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Macro-costing of the use of bortezomib in the treatment of multiple myeloma from the perspective of the SUS

Macrocusteio do uso do bortezomibe no tratamento do mieloma múltiplo na perspectiva do SUS

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ABSTRACT

Introduction: Bortezomib is one of the most widely used medicines in the treatment of multiple myeloma (MM). **Objective**: To conduct a macro-costing study of the use of bortezomib in the treatment of MM from the perspective of the Unified Health System (SUS). **Methods**: Direct costs related to the acquisition of bortezomib were considered. The annual incidence of MM cases and the estimated number of patients undergoing treatment were calculated using data from the Department of Information Technology of the Unified Health System (DATASUS). The cost of bortezomib was obtained from the Health Price Database (BPS). The approximate cost per patient was compared to the amount reimbursed by the Outpatient Procedure Authorization (APAC). Two treatment possibilities were considered: 9 cycles, used for patients who are candidates for autologous hematopoietic stem cell transplantation (ASCT) (30% of the population); and 12 cycles used for patients who are not candidates for ASCT (70%). **Results**: Considering 1.3mg/m^2 and 1.5mg/m^2, and a dose wastage of 10%, the cost per patient in 9 cycles was R$17,678.30 and R$18,023.64, respectively. For 12 cycles the cost was R$23,569.94 for a dose of 1.3mg/m^2 and R$24,030.39 for a dose of 1.5mg/m^2. According to the current APAC value, which is R$5,224.65, the total amount paid for the treatment of 9 cycles is R$47,021.85 and for 12 cycles it is R$62,695.80**. Discussion and Conclusion**: The average cost of treatment with bortezomib per patient was R$22,100.59, and the amount reimbursed by APAC was R$57,993.62. However, it is emphasized that only the direct costs of acquiring bortezomib were computed.

Keywords: Gross Costing; Multiple Myeloma; Bortezomib.

RESUMO

Introdução: O bortezomibe é um dos medicamentos mais utilizados no tratamento do mieloma múltiplo (MM). **Objetivo:** Realizar um estudo de macrocusteio do uso do bortezomibe no tratamento do MM na perspectiva do Sistema Único de Saúde (SUS). **Métodos:** Foram considerados os custos diretos relacionados à aquisição do bortezomibe. A partir dos dados do Departamento de Informática do Sistema Único de Saúde (DATASUS) foram calculadas a incidência anual de casos de MM e a estimativa de pacientes em tratamento. O custo do bortezomibe foi obtido no Banco de Preços de Saúde (BPS). O custo aproximado por paciente foi comparado ao valor reembolsado pela Autorização de Procedimento Ambulatorial (APAC). Foram consideradas duas possibilidades de tratamento: 9 ciclos, utilizados para pacientes candidatos ao transplante autólogo de células-tronco hematopoiéticas (TACTH) (30% da população); e 12 ciclos utilizados para pacientes não candidatos ao TACTH (70%). **Resultados:** Considerando 1,3mg/m^2 e 1,5mg/m^2, e um desperdício de dose de 10%, o custo por paciente em 9 ciclos foi de R$17.678,30 e R$18.023,64, respectivamente. Para 12 ciclos o custo foi R$23.569,94 para dose de 1,3mg/m^2 e R$24.030,39 para dose de 1,5mg/m^2. De acordo com o valor da APAC atual, que é de R$ 5.224,65, o valor total pago pelo tratamento de 9 ciclos é de R$ 47.021,85 e para 12 ciclos é de R$62.695,80. **Discussão e Conclusão:** O custo médio do tratamento com bortezomibe por paciente foi de R$22.100,59, e o valor reembolsado pela APAC R$57.993,62. Entretanto, enfatiza-se que foram computados apenas os custos diretos da aquisição do bortezomibe.

Palavras-chave: Estudo de Macrocusteio; Mieloma Múltiplo; Bortezomibe.

