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Sepsis in Brazilian emergency departments: a prospective multicenter observational study

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Abstract

We aimed to assess the prevalence, patient allocation adequacy, and mortality of adults with sepsis in Brazilian emergency departments (ED) in a point-prevalence 3-day investigation of patients with sepsis who presented to the ED and those who remained there due to inadequate allocation. Allocation was considered adequate if the patient was transferred to the intensive care unit (ICU), ward, or remained in the ED without ICU admission requests. Prevalence was estimated using the total ED visit number. Prognostic factors were assessed with logistic regression. Of 33,902 ED visits in 74 institutions, 183 were acute admissions (prevalence: 5.4 sepsis per 1000 visits [95% confidence interval (CI): 4.6–6.2)], and 148 were already in the ED; totaling 331 patients. Hospital mortality was 32% (103/322, 95% CI 23.0–51.0). Age (odds ratio (OR) 1.22 [95% CI 1.10–1.37]), Sequential Organ Failure Assessment (SOFA) score (OR 1.41 [95% CI 1.28–1.57]), healthcare-associated infections (OR 2.59 [95% CI 1.24–5.50]) and low-resource institution admission (OR 2.65 [95% CI 1.07–6.90]) were associated with higher mortality. Accredited institutions (OR 0.42 [95% CI 0.21–0.86]) had lower mortality rates. Allocation within 24 h was adequate in only 52.8% of patients (public hospitals: 42.4% (81/190) vs. private institutions: 67.4% (89/132, $p < 0.001$) with 39.2% (74/189) of public hospital patients remaining in the ED until discharge, of whom 55.4% (41/74) died. Sepsis exerts high burden and mortality in Brazilian EDs with frequent inadequate allocation. Modifiable factors, such as resources and quality of care, are associated with reduced mortality.

Keywords Sepsis · Low- and middle-income countries · Mortality · Emergency department

Introduction

Sepsis is a leading cause of death worldwide, and is recognized by the World Health Organization as a major global public health issue [1]. The incidence and mortality associated with sepsis are higher in resource-limited settings and are

The SPREAD ED Investigators, the Instituto Latino Americano de Sepsis Network members name listed in acknowledgement section.

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correlated with the social demographic index [2]. Data on sepsis prevalence and burden in low- and middle-income countries (LMICs) is scarce [3], and most existing studies have enrolled only patients admitted to the intensive care unit (ICU) [4–6]. Although nosocomial infections are important contributors to sepsis incidence and mortality, infections (either community-acquired or healthcare-associated) account for a high proportion of cases in emergency departments (ED). Few studies have reported the burden of sepsis in the ED in low- and middle-income countries [7–9]. The prevalence of sepsis among ED visits varies, ranging from 11.7 to 30.0 per 1000 ED visits; this prevalence is influenced by multiple factors, including the sepsis definition used [10, 11]. Sepsis management in the ED is challenging, regardless of the setting, as the condition is difficult to recognize and manage. In resource-limited settings, difficult access [12, 13], low availability of resources and of trained staff increases this challenge. In LMICs, a shortage of ICU beds [5, 14] prolongs ED boarding times, and patients may remain in the ED for the entire duration of their hospitalization. Prolonged ED boarding times are associated with poor patient outcomes, both in LMICs [15–17] and high-income countries (HICs) [18–21]. Nevertheless, the issue of patients with sepsis being managed in the ED for the entirety of their hospitalization is poorly studied.

We hypothesized that the mortality rates associated with sepsis are high and that the burden of sepsis in a resource-limited ED is caused both by acute cases, and by patients with sepsis who remain in the ED for extended time periods or who are not transferred to a ward or ICU. Thus, we conducted a 3-day point-prevalence nationwide study with follow-up to assess the prevalence of sepsis, allocation adequacy, and in-hospital mortality rates amongst adults in a convenience sample of Brazilian EDs. We also assessed ED organizational factors, including the hospitals' primary source of income, accreditation status by international or national accreditation organizations, availability of resources, compliance with treatment guidelines, and their associations with mortality.

