

Factors associated with the hospitalization of users referred from primary health care to follow-up in Psychosocial Care Centers in the city of São Paulo, Brazil

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Abstract *This study evaluated factors associated with hospitalization related to the mental health of people undergoing follow-up in Psychosocial Care Centers (CAPS, in Portuguese) in the city of São Paulo, Brazil, referred from Primary Health Care (PHC). This was an evaluative study conducted with 297 individuals in 24 adult CAPS. This study analyzed the prevalence ratios (PR) and their respective 95% confidence intervals (95% CI), obtained through Poisson Regression with robust variance. A statistically significant association was found with hospitalization during follow-ups in CAPS: having health insurance and/or medical plan; waiting time between the diagnosis and the first consultation with a non-medical professional of more than seven days; not having received medical advice regarding how long to use medication; not having received a psychopharmaceutical prescription at PHC; and having a medical history of the hospitalization due to mental health. The results warn of the need to expand access to the more socially vulnerable population, in addition to a restructuring of the services in order to provide more interactive and inclusive practices geared toward the singularities of the users.*

Key words *Mental health, Mental health services, Community services in mental health, Primary health care, Health evaluation*

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Introduction

The Brazilian Psychiatric Reform denoted an important advance in the way mental health issues are being understood and treated. The regulation of human rights and the provision of community-based care, encouraged by social integration, are some of the examples that stand in opposition to the old model of asylum and exclusion^{1,2}.

In the context of reformulating policies related to mental health, there was an intense implementation of Psychosocial Care Centers (CAPS, in Portuguese), Expanded Family Health Centers (NASF, in português, which necessarily include psychologists)¹⁻³, and the Psychosocial Care Network (PCNs). It is noteworthy that this policy reformulation movement continues the role of primary health care (PHC)²⁻⁵ services as a strategy to encourage preventive action that is more focused on comprehensive care.

It should also be noted that CAPS were open, community-based facilities implemented as a substitute for psychiatric hospitals. Such a substitution is relevant because it affirms a model of approach recommended as having greater diagnostic capacity, favoring the prevention of the condition and hospitalization itself^{2,5-8}.

However, despite the advances made and the proposal for a priority care network for this approach¹, a number of challenges have been reported, including the lack of treatment sharing between services^{6,9,10}, which tends to centralize care in those that have mental health specialists on their teams^{5,10-12}.

The country's current situation is also part of these circumstances, which was already in the throws of an economic and political crisis that tended to increase regional disparities in access to services and health outcomes^{13,14}, reinforced by setbacks in the community-based model of treatment in mental health and PHC funding^{1,5,15,16}. The COVID-19 pandemic is another aggravating factor in this context, which elevated the demand for monitoring these cases and contributed to the disruption of services^{17,18}.

Given this scenario and the persistence of psychiatric hospitalization as a relevant resource, even among the procedures of CAPS professionals, to the detriment of practices involving territorial resources¹⁹, this study aimed to evaluate the factors that influence the hospitalization of people suffering from mental health issues referred by PHC services for surveillance at Psychosocial Care Centers in the city of São Paulo.

Methods

This is an evaluative research with a cross-sectional quantitative approach that used data from 2016, collected through a survey of users referred by PHC services to CAPS in the city of São Paulo, Brazil.

São Paulo was chosen due to its sociodemographic relevance as a large city (11,869,660 inhabitants, 99.1% located in urban areas) with one of the best indices of income concentration and human development (GINI = 0.62 and IDHM = 0.80) in 2019^{20,21}, in addition to its history of reaffirming an ethical-political position of struggle for a more humanized and inclusive model of mental health care, pioneering the implementation of an open, community-based service that would replace the psychiatric hospital – CAPS – in 1987¹. Also noteworthy is the influence of São Paulo's policies on federal proposals aimed at prioritizing mental health care with a community-based approach, such as the implementation of CAPS and the mental health care network¹.

In addition to these criteria, the structure of mental health services stands out as one of the municipalities among the large Brazilian cities that has the lowest supply of full hospital beds (0.33/100,000 inhabitants) and a significant number of consultations by psychologists and psychiatrists at PHCs in relation to the population-year (16.6 and 18.2 per one thousand inhabitants, respectively)²².