Introduction

Multiple myeloma (MM) is a malignant hematological neoplasm characterized by the multiplication of malignant plasma cells in the bone marrow. Bortezomib is one of the most commonly used medications in first-line treatment and subsequent relapses, both in monotherapy and in various combinations with other medications.[1]

MM accounts for about 1% of all neoplasms and 10% of hematological neoplasms. An incidence estimate conducted in 185 countries revealed approximately 160,000 diagnoses made globally in 2018.[2]

The principles of antineoplastic therapy currently rely on an induction period (two to six monthly cycles), followed by autologous hematopoietic stem cell transplantation (ASCT) in eligible patients, and subsequent maintenance until disease progression (relapse) or limiting toxicity. Patients who are not eligible for transplantation receive, after induction, two to four consolidation cycles with the same chemotherapy regimen as the induction and proceed directly to maintenance.[3]

Until the late 1990s, therapy relied on corticosteroids, alkylating agents and anthracyclines (cyclophosphamide, cisplatin, dexamethasone/prednisone, doxorubicin, etoposide, melphalan), resulting in a life expectancy of around two and a half years, with a five-year survival rate of about 30% to 35%.[4]

The last 20 years have been marked by new therapies, significantly improving the survival of patients with MM in developed countries. In the United States and Europe, there has been a five-year survival increase to 50% to 55% during this period.[5,6] This increase in survival was observed after the introduction of thalidomide, bortezomib, and lenalidomide.[7-9] A cohort of 387 patients who relapsed after ASCT, those treated with one or more of these three therapies had a median survival two years higher than those who did not have access to these medications.[4]

Bortezomib is a proteasome inhibitor with antineoplastic action, mainly used in the treatment of MM and, in some cases, lymphomas. Its mechanism of action involves blocking the activity of the proteasome, a cellular structure responsible for degrading regulatory proteins (including those involved in the cell cycle and apoptosis). This leads to the accumulation of damaged proteins and the activation of pathways that induce apoptosis (programmed cell death) in neoplastic cells.[7] Its therapeutic advantages include: rapid response due to direct cytotoxic effect, with improvement in weeks; synergism with other drugs, combining well with immunomodulators (thalidomide/lenalidomide) and chemotherapeutics; and administration preferably via subcutaneous route, performed on an outpatient basis, reducing hospitalizations.[7] In 2016, a systematic review published by the *Cochrane* Collaboration on the use of bortezomib for the treatment of MM showed significant improvement in important outcomes, such as overall survival, reinforcing its indication as standard therapy for the disease.[10]

However, despite the promising effects of bortezomib in the treatment of MM, a retrospective study of a cohort of 1,103 patients from Latin America with MM, followed from 2008 to 2016 (including 287 from Brazil), revealed that bortezomib treatment was predominantly restricted to patients from private clinics and associated with better outcomes, regardless of eligibility for autologous stem cell transplantation.[11] This scenario prompted the evaluation and subsequent incorporation of bortezomib into the Unified Health System (SUS) in September 2020, making it a fundamental pillar in the first-line treatment of the disease and one of the most used medications in subsequent relapses.[12, 13]

The incorporation of bortezomib into the SUS represented a significant advance, expanding therapeutic options for patients with MM. This generated an expectation of increased overall survival, primarily benefiting the portion of the Brazilian population that previously did not have access to these innovative medications.[11] However, bortezomib has a high cost and is therefore made available in the SUS through the completion of the High Complexity Procedure Authorization (APAC). APACs are administrative instruments that authorize the performance of high-complexity and high-cost procedures in the SUS, ensuring adequate funding for these services.

The reimbursement of APACs to health service providers (hospitals and clinics) is carried out by the federal government, based on the values established in a reference table. These amounts cover the direct costs associated with the procedure, whi-

ch include the medication (in this case, bortezomib), the materials used, medical fees, and other costs related to treatment. However, it is important to note that the APAC value may not fully cover all costs involved, necessitating health services to seek other funding sources to complement the budget.[14] In this context, although new health technologies bring improvements in patient prognosis, concerns about their high costs and their potential impact on the health budget remain, which could compromise the principles of equity and comprehensiveness of the SUS.

Thus, the objective of this study was to conduct a macro-costing study of the use of bortezomib in the treatment of MM from the perspective of the SUS, as well as to compare this cost to the amount reimbursed to health systems by APAC.

The realization of this macro-costing, comparing it to the amount transferred by APAC for bortezomib in the SUS, is justified by the need to assess the financial sustainability of large-scale treatment. This study allows estimating the real cost considering the number of eligible patients, the price paid by the SUS versus production/acquisition costs, and the long-term budgetary impact, promoting transparency and expenditure control by identifying possible distortions between the real cost and the amount transferred to providers.