Methods

Study design

The Sepsis PREvalence Assessment Database in Emergency Departments (SPREAD-ED) study was a nationwide 3-day, prospective, point-prevalence study with follow-up. SPREAD-ED was designed to assess the prevalence of sepsis and allocation patterns of patients with sepsis in a convenience sample of ED in all Brazilian regions. A cohort of all identified cases was followed up until hospital discharge or death. The study was coordinated by the Instituto Latino Americano de Sepse (ILAS) and supported by the Associação Brasileira de Medicina de Emergência (ABRAMEDE), the Associação Brasileira de Medicina de Urgência e Emergência (ABRAMURGEM) and the Brazilian Research in Intensive Care Network (BRICNet).

The study was approved by the Research Ethics Committee of the coordinating center (Federal University of São Paulo) under the number CAAE:60,953,816.4.1001.5505. Informed consent was waived because of the study's observational nature and lack of direct patient involvement beyond data collection from their charts.

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Setting

As a national list of all Brazilian EDs is unavailable, a random sample was not feasible. Thus, this study used a convenience sample of Brazilian ED to account for EDs in all Brazilian regions. Participants were recruited at emergency medicine meetings through the societies' social media, as well as personal contacts with key opinion leaders. Participation was voluntary and any hospital willing to participate in the study was considered eligible. There were no exclusion criteria at the site level.

Population

All participating ED teams were asked to enroll patients for 3 days in November 2017. We aimed to measure the full burden of sepsis in ED, including acute cases and those who remained in the ED even after being diagnosed with sepsis. Thus, all patients who fulfilled the inclusion criteria and presented to the ED during the 3 study days with sepsis (acute admissions) were included in the study. We also included those who had been previously admitted and were retained in the ED during the study days without transfer to the ward or ICU. On the first day of the study, all patients admitted to the ED from 7:00 AM onward were included. On the second and third days, only patients who were not included in the preceding study days were enrolled. These patients either had sepsis as the primary cause of their ED visit (previous sepsis admission), or they had been admitted for other diseases and subsequently acquired sepsis as a complication of their ED stay (sepsis after ED admission) (see Supplemental material, Fig. 1).

The inclusion criteria were as follows: age $\geq$ 18 years, presence of sepsis or vasopressor-dependent sepsis, and ongoing organ dysfunction secondary to sepsis, regardless of the day of organ dysfunction onset. Sepsis was defined

