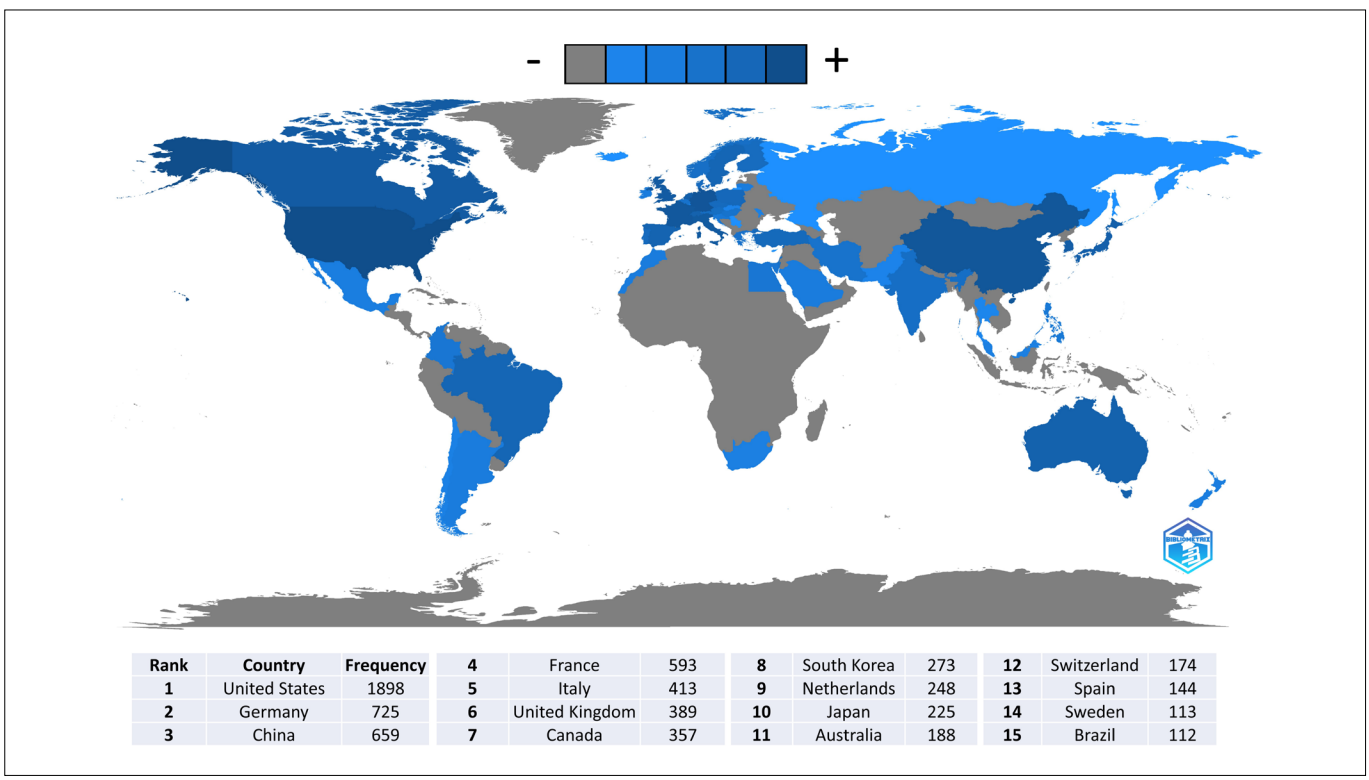


Figure 6. Institutions most involved in research on the subject.

Researchers who published on the subject were from 55 countries. The geographic distribution of the articles is shown in **Figure 7**. The value obtained was based on the co-occurrence of countries according to authors' affiliations, which explains why the frequency was greater than the number of articles evaluated. In the figure, shades of blue, from lightest to darkest, indicate an increase in local authors, while gray indicates the absence of local authors.

When evaluating the collaboration rate (the ratio between the number of multi-country collaborations and the total number of articles attributed) based on the affiliation of the corresponding author (**Table 1**), it is evident that despite having carried out the highest number of collaborations, the United States mainly published with local researchers. In contrast, countries such as the United Kingdom and Canada have high rates of multi-country publications (51% and 50%, respectively).

A total of 1,698 articles were cited 18,591 times, averaging 31.42 citations per item. The 15 most-cited articles ranged from 1,885 to 437 (**Table 2**). These articles were published in eight different journals between the years 2001 and 2010.



Rank	Country	Frequency	4	France	593	8	South Korea	273	12	Switzerland	174
1	United States	1898	5	Italy	413	9	Netherlands	248	13	Spain	144
2	Germany	725	6	United Kingdom	389	10	Japan	225	14	Sweden	113
3	China	659	7	Canada	357	11	Australia	188	15	Brazil	112

Figure 7. Scientific production by country according to authors' affiliation.

Table 1. Production and collaborations of countries according to the corresponding author

Rank	Country	Articles	SCP	MCP	MCP_Rate
1	United States	435	353	82	19%
2	China	192	162	30	16%
3	Germany	170	123	47	28%
4	Italy	99	80	19	19%
5	France	92	66	26	28%
6	United Kingdom	92	45	47	51%
7	Canada	70	35	35	50%
8	Netherlands	55	38	17	31%
9	Japan	53	50	3	6%
10	Korea	51	45	6	12%
11	Spain	39	34	5	13%
12	Switzerland	35	23	12	34%
13	Australia	34	26	8	24%
14	Sweden	30	16	14	47%
15	Brazil	25	16	9	36%

Country = Country of the corresponding author's affiliation; Articles = Number of articles per country of corresponding author's affiliation; SCP = Single Country Publication; MCP = Multi-Country Publication; MCP_rate = Multi-Country Publication rate.

In bibliometric research, keywords can summarize the focus of articles and determine which subjects are being addressed, that is, their conceptual structures.[33] Thus, to demonstrate the conceptual structure of the articles, the 50 most frequent KeyWords Plus™ were used to create **Figure 8** (using the Leiden clustering algorithm), where the size of each box is proportional to the frequency of the term (the more a term appears, the larger its size will be).[34] In the figure, the formation of just one cluster can be observed, demonstrating the centrality of the topic, with terms that refer to structures targeted in DBS surgery for treating PD, especially the subthalamic nucleus.

When observing the evolution of the theme (**Figure 9**), using the most frequent Keywords Plus™ again, it is evident that the first publications were more restricted (1998-2011), encompassing terms such as subthalamic nucleus (STN) stimulation, basal ganglia, dysarthria, high frequency, and duodenal infusion of levodopa. However, recently (2021-2023), there has been diversification in studies on PD and DBS, addressing targets, outcomes, quality of life, non-motor symptoms, and balance.

Table 2. Ranking of the most cited published articles on the subject.

Rank	Author (year), Journal	Title	Total Citations (TC)
1	Deuschl G et al. (2006), N Engl J Med [18]	A randomized trial of deep-brain stimulation for Parkinson's disease	1885
2	Obeso JA et al. (2001), N Engl J Med [19]	Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease.	1161
3	Weaver FM et al. (2009), JAMA-J Am Med Assoc[20]	Bilateral deep brain stimulation vs. best medical therapy for patients with advanced Parkinson's disease: a randomized controlled trial	1025
4	Benabid AL et al. (2009), Lancet Neurol [21]	Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease	897
5	Follett KA et al. (2010), N Engl J Med [22]	Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease	862
6	Rodriguez-Oroz Mc et al. (2005), Brain [23]	Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up	761
7	Little S et al. (2013), Ann Neurol [24]	Adaptive deep brain stimulation in advanced Parkinson's disease	715
8	Bronstein JM et al. (2011), Arch Neurol-Chicago [25]	Deep brain stimulation for Parkinson's disease: an expert consensus and review of key issues	575
9	Stefani A et al (2007), Brain [26]	Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease	541
10	Kumar R et al. (1998), Neurology [27]	Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease	500
11	Williams A et al. (2010), Lancet Neurol [28]	Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomized, open-label trial	493
12	Benabid AL et al. (2003), Curr Opin Neurobiol [29]	Deep brain stimulation for Parkinson's disease	486
13	Witt K et al (2008), Lancet Neurol [30]	Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomized, multicentre study	445
14	Odekerken VJJ et al. (2013), Lancet Neurol [31]	Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomized controlled trial	437
15	Okun MS et al. (2009), Ann Neurol [32]	Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: the COMPARE trial	372