Methods

A macro-costing study of the use of bortezomib in the treatment of MM was conducted. The choice for this analysis was an express demand from the Ministry of Health through Call CNPq/DGITS/SCTIE/MS No. 19/2021, in which this project was contemplated with process 423641/2021-2. Initially, the proposed need was a study evaluating the budgetary impact, but since bortezomib had already been incorporated into the SUS, it was recommended to conduct this macro-costing study.

The eligible population for treatment was estimated considering data from the Brazilian population provided by the information system of the Brazilian Institute of Geography and Statistics (IBGE) and the number of deaths from MM from the Department of Information Technology of the Unified Health System (DATASUS) in the last five years (2017-2021). Since this is a disease with high morbidity and mortality[15] in a period with unavailability of this medication, it was considered that patients with the disease were frequently diagnosed, treated, and progressed to death, as well as that the number of patients in remission is as few as those without diagnoses. Thus, it was considered that the number of deaths equals the number of diagnosed and eligible patients for treatments, allowing a good estimate of the target population for this study. From these data, the annual incidence of MM cases and the approximate estimate of the number of patients affected by MM in Brazil in 2023 were calculated.

The average cost of the bortezomib vial was calculated using the values provided in the Health Price Database (BPS), and the waste calculation was estimated considering a 10% rate based on the routine of a hematology outpatient clinic in the interior of São Paulo.

Cost Assessment and Analysis

Costs from the perspective of the SUS were computed as provided and transferred by the Procedure Table Management System, Medicines and Orthoses, Prosthetics and Special Materials (SIGTAP) regarding the use of bortezomib in the treatment of MM: Multiple Myeloma Chemotherapy - 1st line (Code: 03.04.03.025-2) and Multiple Myeloma Chemotherapy - 2nd line (Code: 03.04.03.026-0). Only direct costs related to the acquisition of bortezomib were considered. Costs with follow-up tests, consultations, hospitalizations, supplies, and human resources were not taken into account, as these costs exist regardless of the use of this medication for treatment.

The cost of bortezomib was computed considering the drug's penetration in the market and the SUS potential to request lower prices from private companies; thus, the negotiated values in the BPS between 09/01/2020 and 12/31/2022 were considered. To homogenize the value of the bortezomib vial, which presented disparate values in different states of the Union at the time researched, a weighted average was chosen considering the unit cost of the vial and the number of items purchased, discarding purchases with fewer than 70 items due to their

lower potential for price negotiation. The number of 70 items was chosen as it is considered the average number of vials needed for the complete treatment of just one individual, thus avoiding that disparate values might distort the analysis, as significantly lower purchases are not expected.

The treatment of MM with bortezomib is administered in cycles, with each treatment cycle corresponding to a weekly application lasting four weeks. The dose administered in each cycle varies, being considered as 1.5mg/m² for 70% of the sample and 1.3mg/m² for the remaining 30%. Other variations were considered, such as administering a smaller number of treatment cycles for the population eligible for autologous hematopoietic stem cell transplantation (ASCT). For patients eligible for ASCT, 30% of the sample population, 9 cycles were considered, while for those not eligible, 70% of the sample, 12 cycles were considered.[13]

The estimates of the percentage of the population eligible for transplantation, the number of cycles and the medication dose were based on discussions with two hematologist specialists: L.O.C and R. D.G. Finally, the dose wastage in the administration of bortezomib was simulated based on information provided by the coordinating nurse of a hematology outpatient clinic in the interior of São Paulo; thus, costs with wastage of 5%, 10%, and 15% were considered, as well as without any dose wastage. The data on the number of cycles, dose, and wastage are described in Table 2. The approximate cost per patient was compared to the amount reimbursed by APAC.

Economic Model

An Excel spreadsheet was prepared to aggregate the necessary information and perform calculations for estimating the cost automatically. It comprises several sub-spreadsheets involving general project information, detailed parameters used as the basis for calculating the different uses of the aforementioned medication (dose, duration, treatment costs), retrospective and prospective costs by scenario, possible dose wastage, and sensitivity analyses.

Table 1. Costs of the Bortezomib Vial in Different States of the Union and the Weighted Average According to the BPS from 01/09/20 to 31/12/22.