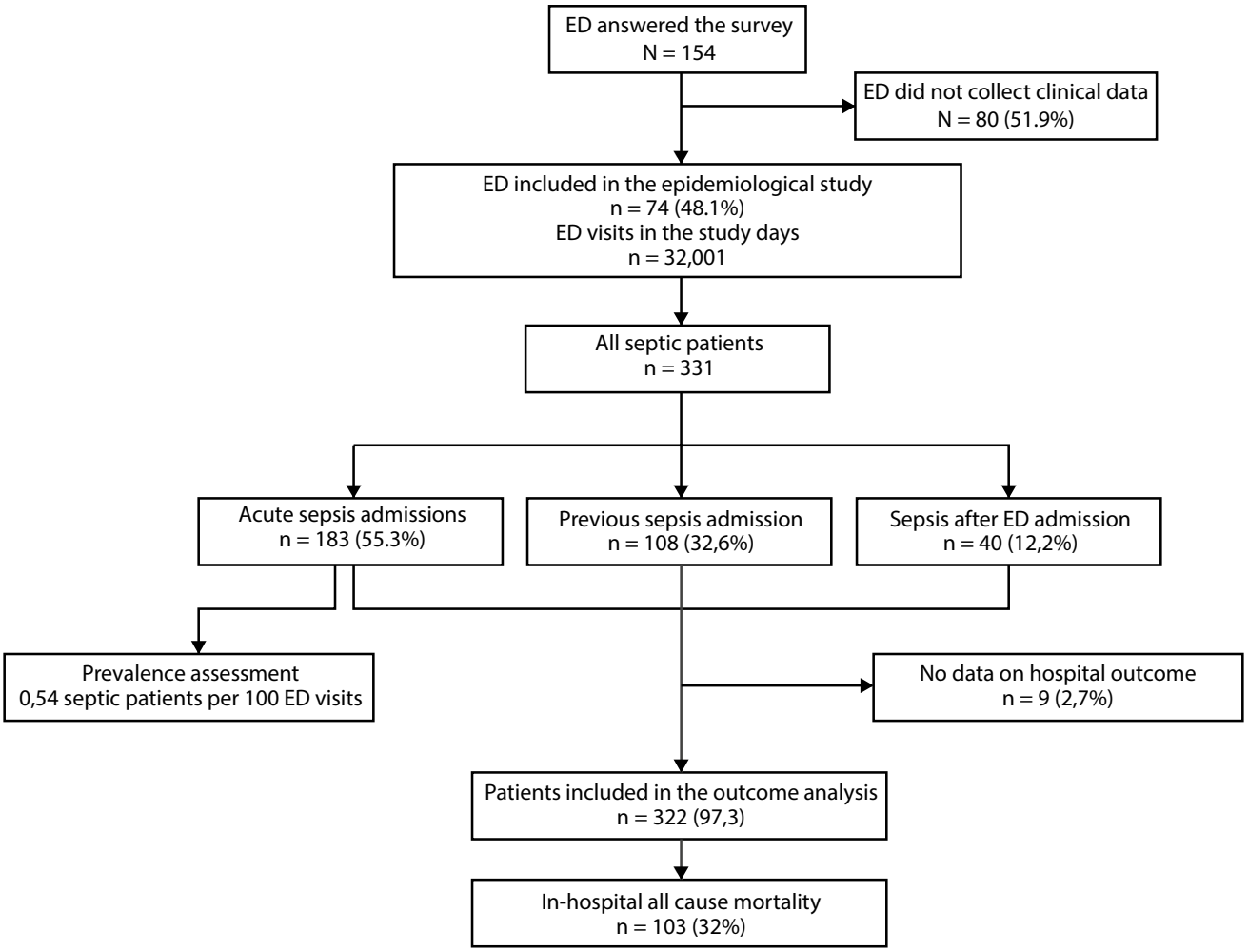

Fig. 1 Study flowchart of emergency departments and participant patients. *ED* emergency department

according to the broad sepsis 3 definition; the presence of infection complicated by any life-threatening organ dysfunction [22] irrespective of the values of the SOFA score. Life-threatening organ dysfunction was defined according to the Surviving Sepsis Campaign (SSC) quality improvement initiative (see definitions in the Supplemental material); these criteria are typically used in Brazilian EDs to define a clinical case of sepsis. We have considered as having vasopressor-dependent sepsis those patients with hypotension that were nonresponsive to fluids and required vasopressors in the first 24 h of the sepsis diagnosis, regardless of lactate levels after fluid replacement. We also collected data on the SOFA score to determine which patients met the Sepsis-3 clinical criteria definition, defined as a SOFA score > 2 on the day of sepsis diagnosis. We excluded patients who had sepsis during their stay and were still in the ED, but no longer had ongoing organ dysfunction. Children and patients admitted to the orthopedic and ophthalmological EDs were also excluded, as the study aimed to assess the prevalence of sepsis in a general ED, and sepsis prevalence in orthopedic and ophthalmological ED is relatively low; therefore, including them would compromise the overall assessment of prevalence. More information on the inclusion criteria and definitions is provided in the supplemental material.

Procedures

All institutions that agreed to participate in the study answered a structured web survey aimed at analyzing their infrastructure, availability of resources, and ED organizational aspects (as proxy indicators of the quality of care). Institutions provided information on their main source of income (public or private). Institutions with accreditation were defined as those having a national (such as Organização Nacional de Acreditação—ONA) or international (such as Joint Commission International or Accreditation Canada) accreditation seal attesting to the quality of their processes of care. To assess the availability of resources, we used a previously described

availability score [5] composed of eight items considered essential for providing care within the first 6 h of admission: (1) blood gas analysis within 3 h; (2) lactate results within 3 h; (3) blood, urine, and tracheal aspirate cultures; (4) antibiotics for both gram-negative and gram-positive coverage; availability of (5) crystalloids; (6) noradrenaline; (7) central venous catheters; and (8) central venous pressure measurement. We defined the optimal availability of resources as having all eight items (high availability), intermediate availability (seven items), and low availability (six or fewer items) (see Supplemental Material for details).