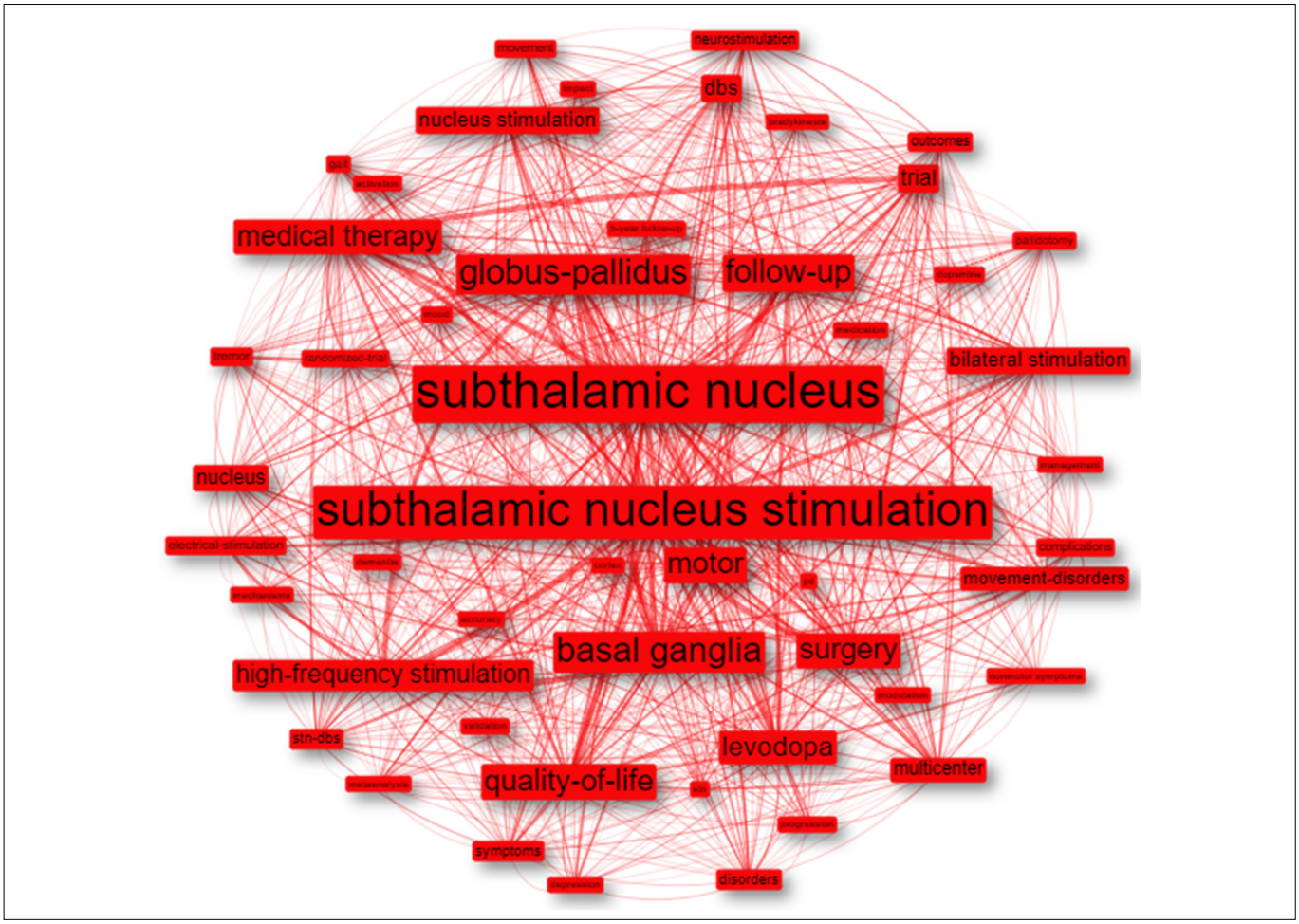


Figure 8. The conceptual structure according to KeyWords Plus™.

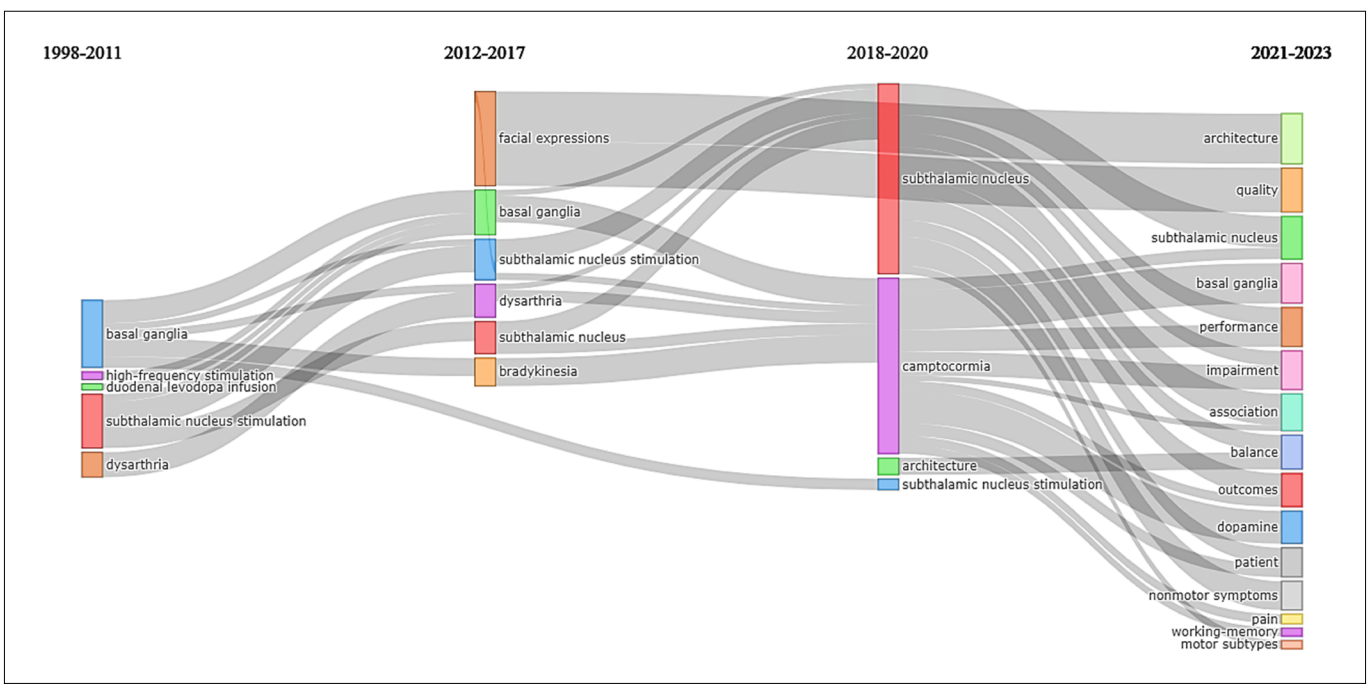


Figure 9. Thematic evolution according to KeyWords Plus™.

DISCUSSION

This bibliometric analysis included articles that addressed the treatment of PD using deep brain stimulation for almost three decades (1998 2023). Notably, from 1990 to 2019, the number of patients diagnosed with PD increased from 2.5 million to 6.1 million globally, owing to population aging and environmental factors, which may have favored this growing incidence.[35]

The growing trend in annual publications indicates continued investment in DBS research for the treatment of PD. However, after 2020, there has been a decline in the number of publications despite growing scientific interest. The explanation for this decrease in studies may be related to the COVID-19 pandemic, which may have delayed the progress of research protocols because research related to the subject requires complex methodological designs that take time to execute and publish.

Regarding scientific journals with the most publications and citations, it was noted that they were mainly dedicated to neuroscience. Only one of the 15 most-cited journals (New England Journal of Medicine) was identified as a general medical journal. In addition, among the 15 journals that published the most articles, seven were also among the most cited. These findings indicate the predominance of journals in the subspecialty mentioned above, which excel in terms of the quantity and quality of published articles.

Although many authors have participated in producing evidence, most have published only one article (65%) and are considered occasional researchers in the area. Therefore, according to Lotka's Law, this theme must be consolidated. This law estimates that only 60% of authors produce a single document in consolidated areas, with an average of 3.5 documents per author. In the present study, 1,146 authors published 3.52 articles.[16]

Notably, the most productive author, Michael Okun, appeared twice in the citation ranking,[25,32] with the most cited article of his career owning 575 citations and ranking eighth among the most cited.[25] The second most productive author, Andrés Lozano, has five articles among the most cited, and his most cited article has 1161 citations.[23,25,27]

Most of these authors began publishing extensively after 2010. Lozano has the longest timeline, spanning from 1998 to 2023, and has been active in the field for almost three decades. Simultaneously, scholars such as Elena Moro, J Volkmann, Leonardo Lopiano, Marjan Jahanshahi, Limousin, and Deuschl, maintain their scientific activity in the area for long periods. Other authors, such as Jianguo Zhang and Alfonso Fasano, who are currently among the main researchers in the area, began publishing their research after 2010.