	Weighted average cost of the ampoule			
State	**Unit Cost ($)**	**Quantity of Items Purchased**	**Subtotal ($)**	**Weighted Average** ($)
PE	116,70	2772	323.492,40	
MS	280,00	175	49.000,00	
PE	280,00	924	258.720,00	
PE	285,00	2394	682.290,00	
ES	287,50	800	230.000,00	
MG	380,00	140	53.200,00	
BA	446,00	300	133.800,00	
SC	550,00**	66	36.300,00	
ES	563,99	500	281.995,00	
TO	579,00	1092	632.268,00	
MG	670,00	140	93.800,00	
SP	749,00**	48	35.952,00	
PE	758,33	798	605.147,34	
SC	904,56	95	85.933,20	
CE	1.260,00**	50	63.000,00	
Total		**10130**	**3.429.645,94**	**338,56**

**Costs with fewer than 70 items purchased were disregarded
Source: Prepared by the authors.

All prices and costs were obtained and presented in Brazilian reais (R$), and the database for updating the cost calculation values was August 2022.Monetary correction for inflation was performed considering the Broad Consumer Price Index (IPCA-IBGE) for the period from August 2020 to August 2021—the dates from which the values were consulted in the sources (BPS and SIGTAP).

To determine the cost per individual, the cost of the medication was considered along with the necessary supply costs for its application. However, the supply costs associated with treatment are not described in detail in the APAC. To standardize the comparison, and considering that the administration of bortezomib overlaps with prior treatment, the value reimbursed by APAC for the treatment of MM before the incorporation of bortezomib was considered as the cost of supplies related to the use of bortezomib, which corresponds to R$1,715.60. To obtain the cost with the medication, the number of vials required per cycle was multiplied by the vial value and the number of cycles needed. The number of vials required was the result of multiplying the dose by the average body surface area of an adult male Brazilian individual weighing 70 kg (1.809 m^2), divided by the vial content (3.5mg).[13] Regarding the treatment cycles with bortezomib, for patients eligible for autologous hematopoietic stem cell transplantation (ASCT) (30% of the population) nine cycles are used, and for patients not eligible for ASCT (70% of the population), twelve cycles are utilized. [13] The formula used for calculating vials was as follows:

Number of vials = (Dose x 1.809) / 3.5

Dose wastage was calculated by multiplying the number of vials by a coefficient of 1.05, 1.10, and 1.15 for 5%, 10%, and 15%, respectively. Thus, the cost per individual resulted from the following calculation:

Cost = (Number of cycles x R$ 1715.60) + (Number of vials x wastage coefficient x Number of cycles)

The average value was obtained from the weighted average according to the percentage considered for each dose application and the number of cycles, in addition to a wastage of 10% (coefficient 1.10). Minimum and maximum values were also generated according to the variation in medication costs and dose wastage.

Sensitivity Analysis

Sensitivity analyses were univariate and considered the dose, drug price, number of cycles, and wastage.

Results

For the year 2023, an average of 3,337 individuals undergoing MM treatment in the SUS was estimated. The average cost of the bortezomib vial was R$338.56. Considering nine treatment cycles, the cost of bortezomib per patient for the dose of 1.3mg/m^2 was R$17,475.17, and for the dose of 1.5mg/m^2 was R$17,790.03. Considering twelve cycles, the cost per patient was R$23,299.09 for dose 1.3mg/m^2 and R$23,718.91 for dose 1.5mg/m^2. The average cost per patient was R$21,823.75 (Table 2).

Considering a dose wastage of 10%, the cost per patient in nine cycles would be R$17,678.30 for the dose of 1.3mg/m^2 and R$18,023.64 for the dose of 1.5mg/m^2, and for twelve cycles, the cost was R$23,569.94 for dose 1.3mg/m^2 and R$24,030.39 for dose 1.5mg/m^2. The average value per patient was R$22,100.59 (Table 2).