Approximately 60% of the population is covered by PHC services, distributed throughout 553 services, 87 of which are part of the Ambulatory Medical Assistance units (AMA). Specialized Care (SC) consists of 25 outpatient clinics specialized in mental health, 39 urgent care and emergency units, 43 hospitals (23 of which in the day-hospital model for mental health care), in addition to 92 CAPS. These 92 CAPS are further divided into different modalities according to the profile of the condition (CAPSad II and III, CAPS Adult II and III, and CAPSi II and III)²³. However, considering the object of analysis, only the Adult CAPS intended for the treatment of people undergoing psychological distress were included in the present study, meaning the CAPSad and CAPSi modalities were excluded.

Considering the interest in evaluating the link between PHC services and CAPS, taking into account users living with severe and persistent mental disorders, only users referred by those services were approached in the thir-

ty-two CAPS Adult II and III that operate within the municipality. Based on the observation that CAPS had a high fluctuation in the average daily number of visits (between 0 and 15.2) in the nine months that preceded the study, the services with the highest daily circulation of users were chosen to make the designed sample feasible in the least amount of time of data collection. As such, twenty-four CAPS were involved in the study.

The same calculation of the daily average of individual consultations during a nine-month period, using data from the SIA-RAAS (SUS Outpatient Information System – Record of Outpatient Health Actions), was used to predict the frequency of users belonging to the study population in these services. Thus, the sample size was calculated from the algebraic expression determined by estimating proportions: $n_0 = P(1 - P)/(d/z)^2$, where P is the proportion to be estimated; z is the value on the reduced normal curve, corresponding to the confidence level used in determining the confidence interval, and d is the sampling error, using $P = 0.50$; $d = 0.05$; $z = 1.96^{22}$.

The collection time was defined equally in five days for all participating services. This option enabled the distribution of users by services to ensure that the characteristics of interest in the sample were similar to the study population, in addition to the weekly monitoring of the services, which favors user continuance after this period.

Other predefined criteria were the inclusion of participants who should have been monitored at CAPS for two years or less, who had been referred by a PHC service in the municipality, who were cognitively able to answer the questionnaire, who currently reside in the municipality, and who were in crisis or hospitalized due to mental health issues. Thus, all users who sought treatment at the 24 CAPS during the collection period were approached before their doctor's appointment, totaling a set of 400 users, with only those who met these criteria being interviewed, resulting in 297 participants.

The interviews were conducted on the premises of the services between April and May 2016 by researchers who were trained and experienced in conducting surveys with digital recording (tablets). A standardized questionnaire was used, constructed by expert consensus and pre-tested in two metropolitan regions, consisting of sixty-six closed questions that addressed the socio-demographic characteristics of the participants and the care offered to users by the PHC and CAPS services. Fourteen variables were selected from this set of questions that, according to the

literature, could be associated with the outcome (Chart 1). The collection instrument and other details pertaining to the study can be accessed at <https://www.fcm.unicamp.br/acessus/>.

The (unfavorable) outcome “Hospitalized with a mental health-related issue (during monitoring at CAPS)” was selected, since evidence shows that permanent and shared monitoring between the CAPS and APS service responds more effectively to the specific needs of each user, resulting in better outcomes, such as stability or improvement in mental health-related suffering, even among groups of psychotic disorders^{2,24}.

Therefore, the Poisson Regression analysis with robust variance was used to estimate the crude and adjusted prevalence ratios (PR) and their respective 95% confidence intervals. To select the factors and establish the respective entry orders in the multiple model, The chi-square test was used to select the factors and establish the respective entry orders in the multiple model, first inserting those with the lowest value up to the maximum threshold of $p < 0.20$. Only those factors with $p < 0.05$ were retained in the final model. The analyses were calculated using the Stata 14.1 statistical software, and the discussion of these results was conducted from the perspective of the references of the Evaluation of Health Services²⁵ and the Theory of the Work Process in Health²⁶.

This study is part of the research *Inquérito sobre o Funcionamento da Atenção Básica à Saúde e do Acesso à Atenção Especializada em Regiões Metropolitanas Brasileiras (AcesSUS)* (in English, *Survey on the Operation of Primary Health Care and Access to Specialized Care in Brazilian Metropolitan Regions*). In accordance with the recommendations of Resolution no. 466 of 2012 of the National Health Council for Scientific Research on Human Beings, this study was approved by the Research Ethics Committee of the State University of Campinas and the School of Public Health of the University of São Paulo, logged under registration no. 43716515.7.1001.5404, and all participants signed the Free and Informed Consent Form.