The University of Florida and the University of Toronto have prominent positions among the institutions that have conducted the most research on the subject, contributing consistent and systematic articles on the topic. It is essential to highlight that Michael Okun, from the University of Florida, and Andrés Lozano, from the University of Toronto, have already published together,[25] demonstrating the importance of teamwork with different research centers of excellence, which have been publishing consistently for decades.

Although authors from different countries contributed, most of them were from the United States, China, and Europe (Germany, France, Italy, and the United Kingdom). However, the fact that the United States has the highest number of authors and a low collaboration rate is noteworthy, suggesting that its protocols are predominantly conducted between local institutions and are not shared with other countries.

Advanced PD has become the most studied and common indication for DBS, using different targets. The 15 most cited articles were related to STN stimulation. Of these, seven compared the STN to the Globus Pallidus Internus (GPi),[20-23,28,31,32] which confirmed that these are the two most common targets for DBS and are both components of the basal ganglia-thalamo-cortical loop. Furthermore, stimulation of these sites has been associated with significant improvements in the cardinal motor signs of PD, including tremors, bradykinesia, and rigidity.[37]

The pedunculopontine nucleus (PPN) has also been evaluated and studied to treat axial symptoms refractory to levodopa, such as freezing of gait. However, it is an important study because this target is not yet well established and is still in the experimental phase.[26]

Among the most cited articles, three validated instruments were identified to assess the quality of life of patients with PD. These instruments include the Parkinson's Disease Questionnaire 39 (PDQ-39),[18,2,28] the Unified Parkinson's Disease Rating Scale (UPDRS),[19,20] and the Parkinson's Disease Quality of Life questionnaire (PDQL).[31] Other studies have associated the PDQ-39 with the Short Form-36 (SF-36)[30] and the PDQ-39 with the UPDRS.[22] Finally, one article described the quality of life in a general way.[29]

It is noteworthy that for the evaluation of patients, it is recommended to associate general and specific instruments with evaluating different aspects of quality of life, producing both general data, which facilitate comparisons between different conditions, and related data, specifically on the impact of the disease on quality of life.[37] However, this association was verified in only one of the most cited studies.[38]

Although not present in **Figure 3A**, the scientific journal "Lancet Neurology," with the first edition released in October 1823 (Journal Citation Reports™ 2021:59.935), appeared four times in the list of most cited articles. Another scientific journal that gained prominence among publications was "The New England Journal of Medicine," published uninterruptedly for more than 200 years (Journal Citation Reports™ 2021:176.082) and appeared three times in the list of the 15 most cited articles. These findings

demonstrate the great scope of these two journals, which are highly relevant to the medical field.

When analyzing the conceptual structure, terms that have already been developed in depth were found to refer to traditional areas related to the study of targets, including the STN, GPi, and basal ganglia. These findings reaffirm the central role that studies on potential targets have played in the subject studied, which has already been addressed when discussing the most cited articles.

The analysis also revealed emerging themes related to DBS in patients with PD, including drug therapy, levodopa, follow-up, and quality of life. This has been gaining prominence as the follow-up of these patients brings up relevant questions about their evolution, such as the combination of drug adjustment with neuromodulation, the importance of considerations about levodopa before and after surgery, and the follow-up of these patients with particular attention to the quality of life, which will ultimately define the success of the treatment.

Through temporal analysis, the trend in the evolution of studies is evident. At the beginning of the research, the study of DBS targets within the thalamocortical basal ganglia loop predominated, with emphasis on the STN, evolving over the years to the approach of cardinal symptoms. Studies have also begun to address axial symptoms (more common in advanced PD), non-motor symptoms, and patients' quality of life.

Finally, it should be noted that this study has some limitations, considering that only a single database, WoS, was used. Although it is a reference platform for scientific citations intended to support scientific and academic research, it does not cover all the available scientific literature.

CONCLUSION

In the bibliometric analysis of DBS in treating PD, it was observed that the publication of articles increased until 2020 and has been declining since then. The top scientific Journal was Movement Disorders, with the highest number of publications and citations. Michael Okun and Andrés Lozano have published the most number of articles.

The institutions that concentrated most on authors were the University of Florida and the University of Toronto; however, it was noted that these authors mainly came from countries in the Northern Hemisphere. The most cited articles and conceptual structure demonstrated the focus of studies on the results of surgery, with the GPi and STN described as the primary targets. When considering the temporal analysis, it became evident that recent studies' addressed axial symptoms (more common in advanced PD), non-motor symptoms, and patients' quality of life.

Further studies with larger patient cohorts and more randomized controlled trials are required to further elucidate the long-term benefits of this technology on motor symptoms and quality of life.

REFERENCES

1. Weaver FM, Follett KA, Stern M, et al. Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes. Neurology. 2012;79(1):55-65. PMID: 22722632; https://doi.org/10.1212/wnl.0b013e31825dcdc1.
2. Odekerken VJ, Boel JA, Schmand BA, et al. GPi vs STN deep brain stimulation for Parkinson disease: three-year follow-up. Neurology. 2016;86(8):755-61. PMID: 26819458; https://doi.org/10.1212/wnl.0000000000002401.
3. Limousin P, Pollak P, Benazzouz A, et al. Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. Lancet. 1995;345(8942):91-95. PMID: 7815888; https://doi.org/10.1016/s0140-6736(95)90062-4.
4. Krack P, Batir A, Van Blercom N, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med. 2003;349(20):1925-34. PMID: 14614167; https://doi.org/10.1056/nejmoa035275.
5. Deuschl G, Antonini A, Costa J, et al. European Academy of Neurology/Movement Disorder Society-European section guideline on the treatment of Parkinson's disease: I. invasive therapies. Mov Disord. 2022;37(7):1360-74. PMID: 35791767; https://doi.org/10.1002/mds.29066.
6. Limousin P, Foltynie T. Long-term outcomes of deep brain stimulation in Parkinson disease. Nat Rev Neurol. 2019;15(4):234-42. PMID: 30778210; https://doi.org/10.1038/s41582-019-0145-9.
7. Zupic I, Čater T. Bibliometric Methods in Management and Organization. Organ Res Methods. 2015;18(3):429-72. https://doi.org/10.1177/1094428114562629.
8. Pajo AT, Espiritu AI, Jamora RDG. Scientific impact of movement disorders research output in Southeast Asian countries: a bibliometric analysis. Parkinsonism Relat Disord. 2020;81:205-12. PMID: 33158748. https://doi.org/10.1016/j.parkreldis.2020.10.043.
9. Listik C, Listik E, Cury RG, et al. Deep brain stimulation treatment in dystonia: a bibliometric analysis. Arq Neuropsiquiatr. 2020;78(9):586-92. PMID: 33053012; https://doi.org/10.1590/0004-282x20200016.
10. Yang C, Wang X, Tang X, Wang R, Bao X. Stem-Cell Research of Parkinson Disease: Bibliometric Analysis of Research Productivity from 1999 to 2018. World Neurosurg. 2020;134:e405-11. PMID: 31655231; https://doi.org/10.1016/j.wneu.2019.10.087.
11. Hu K, Moses ZB, Xu W, Williams Z. Bibliometric profile of deep brain stimulation. Br J Neurosurg. 2017;31(5):587-92. PMID: 28480753; https://doi.org/10.1080/02688697.2017.1324109.
12. Dada O. A model of entrepreneurial autonomy in franchised outlets: A systematic review of the empirical evidence. Int J Manag Rev. 2018;20:206-26. https://doi.org/10.1111/ijmr.12123.
13. Rey-Martí A, Ribeiro-Soriano D, Palacios-Marqués D. A bibliometric analysis of social entrepreneurship. J Bus Res. 2016;69(5):1651-5. https://doi.org/10.1016/j.jbusres.2015.10.033.
14. Moura LKB, de Mesquita RF, Mobin M, et al. Uses of bibliometric techniques in public health research. Iran J Public Health. 2017;46(10):1435-6. PMID: 29308389.