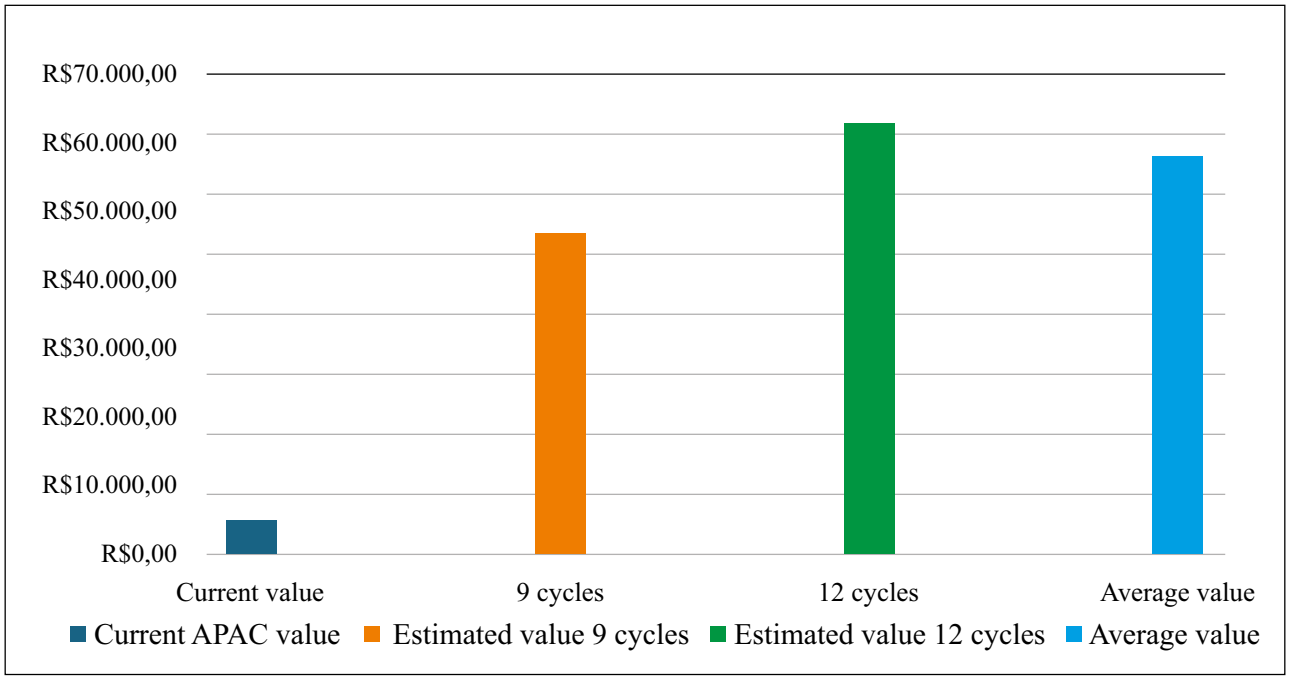
Table 2. Description of Cycles, Doses, Treatment Costs with Bortezomib and Waste Scenarios Costs.

Cycles	Dose	Cost/Patient	Waste Scenarios (10%)
9	1,3mg/m^2	R$17.475,17	R$17.678,30
	1,5mg/m^2	R$17.790,03	R$18.023,64
12	1,3mg/m^2	R$23.299,09	R$23.569,94
	1,5mg/m^2	R$23.718,91	R$24.030,39

Source: Prepared by the authors.

According to the current APAC value, which is R$5,224.65, the total amount paid for the treatment of nine cycles is R$47,021.85 and for twelve cycles, it is R$62,695.80, with an average of R$57,993.62 (Figure 1).

Figure 1. Estimated Values Paid by APAC.



Source: Prepared by the authors.

Discussion

This study conducted a macro-costing of the use of bortezomib in the treatment of MM from the perspective of the SUS, comparing it to the value transferred by APAC. The project met the demand of Call CNPq/DGITS/SCTIE/MS No. 19/2021 - Evaluation of Health Technologies Incorporated into the SUS and was contemplated with process No. 423641/2021-2.

Cost studies can support the optimization of public resources,[16] revising transfers to other areas of health if the real cost is lower than the APAC value, or justifying adjustments and seeking alternatives such as price negotiations with suppliers if the real cost is higher. Moreover, they align with the health management policies of the SUS, using economic evaluation methodologies to underpin the review of clinical protocols and the incorporation of new medications, even though bortezomib is already included, allowing for adjustments in indications or dosages. Macro-costing studies operate with aggregated cost item data, usually sourced from electronic databases.[16-18] In macro-costing, only the cost elements that impact the healthcare service being studied are identified.[18]

The analysis addressed the cost to the SUS of treating MM patients with bortezomib, including only the direct costs related to its acquisition through the total APAC value. The APAC value covers the costs associated with procedures and health treatments considered high complexity, which are funded by the SUS. This value is transferred by the Ministry of Health or by state/municipal health departments to service providers (hospitals, clinics, etc.) that perform these procedures. Generally, these costs involve: main medical procedure, materials and medical supplies, multidisciplinary team, hospital structure, and operational costs.[19]