Results

The profile of the 297 users interviewed at CAPS in the city of São Paulo were predominantly females (62.3%), over 40 years of age (57.6%), and with less than nine years of education (49.8%). Most of them did not have health insurance and/

Chart 1. Selection of sociodemographic characterization variables of the interviewed users and the care offered to users by Primary Health Care (PHC) services and Psychosocial Care Centers (CAPS), São Paulo, 2016.

Variables/Questions	Answer categories
Sociodemographic characteristics of users	
Self-reported sex	1: Female 2: Male
Age at the time of the interview	1: 18 to 39 years 2: \geq 40 years
Self-reported skin color	1: White 2: Not white
Education (in years of study)	1: < 9 years 2: 9 to 11 years 3: > 11 years
Have health insurance and/or a medical plan	1: No 2: Yes
Time of diagnosis (in years)	1: \leq 6 years 2: > 6 years
Monitoring time at CAPS (in months)	1: \leq 7 months 2: > 7 months
Occurrence of mental health-related hospitalization (prior to monitoring at CAPS)	1: No 2: Yes
Characteristics of the care offered to users by the PHC and CAPS services	
Time between diagnosis and the first consultation with the CAPS psychiatrist (in days)	1: \leq 7 days 2: > 7 days
Time between diagnosis and the first consultation with a CAPS non-medical professional (in days)	1: \leq 7 days 2: > 7 days
Received a prescription for psychopharmaceutical medication at PHC	1: Yes 2: No
Received guidance at CAPS on how long to use the medication	1: Yes 2: No
Difficulty in accessing some psychopharmaceutical medication (in the last 6 months)	1: No 2: Yes, once 3: Yes, more than once
Hospitalized with a mental health-related issue (during the monitoring at CAPS) ^a	1: No 2: Yes

^a Considered a dependent variable in the analysis (unfavorable outcome).

Source: Authors.

or a medical plan (94.3%) and were being monitored at CAPS for under seven months (51.8%), with approximately 50.0% having been diagnosed for more than six years (Table 1).

Regarding the care that was offered, users who reported a waiting time of less than a week

for the first consultation at CAPS with a psychiatrist represented 44.2% and with a non-medical professional, 66.8%. Most participants claimed to have received guidance on how long to take the medication (59.3%), how to attain prescriptions for psychopharmaceutical medication at the PHC services (64.0%), and found no difficulty in accessing the medication in the past six months (61.8%) (Table 1).

Table 1 also shows that practically half of the interviewees had already been hospitalized prior to the beginning of monitoring at CAPS (56.7%) and a much lower number during monitoring at the service (5.4%).

The following variables were selected to construct the regression model: education ($p = 0.135$), having health insurance and/or a medical plan ($p = 0.014$), monitoring time at CAPS ($p = 0.013$), time between diagnosis and the first consultation with a non-medical CAPS professional ($p = 0.100$), whether or not they received a prescription for psychopharmaceutical medication at the PHC ($p = 0.135$), whether they received guidance at CAPS on how long they should take the medication ($p = 0.023$), difficulty accessing psychopharmaceutical medication ($p = 0.107$), and hospitalization due to a mental health-related issue (0.029).

Out of these variables, five remained in the final adjusted model. Regarding the users' sociodemographic variables, only having health insurance and/or a medical plan increased the probability of hospitalization for users who were monitored at CAPS (PR: 3.56; CI: 1.43-8.88). However, a different picture emerged with regard to the care offered by the services, where users were twice as likely to have waited more than seven days for the first consultation with non-medical professionals (PR: 2.44; CI: 1.17-5.07), not to have received guidance on the duration of medication use (PR: 2.51; CI: 1.14-5.52), not to have received a prescription for psychopharmaceutical medication from the PHC service (PR: 2.23; CI: 1.02-4.84), and to have reported previous hospitalizations (PR: 2.24; CI: 1.03-4.86) (Table 2).

Discussion

The results made it possible to identify that both the individual characteristics of the users monitored at CAPS in the city of São Paulo, such as having health insurance and/or a medical plan, as well as the organizational model operationalized in the services, such as providing prescriptions

Table 1. Association between hospitalization during follow-up in the Psychosocial Care Centers (CAPS) and the variables related to the sociodemographic characteristics and the care offered by Primary Health Care (PHC) services and CAPS. São Paulo, 2016.