15. Sousa Neto AR, Carvalho ARB, Ferreira da Silva MD, et al. Bibliometric analysis of global scientific production on COVID-19 and vaccines. Int J Environ Res Public Health. 2023;20(6):4796. PMID: 36981704; https://doi.org/10.3390/ijerph20064796.
16. Aria M, Cuccurullo C. ***bibliometrix***: An R-tool for comprehensive science mapping analysis. J Informetr. 2017;11(4):959-75. https://doi.org/10.1016/j.joi.2017.08.007.
17. Araújo CAA. Bibliometria: evolução histórica e questões atuais. EQ. 2006;12(1):11-32. Available from: https://seer.ufrgs.br/index.php/EmQuestao/article/view/16. Accessed in 2023 (Jun. 22).
18. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med. 2006;355(9):896-908. PMID: 16943402; https://doi.org/10.1056/nejmoa060281.
19. Deep-Brain Stimulation for Parkinson's Disease Study Group, Obeso JA, Olanow CW, et al. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med. 2001;345(13):956-63. PMID: 11575287; https://doi.org/10.1056/nejmoa000827.
20. Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. JAMA. 2009;301(1):63-73. PMID: 19126811; https://doi.org/10.1001/jama.2008.929.
21. Benabid AL, Chabardes S, Mitrofanis J, Pollak P. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. Lancet Neurol. 2009;8(1):67-81. PMID: 19081516; https://doi.org/10.1016/s1474-4422(08)70291-6.
22. Follett KA, Weaver FM, Stern M, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N Engl J Med. 2010;362(22):2077-91. PMID: 20519680; https://doi.org/10.1056/nejmoa0907083.
23. Rodriguez-Oroz MC, Obeso JA, Lang AE, et al. Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. Brain. 2005;128(10):2240-9. PMID: 15975946; https://doi.org/10.1093/brain/awh571.
24. Little S, Pogosyan A, Neal S, et al. Adaptive deep brain stimulation in advanced Parkinson disease. Ann Neurol. 2013;74(3):449-57. PMID: 23852650; https://doi.org/10.1002/ana.23951.
25. Bronstein JM, Tagliati M, Alterman RL, et al. Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. Arch Neurol. 2011;68(2):165. PMID: 20937936; https://doi.org/10.1001/archneurol.2010.260.
26. Stefani A, Lozano AM, Peppe A, et al. Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. Brain. 2007;130(6):1596-607. PMID: 17251240; https://doi.org/10.1093/brain/awl346.
27. Kumar R, Lozano AM, Kim YJ, et al. Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. Neurology. 1998;51(3):850-5. PMID: 9748038; https://doi.org/10.1212/wnl.51.3.850.
28. Williams A, Gill S, Varma T, et al. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. Lancet Neurol. 2010;9(6):581-91. PMID: 20434403; https://doi.org/10.1016/s1474-4422(10)70093-4.
29. Benabid AL. Deep brain stimulation for Parkinson's disease. Curr Opin Neurobiol. 2003;13(6):696-706. PMID: 14662371; https://doi.org/10.1016/j.conb.2003.11.001.
30. Witt K, Daniels C, Reiff J, et al. Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study. Lancet Neurol. 2008;7(7):605-14. PMID: 18538636; https://doi.org/10.1016/s1474-4422(08)70114-5.
31. Odekerken VJ, van Laar T, Staal MJ, et al. Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial. Lancet Neurol. 2013;12(1):37-44. PMID: 23168021; https://doi.org/10.1016/s1474-4422(12)70264-8.
32. Okun MS, Fernandez HH, Wu SS, et al. Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: the COMPARE trial. Ann Neurol. 2009;65(5):586-95. PMID: 19288469; https://doi.org/10.1002/ana.21596.
33. Hubert JJ. Linguistic indicators. Soc Indic Res. 1980;8(2):223-55. https://doi.org/10.1007/bf00286478.
34. Traag VA, Waltman L, van Eck NJ. From Louvain to Leiden: guaranteeing well-connected communities. Sci Rep. 2019;9(1):5233. PMID: 30914743; https://doi.org/10.1038/s41598-019-41695-z.
35. Zhong QQ, Zhu F. Trends in Prevalence Cases and Disability-Adjusted Life-Years of Parkinson's Disease: Findings from the Global Burden of Disease Study 2019. Neuroepidemiology. 2022;56(4):261-70. PMID: 35320800; https://doi.org/10.1159/000524208.
36. Fujikawa J, Morigaki R, Yamamoto N, et al. Therapeutic devices for motor symptoms in Parkinson's disease: current progress and a systematic review of recent randomized controlled trials. Front Aging Neurosci. 2022;14:807909. PMID: 35462692; https://doi.org/10.3389/fnagi.2022.807909.
37. Tiago MSF, Almeida FO, Santos LS, Veronezi RJB. Instrumentos de avaliação de qualidade de vida na doença de Parkinson. Rev Neurocienc. 2010;18(4):538-43. https://doi.org/10.34024/rnc.2010.v18.8437.
38. Barcelos RMFM, Sousa GSS, Almeida MV, et al. Qualidade de vida de pacientes com hanseníase: uma revisão de escopo. Rev Esc Enferm USP. 2021;55:e20200357. https://doi.org/10.1590/1980-220x-reeusp-2020-0357.

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hTERT gene methylation in circulating DNA, tumor, and surrounding tissue in breast cancer: a prospective study

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ABSTRACT

BACKGROUND: The human telomerase reverse transcriptase (hTERT) enzyme, encoded by the *hTERT* gene, synthesizes protective telomeric sequences on chromosomes and plays a fundamental role in cancer formation. Methylation of the *hTERT* gene has an upregulatory effect, increasing hTERT enzyme synthesis and allowing continuous tumor cell division.

OBJECTIVE: In a group of patients with breast cancer, we aimed to analyze the methylation status of *hTERT* in the tumor, surrounding tissue, and circulating free deoxyribonucleic acid (cfDNA) of blood collected on the day of mastectomy and then approximately one year later.

DESIGN AND SETTING: A prospective study was conducted at a university hospital in Rio de Janeiro, Brazil.

METHODS: Samples were collected from 15 women with breast cancer on the day of mastectomy and approximately one year postoperatively. cfDNA was analyzed by sodium bisulfite conversion, followed by polymerase chain reaction, electrophoresis, and silver nitrate staining.

RESULTS: Methylation of *hTERT* was detected in the tumors and surrounding tissues of all 15 patients. Five patients displayed *hTERT* methylation in the cfDNA from the blood of the first collection. Of the ten patients who returned for the second collection, three showed methylation. Two patients with methylation in the first collection did not display methylation in the second collection. One patient with no methylation in the first collection displayed methylation in the second collection, and one patient had a diminished level of methylation in the second collection.

CONCLUSION: Only one-third of patients displayed methylation in their cfDNA, which may be related to the success of chemotherapy.

INTRODUCTION

Telomeres are repetitive deoxyribonucleic acid (DNA) sequences found at the ends of chromosomes that protect the chromosomes from degradation and ensure their stability. In each round of normal cell division, telomeres shorten, leading to cellular senescence and, on critical shortening, eventual cell death.[1,2] Human telomerase reverse transcriptase(hTERT) is an enzyme that synthesizes telomeric DNA sequences.[3] The hTERT enzyme is encoded by the *hTERT* gene and contains both a protein component and a ribonucleic acidcomponent.[2] The *hTERT* gene is not expressed in normal postnatal somatic cells, but its expression is elevated in stem, germ, and cancer cells.[4] The expression of *hTERT* in cancer cells allows their continued division, maintains telomere length, and inactivates apoptosis. Various mechanisms enhance the regulation of *hTERT* in tumors, including amplifications, structural changes, mutations, and epigenetic changes.[5] Epigenetic changes are DNA modifications, such as methylation, that do not alter the base sequence but may affect DNA expression. Methylation involves the addition of a methyl group to the cytosine base of cytosine-guanine dinucleotides.[5]

Circulating cell-free DNA (cfDNA) is single or double-stranded extracellular DNA that is released into the bloodstream as a result of cell apoptosis, necrosis, and secretion.[6] Increased levels of cfDNA and epigenetic changes are commonly observed in cancer patients and are associated with the progression of the disease and response to treatment.[7,8] In cancer patients, cfDNA contains sequences from tumors which can serve as biomarkers for early-stage detection or for guiding therapy.[9,10] A better understanding of cfDNA properties, in particular the methylation status, could guide future protocols for monitoring tumor composition and stage.[11] In addition, cfDNA

analysis allows cancer screening through liquid biopsy,[9,6] which has multiple advantages over tissue biopsies, such as not being limited to a single observational region, less invasiveness, and lower cost.[12]

OBJECTIVE

This study aimed to investigate the methylation status of the *hTERT* gene in the tumors, surrounding tissues, and cfDNA of patients with breast cancer. Furthermore, the methylation status of *hTERT* in the cfDNA from blood collected on the day of mastectomy was compared with that from blood collected approximately one year later. To the best of our knowledge, this is the first study to track *hTERT* promoter methylation in cfDNA obtained at two different time points after breast cancer treatment.