The average cost of treatment with bortezomib per patient was R$22,100.59, while the amount reimbursed by APAC is R$57,993.62, which indicates that the treatment of MM with bortezomib is financially viable for the SUS. This difference can be interpreted as a margin that covers other costs associated with high-complexity care, such as medical procedures and supplies. However, it is important to note that only direct costs related to the acquisition of bortezomib were considered, excluding crucial expenditures, such as human resources and the infrastructure necessary for administering treatment. This limitation may generate a distorted perception

of the real financial sustainability of treatment, as it does not take into account all the expenses that the health system needs to support.

Moreover, this lack of consideration may result in funding decisions that do not reflect the totality of the costs involved, creating risks of distortions in understanding incentives and the equitable allocation of health resources. However, as established by Complementary Law No. 141 of January 13, 2012, the SUS is decentralized, with shared management among municipalities, states, and the Union.[20] Therefore, public hospitals need to seek alternative funding to complement SUS resources. Thus, the fact that the average cost of treating MM with bortezomib is lower than the total APAC value reinforces its viability in the context of the SUS.

The comparison between macro-costing and the APAC value, even for medications already incorporated like bortezomib, is essential to ensure that the SUS is paying a fair price, optimizing resources, and maintaining the sustainability of the system. his practice is crucial for the efficient management of public health.

Regarding the funding of bortezomib in other countries, in the United States, MM treatment with bortezomib can be funded from various sources, depending on the type of health coverage of the patient. This includes private health insurance, *Medicare* and *Medicaid* systems, as well as patient assistance programs offered by the pharmaceutical industry.[21]In the United Kingdom, treatment of MM with bortezomib is primarily funded by the *National Health Service (NHS)*, following specific guidelines, and is available to patients who meet clinical criteria.[21] In Europe, the funding of MM treatment with bortezomib varies according to each country's health system, but generally follows models of public coverage, private insurance, or assistance programs.[23]

Study Limitations

This study presented some limitations. One of them was the scarcity of data regarding dose wastage. In the hematology outpatient clinic assessed in the study, this situation does not occur, as they have a well-structured and organized routine, preventing doses from being prepared without certainty that the patient will be present to receive the dose. However, it is known that this scenario does not reflect the reality of all services providing this type of care in Brazil. Another limitation was the difficulty concerning the values negotiated in the BPS; values regarding the acquisition of bortezomib were not found in all Brazilian states, and the states of the Union that appeared in the research presented quite disparate values among them. A third limitation found was the issue of not finding a complete and detailed description of the items covered by the amount offered by the APAC paid by the SUS.

A macro-costing study is a useful type of study for an initial analysis or an overview of the costs related to a health technology. However, it has some limitations: it is a study that works with aggregated costs, therefore not considering indirect costs, and since it uses average data and global estimates, the results tend to be less precise than those obtained by more detailed methods.[24]

Conclusion

It was observed that the cost covered by the current APAC is higher than the direct cost of acquiring bortezomib. However, it is important to emphasize that, in this study, only direct expenditures related to the acquisition of bortezomib were considered. As this is a macro-costing study, follow-up exam costs, consultations, hospitalizations, supplies, and human resources were not taken into account, although these additional costs are covered by the APAC. Despite this, the fact that the cost of acquiring bortezomib in the treatment of multiple myeloma is lower than the APAC value represents a positive impact on patients' access to this health technology, in addition to favoring the sustainability and quality of MM treatment in the SUS.

Ethical and Legal Aspects

This research project used only secondary data from public databases and literature review. Therefore, it is exempt from registration or evaluation by the CEP/CONEP system, according to Article 1 of the CNS Resolution No. 510, of April 2016, Sole Paragraph, items V and VI, which states that

research with databases, whose information is aggregated, without the possibility of individual identification, and research conducted exclusively with scientific texts for review of scientific literature will not be registered or evaluated by the CEP/CONEP system.

Authors' contributions
MAFMN, LOC, RDG, and VSNN: Concept and design and critical review of the article for relevant intellectual content; MAFMN, LFOS; VSNN: Data acquisition and data analysis and interpretation; MAFMN and VSNN: Writing of the manuscript.

Conflicts of Interest
There are no conflicts of interest in this project.

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Data Availability Statement
The contents are already available in the article.

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