Variables	N	Hospitalization related to mental health during follow-up at CAPS		p-value [*]
		Yes N (%)	No N (%)	
Sociodemographic characteristics of the users				
Self-reported sex				
Female	185	14(7.6)	171(92.4)	0.498**
Male	112	11(9.8)	101(90.2)	
Age at time of interview				
18-39 years	126	13(10.3)	113(89.7)	0.311**
≥40 years	171	12(7.0)	159(93.0)	
Skin color (self-reported)				
White	144	12(8.3)	132(91.7)	0.932**
Not white	151	13(8.6)	138(91.4)	
Education (in years of study)				
< 9 years	148	9(6.1)	139(93.9)	0.135
9-11 years	37	6(16.2)	31(83.8)	
> 11 years	110	10(9.1)	100(90.9)	
Has health insurance and/or medical plan ^a				
No	280	21(7.5)	259(92.5)	0.014
Yes	16	4(25.0)	12(75.0)	
Time of diagnosis (in years) ^a				
≤ 6 years	145	10(6.9)	135(93.1)	0.271**
> 6 years	142	15(10.6)	127(89.4)	
Time of follow-up at CAPS				
≤ 7 months	154	7(4.5)	147(95.5)	0.013
> 7 months	143	18(12.6)	125(87.4)	
Hospitalization related to mental health (before follow-up at CAPS) ^a				
No	128	16(12.5)	112(87.5)	0.029
Yes	168	9(5.4)	159(94.6)	
Characteristics of care provided to the users through PHC and CAPS services				
Time between diagnosis and first consultation with a psychiatrist at CAPS (in days) ^a				
≤ 7 days	125	12(9.6)	113(90.4)	0.420**
> 7 days	158	11(7.0)	147(93.0)	
Time between diagnosis and first consultation with non-medical CAPS professional (in days) ^a				
≤ 7 days	191	13(6.8)	178(93.2)	0.100
> 7 days	95	12(12.6)	83(87.4)	
Received psychopharmaceutical prescription at PHC ^a				
Yes	174	12(6.9)	162(93.1)	0.135
No	98	12(12.2)	86(87.8)	
Received medical advice at CAPS about how long to use the medication ^a				
Yes	169	9(5.3)	160(94.7)	0.023
No	116	15(12.9)	101(87.1)	
Difficult access to some psychopharmaceuticals (last 6 months) ^a				
No	178	12(6.7)	166(93.3)	0.107
Yes, once	49	8(16.3)	41(83.7)	
Yes, more than once	61	5(8.2)	56(91.8)	

* Chi-square test. ** Did not enter the Poisson Regression model as it presented a p-value > 0.20. ^aVariables that did not contemplate the total sample, considering the routine used for data collection.

Source: Authors.

Table 2. Gross and adjusted analysis between the variable of hospitalization related to mental health during follow-up in Psychosocial Care Centers (CAPS) and the independent variables. São Paulo, 2016.

Variables	Gross values			Adjusted values		
	PR	CI	p-value*	PR	CI	p-value*
Sociodemographic characteristics of the users						
Education (in years of study)						
< 9 years	1.00					
9 - 11 years	2.67	1.01-7.03	0.047			
> 11 years	1.50	0.63-3.56	0.364			
Has health insurance and/or medical plan						
No	1.00	-	-	1.00		
Yes	3.33	1.29-8.57	0.012	3.56	1.43-8.88	0.006
Time of follow-up at CAPS (in months)						
≤ 7 months	1.00	-	-			
> 7 months	2.77	1.19-6.44	0.018			
Hospitalization related to mental health (before follow-up at CAPS)						
No	1.00			1.00		
Yes	2.33	1.06-5.11	0.034	2.24	1.03-4.86	0.041
Characteristics of care provided to users through PHC and CAPS services						
Time between diagnosis and first consultation with non-medical CAPS professional (in days)						
≤ 7 days	1.00	-	-	1.00	-	
> 7 days	1.85	0.88-3.91	0.104	2.44	1.17-5.07	0.017
Received psychopharmaceutical prescription at PHC						
Yes	1.00			1.00		
No	1.77	0.83-3.80	0.140	2.23	1.02-4.84	0.043
Received medical advice at CAPS about how long to use the medication						
Yes	1.00			1.00		
No	2.43	1.10-5.37	0.028	2.51	1.14-5.52	0.022
Difficult access to some psychopharmaceuticals (last 6 months)						
No	1.00					
Yes, once	2.42	1.05-5.60	0.039			
Yes, more than once	1.21	0.44-3.32	0.703			

PR = gross and adjusted prevalence ratios. CI = 95% confidence intervals. * Poisson Regressão model.