METHODS

Study design and patient recruitment

This prospective study included 15 women aged 44 to 78 years (mean age 56.7 ± 9.6 years) diagnosed with breast carcinoma. Patients were admitted to the Institute of Gynecology, Universidade Federal do Rio de Janeiro, Brazil. All women underwent a total mastectomy as part of their treatment. Before surgery, patients were invited to voluntarily participate in the study, and those who agreed to participate signed a consent form after receiving all further clarifications. Recruitment took place between October 2018 and July 2021.The sample size was determined based on the availability of patients who met the study criteria during the recruitment period.

Data collection and ethical approval

Demographic and clinical data were obtained from the patients' medical records. This study was approved by the Clinical Research Ethics Committee of Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Brazil. Certificate: (CAAE) # 91406118.6.0000.5257, August 29, 2018.

Material collection

During mastectomy, sections measuring approximately 1 cm^3 were collected from the tumor and surrounding tissue of each patient for DNA analysis. In addition, 5 ml of peripheral blood was collected to analyze cfDNA. Another blood collection was made approximately one year later for the second cfDNA analysis. Sample collection and histopathological examination were performed at the Institute of Gynecology. Molecular analyses were performed at the Laboratório de Patologia Molecular, Hospital Universitário Clementino Fraga Filho.

Circulating free DNA extraction

DNA was extracted from fresh blood serum using a Quick-gDNA MiniPrep kit (Zymo Research, Orange County, United States), nº D3024, according to the manufacturer's standard protocol.

Extraction of DNA from the tumor and surrounding tissue

DNA extraction from the tumor and surrounding tissue was performed as previously described by McCormick et al.,[13] using the Ultra Pure™ Phenol: Chloroform: Isoamyl Alcohol kit (Invitrogen™, Carlsbad, United States) Cat. No. 15593-031.

Methylation mechanism

DNA samples were modified with sodium bisulfite and analyzed using the Methylation-Specific Polymerase Chain Reaction method. DNA modification was performed using an EZ DNA Methylation-Gold™ Kit (Cat. No: D5005 Zymo Research, Orange County, United States), according to the standard protocol established by the manufacturer.

Polymerase chain reaction (PCR)

To confirm the integrity of the DNA extracted from the samples, a fragment of exon 5 of the *p53* gene was amplified by polymerase chain reaction (PCR). The amplification reaction was performed according to Pestaner et al.,[14] generating a 274-base pair product. For the *hTERT* amplification, two pairs of primers were used as follows: *hTERT-U*(unmethylated) forward, 5′-GAGGTATTTCGGGAGGTTTCGC-3′ and *hTERT-U*reverse, 5′-ACTCCGAACACCACGAATACCG-3′ producing a fragment of 126 base pairs,[15] and *hTERT-M* (methylated) forward, 5′-GGAGGTATTTTGGGAGGTTTTGT-3′and *hTERT-M* reverse, 5′CAAACTCCAAACACCACAAATACCA-3′ producing a fragment of 121 base pairs.[15] PCR conditions were: initial denaturation at 96°C for 7 min followed by 35 cycles of 95°C for 1 min, 62°C for 1 min, and 72°C for 1 min. The final extension step was performed at 72°C for 5 min.

Gel electrophoresis and staining

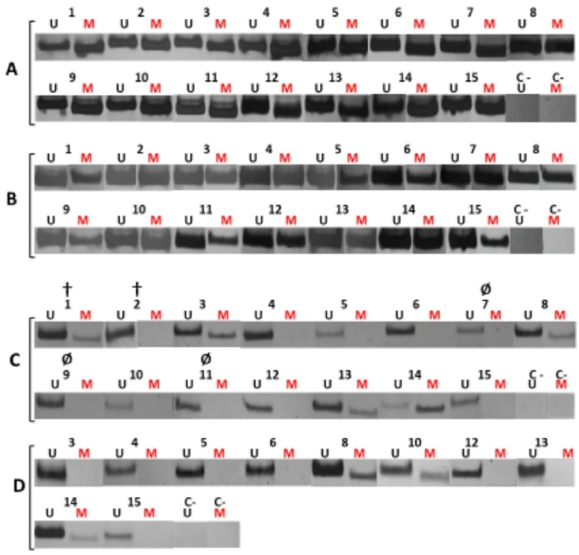
PCR products were electrophoresed on 10% polyacrylamide gels. along with a negative control and a DNA marker. Gels were stained by the silver nitrate method.[16] Briefly, the DNA-containing gels were first fixed with ethanol and acetic acid, followed by impregnation with silver nitrate, and finally, incubation in sodium hydroxide and formaldehyde to reveal the DNA bands.

RESULTS

Methylation of the *hTERT* gene was detected in all 15 patients in tumor cells and surrounding tissues (**Figures 1A** and **B**). Five patients (1, 3, 8, 13, and 14) displayed *hTERT* methylation in cfDNA from the blood of the first collection (**Figure 1C**). Two patients died after the first blood collection and three failed to return for the second blood collection for other reasons. Of the ten patients who returned for the second blood collection, three (8, 10, and 14) displayed *hTERT* methylation (**Figure 1D**). Methylation of *hTERT* was measured in patients 3 and 13in the

first collection, but not in the second collection. Patient14 displayed less methylation in the second collection than in the first.

Figure 2 shows the total breast section removed from a patient (**A**), the tumor fragment (**B**), and the fragment of the surrounding tissue (**C**).



U = unmethylated, M = methylated. †Death after the first collection; ⁰No return to the second collection for reason other than death; C- DNA negative control.

Figure 1. Methylation of the human telomerase reverse transcriptase (*hTERT*) gene. Numbers correspond to patients. A) tumor; B) tumor surrounding tissue; C) blood of the first collection; D) blood of the second collection.

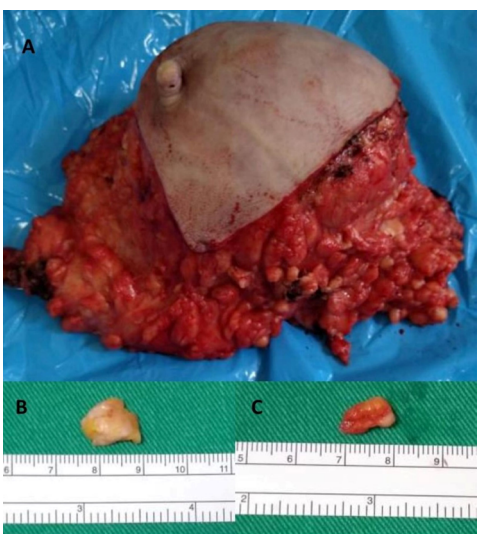


Figure 2. A) total breast section; B) tumor fragment; C) fragment of tumor-surrounding tissue. The top of the ruler is graduated in centimeters.

Table 1 shows the methylation panel of the *hTERT* gene in tumors, surrounding tissues, and blood cfDNA from the first and second collections.

Table 2 shows the patients' age and clinical data (type of treatment and tumor stage).

DISCUSSION

The hTERT enzyme (encoded by the *hTERT* gene) plays a fundamental role in cancer formation by extending telomeres, thereby allowing tumors to avoid cellular senescence and apoptosis.[17] Activity of hTERT is apparent in many cancers, but its

Table 1. Panel of the *hTERT* gene methylation status

Patient	Tumor	Tumor-surrounding tissue	cfDNA of blood of first collection	cfDNA of blood of second collection
1	M	M	M	Death
2	M	M	U	Death
3	M	M	M	U
4	M	M	U	U
5	M	M	U	U
6	M	M	U	U
7	M	M	U	NR
8	M	M	M	M
9	M	M	U	NR
10	M	M	U	M
11	M	M	U	NR
12	M	M	U	U
13	M	M	M	U
14	M	M	M	M
15	M	M	U	U

hTERT = human telomerase reverse transcriptase; M = presence of methylated *hTERT*; U = no presence of methylated *hTERT*; NR = no return for second blood collection for reasons other than death; cfDNA = circulating free DNA.