Source: Authors.

for psychopharmaceutical medication and guidance on how long it should be taken, were factors associated with a greater probability of being hospitalized with a mental health-related issue during the users' monitoring time at the service.

Although the study focused exclusively on users referred by PHC services in only one municipality, which may not reflect the reality of all CAPS users, the profile of the people evaluated in this study corroborates what is mentioned in the literature, which shows a higher prevalence of adult women^{7-9,12,27-29}.

Considering that socioeconomic conditions and hospitalization can be cited as reasons for family distancing and that, at the same time, CAPS users with a smaller support network tend

to go through more frequent episodes of readmissions, such results make it even more worrisome^{19,27,30}.

It should be noted that even understanding CAPS as an important entry point for people with mental health-related issues into the health system^{6,9}, the scope of the study only addressed users referred by PHC services. In that sense, the identification of individual characteristics, such as a higher level of education, calls attention to the access of a user profile, suggesting a characteristic of CAPS users with better socioeconomic conditions.

However, specifically with regard to the condition of people's mental suffering, the highest level of education does not always match the best

socioeconomic level since, in many cases, these are people who have trouble entering the workforce³¹. It is not difficult to imagine that long-term monitoring in a health service, as is the case of people with intense, persistent mental suffering, is only possible to the extent that there is a consistent family support network that provides the conditions necessary for such an individual to coexist in a community.

Another result worth mentioning is that, despite being represented in smaller numbers in this study, the prevalence of psychiatric hospitalization was higher among those who claimed to have health insurance and/or a medical plan. In addition to having easier access to a psychiatric bed due to coverage by a medical plan, this may also be a result of family members seeing hospitalization as the first treatment option. This understanding of hospitalization is a reminder of the stigma surrounding mental illness and its history of social exclusion³⁰.

However, one cannot fail to consider that, despite being designed within the model of Psychiatric Reform - as a substitute for hospitals - the incentive of short-term hospitalization has always been maintained by public policies and continues to influence the practice of healthcare professionals^{1,6,13,14,16,32}.

The use of psychiatric hospitals as a form of mental health treatment reinforces recent changes in guidelines in the field. Such changes value compulsory hospitalization and the expansion of therapeutic communities¹, as well as more funding for psychiatric beds, to the detriment of community and NASF follow-up services^{16,33,34}.

The low investment in the implementation of services that comprise the psychosocial care network^{1,15} and the inadequacies identified in PHC services^{5,6,10} for the care of this population group arouse great concern. Such weaknesses, also identified in the literature, suggest important limitations ranging from access^{9,15} to the reproduction of a care model that has long been outdated. This model upholds the “stigma of madness” and the deterioration of clinical conditions, including the increased use of medication and hospitalization^{1,10,16,19,24,35}.

Scenarios such as this, which involve the organization of services relative to the care provided to CAPS users, take on greater relevance when identifying those who managed to access the service have a lower probability of being hospitalized during surveillance, signaling these services' ability to effectively help the users. Effects of this type were referenced in studies that demonstrate

the inverse relationship between the increase in CAPS supply and the reduction in hospitalization rates²⁴, as well as in the decline in the number of crises as the user's monitoring time in the service increases²⁹.

Specifically, in relation to CAPS, it is relevant to note that the waiting time for the first consultation with a professional who was not a psychiatrist showed a greater probability of being hospitalized during the user's monitoring period. This may be justified by the fact that these are the professionals who most often perform this type of reception in CAPS^{36,37}.

However, they call attention to two different, yet complementary, issues. The first pertains to the delay in care, which can either lead to the condition becoming more aggravated or to the family members hastily seeking hospitalization³⁰, yet mainly pay attention to the approach used by non-medical health professionals^{2,36,38}. Such evidence reinforces the importance of this kind of reception when searching for the service.