Table 2. Age and clinical data of patients

Patient	Age	Treatment	TNM stage
1	53	NC	T4b N2 Mx
2	73	WD	WD
3	50	NC	WD
4	44	NC	T3 N0 M0
5	49	NC	CT3 CN2 CM0
6	59	NC	T4 N0 Mx
7	44	NC	T4B N1 Mx
8	49	NC	T3 N1 Mx
9	78	WD	WD
10	57	No treatment	T4 N0 Mx
11	57	NC	T4 N1 Mx
12	56	NC	T4B N0
13	59	Chemotherapy	T3 N1 M0
14	54	No treatment	T4b N2 Mx
15	69	NC	T3 N0 M0

TNM = tumor, node, metastasis; NC = neoadjuvant chemotherapy; WD = TNM stage not described in the records.

expression is not observed in normal somatic cells. In contrast to other cancer-related genes, methylation of the *hTERT* promoter region does not lead to gene silencing, but instead has an upregulatory effect, increasing hTERT protein synthesis in tumor cells.[15] For example, Haraguchi et al showed that hypermethylation of the *hTERT* gene in oral squamous cell carcinoma positively regulated hTERT enzyme synthesis, which was confirmed by immunohistochemistry.[15]

According to the scientific literature, changes in DNA methylation are an early event in tumorigenesis.[10] For instance; one study showed that changes in methylation were detected in plasma four years before clinical diagnosis.[18] Our study investigated the *hTERT* gene methylation status in breast cancer patients. DNA was extracted from tumors, surrounding tissues, and peripheral blood (cfDNA). The analyses revealed *hTERT* hypermethylation in tumors and surrounding tissues of all patients. This is very similar to the results reported by Masood et al.,[19] who found that 94% of breast carcinomas displayed hypermethylation levels at least 2-fold higher than those measured in normal breast tissue. In contrast, in our study, only five of the fifteen patients presented *hTERT* methylation in their cfDNA. This may be due to the efficacy of neoadjuvant chemotherapy before mastectomy; a successful treatment tends to considerably diminish the release of tumor cfDNA into the bloodstream. Furthermore, two patients (3 and 13) displayed methylation in the first blood collection but not in the second, which may also be indicative of the success of treatment before surgery. Similarly, patient 14 showed less methylation in the second collection than in the first, suggesting the effectiveness of neoadjuvant chemotherapy in reducing tumor cfDNA release into the bloodstream.

CONCLUSION

Our finding that only one-third of patients displayed methylation in their circulating DNA may be related to the success of chemotherapy. These results suggest that analysis of *hTERT* methylation in cfDNA could be useful in the follow-up of patients with breast cancer and in the evaluation of their response to treatment. Further studies are required to analyze the methylation of other cancer-related genes in the cfDNA of patients with breast cancer.

REFERENCES

1. Nguyen E, Richerolle A, Sánchez-Bellver J, Varennes J, Ségal-Bendirdjia E. *hTERT* DNA Methylation Analysis Identifies a Biomarker for Retinoic Acid-Induced *hTERT* repression in Breast Cancer Cell Lines. Biomedicines. 2022;10(3):695. PMID: 35327497; https://doi.org/10.3390/biomedicines10030695.
2. Welfer GA, Borin VA, Cortez LM et al. Altered Nucleotide Insertion Mechanisms of Disease-Associated TERT Variants. Genes. 2023;14(2):281. PMID: 36833208; https://doi.org/10.3390/genes14020281.
3. Liu T, Li S, Xia C, Xu D.*TERT* promoter mutations and methylation for telomerase activation in urothelial carcinomas: New mechanistic insights and clinical significance. Front Immunol. 2023;13:1071390. PMID: 36713366; https://doi.org/10.3389/fimmu.2022.1071390.
4. Taheri M, Ghafouri-Fard S, Najafi S, et al. Hormonal regulation of telomerase activity and *hTERT* expression in steroid-regulated tissues and cancer. Cancer Cell Int. 2022;22(1):258. PMID: 35974340; https://doi.org/10.1186/s12935-022-02678-9.
5. Leão R, Apolónio JA, Lee D, et al. Mechanisms of human telomerase reverse transcriptase (h*TERT*) regulation: clinical impacts in cancer. J Biomed Sci. 2018;25(1):22. PMID: 29526163; https://doi.org/10.1186/s12929-018-0422-8.
6. Pfeiferova L, Safarikova M, Ulrych J, et al.Circulating Cell-Free DNA Extraction from Liquid Biopsy for Cancer Research. Folia Biol. 2022;68(4):153-7. PMID: 36871171.
7. Hassan F, Wang JH, Cullinane C, et al. Assessment of cell-free DNA (cfDNA) concentrations in the perioperative period can predict risk of recurrence in patients with non-metastatic breast cancer. Surg Oncol. 2022;42:101753. PMID: 35594723; https://doi.org/10.1016/j.suronc.2022.101753.
8. Stejskal P, Goodarzi H, Srovnal J, et al. Circulating tumor nucleic acids: biology, release mechanisms, and clinical relevance. Mol Cancer. 2023;22(1):15. PMID: 36681803; https://doi.org/10.1186/s12943-022-01710-w.
9. Song P, Wu LR, Yan YH, et al. Limitations and opportunities of technologies for the analysis of cell-free DNA in cancer diagnostics. Nat Biomed Eng. 2022;6(3):232-45. PMID:35102279;https://doi.org/10.1038/s41551-021-00837-3.
10. Gao Q, Zeng Q, Wang Z, et al.Circulating cell-free DNA for cancer early detection. Innovation. 2022;3(4):100259. PMID: 35647572; https://doi.org/10.1016/j.xinn.2022.100259.
11. Birknerova N, Mancikova V, Paul ED, et al. Circulating Cell-Free DNA-Based Methylation Pattern in Saliva for Early Diagnosis of Head and Neck Cancer. Cancers. 2022;14(19):4882. PMID: 36230805; https://doi.org/10.3390/cancers14194882.
12. Chantre-Justino M, Delmonico L, Lage C, et al. Tracking the history of circulating nucleic acids for cancer research in Brazil: A systematic review. Braz J Health Biomed Sci. 2021;20(2):135-43. https://doi.org/10.12957/bjhbs.2021.63966.
13. Maccormick TM, Carvalho CES, Bravo Neto GP, Carvalho MGC. Comparative analysis of glutathione transferase genetic polymorphism, Helicobacter pylori and Epstein-Barr virus between the tumor area and the proximal and distal resection margins of gastric cancer. Rev Col Bras Cir. 2018;46(1):e2068. PMID: 30726307; https://doi.org/10.1590/0100-6991e-20192068.
14. Pestaner JP, Bibbo M, Bobroski L, Seshamma T, Bagasra O. Potential of the *in situ* polymerase chain reaction in diagnostic cytology. Acta Cytol. 1994;38(5):676-80. PMID: 8091896.
15. Haraguchi K, Yada N, Sato S, et al. The methylation status and expression of human telomerase reverse transcriptase is significantly high in oral carcinogenesis. APMIS. 2017;125(9):797-807. PMID: 28766760;https://doi.org/10.1111/apm.12723.

16. Silva MM, Fonseca CO, Moura-Neto R, et al. Influence of *GSTM1* and *GSTT1* polymorphisms on the survival rate of patients with malignant glioma under perillyl alcohol-based therapy. Genet Mol Res. 2013;12(2):1621-30. PMID: 23765968;https://doi.org/10.4238/2013.May.14.2.
17. Dratwa M, Wysoczanska B, Łacina P, Kubik T, Bogunia-Kubik K. TERT—Regulation and Roles in Cancer Formation. Front Immunol. 2020;11:589929. PMID: 33329574; https://doi.org/10.3389/fimmu.2020.589929.
18. Chen X, Gole J, Gore A, et al. Non-invasive early detection of cancer four years before conventional diagnosis using a blood test. Nat. Commun. 2020;11(1):3475. PMID: 32694610; https://doi.org/10.1038/s41467-020-17316-z.
19. Masood S, El-Gabry E, Zhang C, Wang Z. The potential of identification of a malignancy-associated biomarker in breast cancer diagnosis and research: *hTERT* gene DNA methylation. Diagn Cytopathol. 2016;44(8):670-5. PMID: 27229911; https://doi.org/10.1002/dc.23505.

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After receipt of the article through the electronic submission system, it will be read by the editorial team, who will check whether the text complies with the Journal's Instructions for Authors regarding format. The Journal has adopted the *CrossRef Similarity Check* system for identifying plagiarism and any text that has been plagiarized, in whole or in part, will be promptly rejected. Self-plagiarism will also be monitored.

When the general format of the manuscript is deemed acceptable and fully compliant with these Instructions for Authors, and only then, the editorial team will submit the article to the Editor-in-Chief, who will firstly evaluate its scope. If the editor finds that the topic is of interest for publication, he will assign at least two reviewers/referees with expertise in the theme, to evaluate the quality of the study. After a period varying from one to several weeks, the authors will then receive the reviewers' evaluations and will be required to provide all further information requested and the corrections that may be necessary for publication. These reviewers, as well as the Editorial Team and the Editor-in-Chief, may also deem the article to be unsuitable for publication by *São Paulo Medical Journal* at this point.

At the time of manuscript submission, the authors will be asked to indicate the names of three to five referees. All of them should be from outside the institution where the authors work and at least two should preferably be from outside Brazil. The Editor-in-Chief is free to choose them to review the paper or to rely on the *São Paulo Medical Journal's* Editorial Board alone.

Articles will be rejected without peer review if:

- they do not present Ethics Committee approval (or a justification for the absence of this);
- they fail to adhere to the format for text and figures described here.

After peer review

Peer reviewers, associated editors and the Editor-in-Chief may ask for clarifications or changes to be made to the manuscript. The authors should then send their article back to the Journal, with the modifications made as requested. Changes to the text should be highlighted (in a different color or using a text editor tool to track changes). Failure to show the changes clearly might result in the paper being returned to the authors.

The modified article must be accompanied by a letter answering the referees' comments, point by point. The modified article and the response letter are presented to the editorial team and reviewers, who will verify whether the problems have been resolved adequately. The text and the reviewers' final evaluations, along with the response letter, will then be sent to the Editor-in-Chief for a decision.

Manuscripts that are found to be suitable for publication through their scientific merit will be considered "provisionally accepted". However, all articles will subsequently be scrutinized to check for any problems regarding the reporting, i.e. sentence construction, spelling, grammar, numerical/statistical problems, bibliographical references and other matters that may arise, especially in the Methods section. The adherence to reporting guidelines will be checked at this point, and the staff will point out any information regarding methodology or results that the authors should provide. This is done in order to ensure transparency and integrity of publication, and to allow reproducibility.

The editorial team will then provide page proofs for the authors to review and approve. No article is published without this final author approval. All authors should review the proof, although the Journal asks the corresponding author to give final approval.

Submission

Articles should be submitted only after they have been formatted as described below. Texts must be submitted exclusively through the Internet, using the Journal's electronic submission system, which is available at http://mc04.manuscriptcentral.com/spmj-scielo. Submissions sent by e-mail or through the post will not be accepted.

The manuscript should be divided into two files. The first of these, the main document ("blinded"), should contain the article title, article type, keywords and abstract, article text, references and tables, but must omit all information about the authors. The second of these, the "title page", should contain all the information about the authors.

To format these documents, use Times New Roman font, font size 12, line spacing 1.5, justified text and numbered pages.

The corresponding author is responsible for the submission. However, all authors should approve the final version of the manuscript that is to be submitted and should be aware of and approve any changes that might be made after peer review.

Covering letter

All manuscripts must be submitted with a covering letter signed at least by the corresponding author. The letter must contain the following five essential items relating to the manuscript:

1. a declaration that the manuscript is original and that the text is not under consideration by any other journal;
2. a statement that the manuscript has been approved by all authors, who agree to cede the copyrights to the Journal, disclose all sources of funding and declare all potential conflicts of interest;
3. a statement that the study protocol was endorsed by an Internal Review Board (Ethics Committee), including the date and number of the approval (in the case of original articles). This is required for absolutely all studies involving human subjects or patient data (such as medical records), in accordance with the Committee on Publication Ethics (COPE) guidelines, and even for case reports. A copy of the approval document must be submitted to the Journal;
4. each author should indicate a valid, up-to-date email address for contact;
5. a list of a minimum of five potential referees outside of the authors' institutions, who could be invited, at the Editor-in-Chief's discretion, to evaluate the manuscript.

General guidelines for original articles

The following are considered to be full-text original articles: clinical trials; cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies; case series (i.e. case reports on more than three patients analyzed together); and systematic reviews with or without meta-analysis. These types of article should be written with a maximum of 3,500 words (from the introduction to the end of the conclusion).

Typical main headings in the text include Introduction, Methods, Results, Discussion and Conclusion. The authors can and should use short subheadings too, especially those concerning the reporting guideline items.

Trial and systematic review registration policy

São Paulo Medical Journal supports the clinical trial registration policies of the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) and recognizes the importance of these initiatives for registration and international dissemination of information on randomized clinical trials, with open access. Thus, since 2008, manuscripts on clinical trials are accepted for publication if they have received an identification number from one of the public clinical trial registration database (such as ClinicalTrials.gov and/or REBEC and/or the World Health Organization; the options are stated at http://www.icmje.org). The identification number should be declared at the end of the abstract. Articles describing systematic reviews must provide the protocol registration number from a reliable database, such as PROSPERO, Open Science Framework, Cochrane, Joanna Briggs and others. Articles presenting clinical trials or systematic reviews without registration protocols will be promptly rejected without peer review.

Results from cases with DNA sequences must be deposited in appropriate public databases. The protocol number or URL can be requested at any time during the editorial review. Publication of other research data in public repositories is also recommended, since it contributes towards replicability of research, increases article visibility and possibly improves access to health information.

Sample size

All studies published in SPMJ must present a description of how the sample size was arrived at. If it was a convenience or purposive sample, the authors must declare so and explain the characteristics of this sample and recruitment method. For clinical trials, for instance, it is mandatory to inform each of the three main values used to calculate sample size:

- power (usually 80% or more);
- level of significance (usually 0.05 or lower);
- clinically meaningful difference (effect size targeted), according to the main outcome measurement.

Regardless of study results (if "positive" or "negative"), the journal will probably reject articles of trials using underpowered samples, when sample size has not been properly calculated or the calculation has not been fully described as indicated above.

Abbreviations, acronyms and products

Abbreviations and acronyms must not be used, even those in everyday use, unless they are defined when first used in the text. However, authors should avoid them for clarity whenever possible. Drugs or medications must be referred to using their generic names (without capital letters), with avoidance of casual mention of commercial or brand names.

Interventions

All drugs, including anesthetics, should be followed by the dosage and posology used.

Any product cited in the Methods section, such as diagnostic or therapeutic equipment, tests, reagents, instruments, utensils, prostheses, orthoses and intraoperative devices, must be described together with the manufacturer's name and place (city and country) of manufacture in parentheses. The version of the software used should be mentioned.

Any other interventions, such as exercises, psychological assessments or educational sessions, should be described in enough details to allow reproducibility. The Journal recommends that the TIDieR reporting guidelines should be used to describe interventions, both in clinical trials and in observational studies.[13]

Supplementary material

Because supplementary material comprises documents that do not form part of the text of the manuscript, São Paulo Medical Journal will not publish it. The authors should cite an access link that allows readers to view the supplementary material.

Short communications

Short communications are reports on the results from ongoing studies or studies that have recently been concluded for which urgent publication is important. They should be structured in the same way as original articles. The authors of this kind of communication should explain, in the covering letter, why they believe that publication is urgent. Short communications and case reports must be limited to 1,000 words (from the introduction to the end of the conclusion).

Case reports, case series, narrative reviews and letters to the editor

Starting in June 2018, only individual case reports dealing with situations of public health emergencies will be accepted by *São Paulo Medical Journal*. Case reports that had already been accepted for publication up to May 2018 will still be published in a timely manner.

After initial evaluation of scope by the editor-in-chief, case reports, case series and narrative reviews will be considered for peer-review evaluation only when accompanied by a systematic search of the literature, in which relevant studies found (based on their level of evidence) are presented and discussed.[12] The search strategy for each database and the number of articles obtained from each database should be shown in a table. This is mandatory for all case reports, case series and narrative reviews submitted for publication. Failure to provide the search description will lead to rejection before peer review.

The access route to the electronic databases used should be stated (for example, PubMed, OVID, Elsevier or Bireme). For the search strategies, MeSH terms must be used for Medline, LILACS, and Cochrane Library. DeCS terms must be used for LILACS. EMTREE terms must be used for Embase. Also, for LILACS, the search strategy must be conducted using English (MeSH), Spanish (DeCS) and Portuguese (DeCS) terms concomitantly. The search strategies must be presented exactly as they were used during the search, including parentheses, quotation marks and Boolean operators (AND, OR, and NOT). The search dates should be indicated in the text or in the table.

Patients have the right to privacy. Submission of case reports and case series must contain a declaration that all patients gave their consent to have their cases reported (even for patients cared for in public institutions), in text and images (photographs or imaging examination reproductions). The Journal will take care to cover any anatomical part or examination section that might allow patient identification. For deceased patients whose relatives cannot be contacted, the authors should consult the Editor-in-Chief. All case reports and case series must be evaluated and approved by an ethics committee.

Case reports should be reported in accordance with the CARE Statement,[7] including a timeline of interventions. They should be structured in the same way as original articles.

Case reports must not be submitted as letters. Letters to the editor address articles that have been published in the *São Paulo Medical Journal* or may deal with health issues of interest. In the category of letters to the editor, the text has a free format, but must not exceed 500 words and five references.