According to the literature, this type of reception with treatment guidelines supports the establishment of a bond between the user and the health service team^{5,7}. It also encourages adherence to monitoring and leads to an improvement in the clinical symptoms, as well as in a reduced number of hospitalizations^{2,7,39,40}. Contributing to this evidence is a greater number of hospitalizations among users who did not receive a prescription for psychopharmaceutical medication at PHC services, as well as those who were not instructed on the amount of time it should be taken or who had trouble accessing the medication (even if only once).

The results reinforce the importance of shared treatment management^{6,9,27} and demonstrate how much these issues can influence monitoring. Moreover, studies have pointed out that people who were hospitalized for the first time did not have a strong connection with PHC services, using the hospital as a gateway for their mental health needs^{27,30}, and that the expansion of PHC coverage was related to fewer hospitalizations²⁴.

Considering the scenario of setbacks in mental health policies in the psychosocial and anti-asylum approach^{1,16}, the results corroborate studies that highlight PHC services as being strategic for consolidating a more resolute treatment model, as they are closer to the users and advance in comprehensive care in the network^{3,5,6}. The incorporation of practices, such as dispensing medication^{10,11,22,36}, providing matrix support, and sharing treatment with other services and

levels of care^{2,5,6,9,10,12,36}, are presented as qualifying mechanisms of care for people suffering from mental health issues^{10,28,37,41-43}.

This scenario is validated by the number of respondents who reported a history of hospitalization resulting from mental health issues (before and during) monitoring at CAPS, suggesting an improvement in the clinical condition when being treated at the service. This difference in the frequency of hospitalization after monitoring at CAPS is also evident in other parts of the country^{37,29}, reaffirming the importance of a support network for this group of users²⁸.

In view of these results, the current weakening of the PCNs makes this scenario look even worse, making its reconstruction more urgent to ensure assistance from outpatient services.

Methodological limitations deserve to be pointed out, especially in relation to the use of retrospective information collected through interviews with service users, thereby presenting possible memory biases. In addition, it was deemed impossible to adjust the analysis model considering the diagnostic severity as a confounding and/or moderating variable.

Despite such limitations, it should be noted that the analysis model met the study's proposal, allowing it to be replicated for the identification of factors associated with the hospitalization of users that were being monitored at CAPS, showing pertinent results for the organization of PHC and CAPS services.

Considering that the CAPS user's diagnostic profile changes very little, essentially in the type of service, the present study brings originality to the subject, giving indications of determinants of hospitalization in users while being monitored, requiring special attention to avoid psychiatric hospitalization, which is generally detrimental to the lives of people suffering from mental health issues.

The history of hospitalization prior to being monitored at the service, as well as the identification of those characteristics related to the users' profile, influences the prevalence of psychiatric hospitalization and calls attention to an expanded approach to the singularities of these users. They also suggest that greater attention should be given to those users who have health insurance and/or a medical plan.

At the same time, these results signal issues related to people's access to CAPS, suggesting barriers that are not only socioeconomic, but also the absence of a family support network or one involving the community/territory, which needs to be overcome through broader, more inclusive strategies.

The findings presented here could be used to support discussions aimed at strengthening CAPS by using a range of internal territorial devices to minimize possible hospitalization in the region evaluated by the study.

Other highlighted weaknesses refer to the absence of psychopharmaceutical prescriptions by PHC professionals and the lack of guidance on how long medication should be taken. A wait of more than one week for the first consultation with CAPS non-medical professionals is another aspect linked to the modalities of treatment management.

It should also be noted that, although CAPS is intended for users with a diagnostic profile of persistent, serious disorders, the changes driven by the COVID-19 pandemic may have affected the demand for treatment for other clinical conditions, in addition to a possible worsening of users being treated at CAPS during lockdown due to the need for social isolation.

With that in mind, the results presented in this study are even more relevant as they reinforce the importance of the role of CAPS as a place that supports the treatment of people suffering from mental health issues while living in the community.

Collaborations

PR Sanine contributed to the interpretation of data, writing of the article and approval of the version to be published. LPS Godoi, EM Garcia and L Belotti contributed to the conception, analysis and interpretation of data and approval of the version to be published. TEC Rosa and RTO Campos contributed to the review of the article's writing and approval of the version to be published. OY Tanaka contributed to the interpretation of data, review of the article's writing and approval of the version to be published.

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