FORMAT: FOR ALL TYPES OF ARTICLES

Title page

The title page must contain the following items:

1. Type of paper (original article, review or updating article, short communication or letter to the editor);
2. Title of the paper in English, which should be brief but informative, and should mention the study design.[14] Clinical trial, cohort, cross-sectional or case-control study, and systematic review are the most common study designs. Note: the study design declared in the title should be the same in the methods and in the abstract;
3. Full name of each author. The editorial policy of the *São Paulo Medical Journal* is that abbreviations of authors' names must not be used; therefore, we ask that names be stated in full, without using abbreviations;
4. Place or institution where the work was developed, city and country;
5. Each author should indicate the way his/her name should be used in indexing. For example: for "João Costa Andrade", the indexed name could be "Costa-Andrade J." or "Andrade JC", as preferred;
6. The author's professional background (Physician, Pharmacist, Nurse, Dietitian or another professional description, or Undergraduate Student); and his/her position currently held (for example, Master's or Doctoral Student, Assistant Professor, Associate Professor or Professor), in the department and institution where he/she works, and the city and country (affiliations);

7. Each author should present his/her ORCID identification number (as obtained from HYPERLINK "http://www.orcid.org/" www.orcid.org);
8. Each author must inform his contribution, preferably following the CRediT system (see above in Authorship);
9. Date and venue of the event at which the paper was presented, if applicable, such as congresses, seminars or dissertation or thesis presentations.
10. Sources of financial support for the study, bursaries or funding for purchasing or donation of equipment or drugs. The protocol number for the funding must be presented with the name of the issuing institution. For Brazilian authors, all grants that can be considered to be related to production of the study must be declared, such as fellowships for undergraduate, master's and doctoral students; along with possible support for postgraduate programs (such as CAPES) and for the authors individually, such as awards for established investigators (productivity; CNPq), accompanied by the respective grant numbers.
11. Description of any conflicts of interest held by the authors (see above).
12. Complete postal address, e-mail address and telephone number of the author to be contacted about the publication process in the Journal (the "corresponding author"). This author should also indicate a postal address, e-mail address and telephone number that can be published together with the article. *São Paulo Medical Journal* recommends that an office address (rather than a residential address) should be informed for publication.

Second page: abstract and keywords

The second page must include the title and a structured abstract in English with a maximum of 250 words. References must not be cited in the abstract.

The following headings must be used in the structured abstract:

- Background – Describe the context and rationale for the study;
- Objectives - Describe the study aims. These aims need to be concordant with the study objectives in the main text of the article, and with the conclusions;
- Design and setting – Declare the study design correctly, and the setting (type of institution or center and geographical location);
- Methods – Describe the methods briefly. It is not necessary to give all the details on statistics in the abstract;
- Results – Report the primary results;
- Conclusions – Make a succinct statement about data interpretation, answering the research question presented previously. Check that this is concordant with the conclusions in the main text of the article;
- Clinical Trial or Systematic Review Registration – Mandatory for clinical trials and systematic reviews; optional for observational studies. List the URL, as well as the Unique Identifier, on the publicly accessible website on which the trial is registered.
- MeSH Terms - Three to five keywords in English must be chosen from the Medical Subject Headings (MeSH) list of Index Medicus, which is available at http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh.These terms will help librarians to quickly index the article.
- Author keywords - The authors should also add three to six "author keywords" that they think express the main article themes. These keywords should be different from the MeSH terms and preferably different from words already used in the title and abstract, so as to improve the discoverability of the article by readers doing a search in PubMed. They provide an additional chance for the article to be retrieved, read and cited. Combinations of words and variations (different wording or plurals, for example) are encouraged.

References

For any manuscript, all statements in the text that do not result from the study presented for publication in the *São Paulo Medical Journal* but from other studies must be accompanied by a quotation of the source of the data. All statements regarding health statistics and epidemiological data should generally be followed by references to the sources that generated this information, even if the data are only available electronically.

São Paulo Medical Journal uses the reference style known as the "Vancouver style," as recommended by the International Committee of Medical Journal Editors (ICMJE). Follow the instructions and examples at www.icmje.org, item "References", for the format.

In the text, the references must be numbered in the order of citation. The citation numbers must be inserted after periods/full stops or commas in sentences, and in superscript (without parentheses or square brackets). References cited in the legends of tables and figures must maintain sequence with the references mentioned in the text.

In the list of references, all the authors must be listed if there are up to and including five authors; if there are six or more, the first three should be cited, followed by the expression "et al." For books, the city of publication and the name of the publishing house are mandatory. For texts published on the internet, the complete uniform resource locator (URL) or address is necessary (not only the main home page of a website or link), so that by copying the complete address into a computer internet browser, the Journal's readers will be taken to the exact document cited, and not to a general website.

At the end of each reference, please insert the "PMID" number (for papers indexed in PubMed) and the link to the "DOI" number if available.

Authors are responsible for providing a complete and accurate list of references. All references cited in the text must appear in the reference list, and every item in the reference list must be cited in the text. Also, citations must be in the correct sequence.

Manuscripts that do not follow these guidelines for references will be returned to the authors for adjustments.

The reference list should be inserted after the conclusions and before the tables and figures.

Figures and tables

Images must be submitted at a minimum size that is reproducible in the printed edition. Figures should be sent at a resolution of 300 DPI and minimum size of 2,500 pixels (width) and be recorded in ".jpg" or ".tif" format. Images submitted in inadequate formats will not be accepted.

Images must not be embedded inside Microsoft PowerPoint or Microsoft Word documents, because this reduces the image size. Authors must send the images separately, outside of .doc or .ppt documents. Failure to send the original images at appropriate sizes leads to paper rejection before peer review.

Flowcharts are an exception: these must be drawn in an editable document (such as Microsoft Word or PowerPoint), and should not be sent as an image that can't be changed.

Figures such as bars of line graphs should be accompanied by the tables of data from which they have been generated (for example, sending them in the Microsoft Excel spreadsheets, and not as image files). This allows the Journal to correct legends and titles if necessary, and to format the graphs according to the Journal's style. Graphs generated from software such as SPSS or RevMan must be generated at the appropriate size, so that they can be printed (see above). Authors must provide internal legends/captions in correct English.

All the figures and tables should be cited in the text. All figures and tables must contain legends or titles that precisely describe their content and the context or sample from which the information was obtained (i.e. what the results presented are and what the kind of sample or setting was). The reader should be able to understand the content of the figures and tables simply by reading the titles (without the need to consult the text), i.e. titles should be complete. Acronyms or abbreviations in figure and table titles are not acceptable. If it is necessary to use acronyms or abbreviations inside a table or figure (for better formatting), they must be spelled out in a legend below the table or figure.

For figures relating to microscopic findings (i.e. histopathological results), a scale must be embedded in the image to indicate the magnification used (just like in a map scale). The staining agents (in histology or immunohistochemistry evaluations) should be specified in the figure legend.

DOCUMENTS CITED

1. Internal Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Available from: http://www.icmje.org/recommendations/. Accessed in 2019 (March 11).
2. The CONSORT Statement. Available from: http://www.consort-statement.org/. Accessed in 2018 (May 3).
3. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Br J Surg 2002. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1365-2168.2000.01610.x. Accessed in 2019 (April 4).
4. PRISMA. Transparent Reporting of Systematic Reviews and Meta-Analyses. Available from: www.prisma-statement.org. Accessed in 2019 (April 4).
5. STROBE Statement. Strengthening the reporting of observational studies in epidemiology. What is strobe? Available from: http://www.strobe-statement.org/. Accessed in 2018 (May 3).
6. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(4):344-9. PMID: 18313558. doi: 10.1016/j.jclinepi.2007.11.008.
7. The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development. Enhancing the QUAlity and Transparency Of health Research. Available from: https://www.equator-network.org/reporting-guidelines/care/. Accessed in 2018 (May 3).
8. STARD Statement. STAndards for the Reporting of Diagnostic accuracy studies. Available from: http://www.equator-network.org/reporting-guidelines/stard/. Accessed in 2018 (May 3).
9. Rennie D. Improving reports of studies of diagnostic tests: the STARD initiative. JAMA. 2003;289(1):89-90. doi:10.1001/jama.289.1.89.
10. International Committee of Medical Journal Editors (ICMJE). Defining the Role of Authors and Contributors. Available from: http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html. Accessed in 2019 (March 11).
11. International Committee of Medical Journal Editors. Overlapping Publications. Available from: http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/overlapping-publications.html. Accessed in 2018 (Feb 18).
12. Phillips B, Ball C, Sackett D, et al. Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009). Available from: https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Accessed in 2018 (May 3).
13. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014;348:g1687. PMID: 24609605; doi: 10.1136/bmj.g1687.
14. Non-randomised controlled study (NRS) designs. Available from: http://childhoodcancer.cochrane.org/non-randomised-controlled-study-nrs-designs. Accessed in 2018 (May 3).

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