On the day of the study, all data were collected using an electronic case-report form. We assessed the adequacy of ICU allocation within the first 24 h after ED admission or sepsis diagnosis. We used all the patients with sepsis as the denominator. Adequate allocation was defined as follows: transfer to an ICU, transfer to the ward or remaining in the ED with no request for ICU admission and no criteria for ICU admission in the assessment of the study team, no transfer to an ICU in a patient receiving end-of-life care, or no transfer to an ICU in those who died immediately after ED presentation. As the criteria for ICU admission might vary among institutions based on the availability of ICU beds, and to ensure that the ED team did not fail to request ICU admission for a patient who required it, we asked the study team to determine if the patient required ICU or ward admission according to the institutional criteria. To standardize the admission criteria, we instructed all sites to consider the use of mechanical ventilation and vasoactive drugs as ICU admission criteria. In patients with requests or clinical criteria for ICU admission who had not been transferred to the ICU within the first 24 h of ED admission, sites were requested to provide an explanation. Sites had to identify one of the following reasons for a patient not been transferred: death < 6 h after ED presentation, death after at least 6 h from ED presentation and before an ICU bed request, no ICU bed available, ICU physician refusal, no healthcare insurance coverage, or end-of-life care. Lack of insurance was a potential reason in private institutions only, as, according to the Brazilian law, public institutions are obliged to provide universal free access to healthcare.

As patients could have remained in the ED during their entire hospital stay, we requested the sites to specify which was the first destination after the ED, as follows: transfer to the ICU, transfer to the ward, transfer to another hospital, or discharge directly from the ED. If the patient remained in the ED during the entire hospital stay, sites were asked to define the reason as follows: early death (< 6 h after ED presentation), death before ICU request (after at least 6 h after ED presentation), no indication for ICU/ward admission, no ICU bed available, no ward bed available, no insurance coverage, and end-of-life care. As the criteria for ward/ICU admission might vary among institutions, this criterion was determined by the study team for each patient according to the institutional criteria.

Patients were followed-up until hospital discharge, which was truncated at 60 days. Details are available in the Supplemental Material.

Outcomes

The primary endpoint was the prevalence of sepsis in the participating EDs. The secondary endpoints were mortality and rate of adequate allocation.

Statistical analysis

Percentages were used to describe categorical variables, while the median and interquartile range were used to describe continuous variables. To assess prevalence, we opted for a standard approach and considered only those patients who presented with sepsis to the ED during the 3 study days (acute admissions patients), and not those who had been previously admitted and remained in the ED, because they were not transferred to a ward or ICU. The denominator comprised all ED visits during the 3 study days. We reported the results as absolute numbers, percentages, and respective 95% confidence intervals (CIs).

In-hospital mortality was assessed by considering all cases and the results were reported as absolute numbers and percentages. The mortality rates in different groups of patients were compared using Cox proportional hazards regression and the results were expressed as hazard ratios and their respective 95% CIs. In the univariate analysis used to assess the prognostic factors, categorical data were tested using the Fisher's exact test or the chi-square test, continuous data with a normal distribution by using the Student's t-test, and those without a normal distribution using the Mann–Whitney U test. Kaplan–Meier curves were plotted to assess the time to death according to the hospital type and patient type; these curves were compared using the Cox proportional hazards model.

Multivariate analysis was performed using logistic regression models to determine the variables associated with death after controlling for disease severity and other mortality predictors. We excluded all patients for whom end-of-life care measures were instituted within 48 h of sepsis diagnosis from this model. We included in the model all variables with a p value < 0.05 in the univariate analysis. To minimize the possibility of missing a potential confounding variable, we also included variables based on plausibility, even if the p value did not reach the predefined value. Collinearity was first assessed by examining either the scatter plot matrix or Pearson's correlation coefficient for continuous variables, or cross-tabulation for categorical variables. In the presence of collinearity (SOFA score at admission and SOFA score

within 24 h, use of mechanical ventilation and SOFA score, type of hospital, and accreditation status), the most clinically relevant variable was maintained in the model. The results of the multivariate analysis are expressed as odds ratios (OR) and 95% CI.

A two-tailed p value < 0.05 was considered statistically significant. Analyses were performed using the R software (R Core Team, 2017). Missing values were not imputed and cases with missing data were not considered in the analyses of the corresponding variables.

Results

Characteristics of the ED

Of 154 EDs that completed the resources survey, 74 (48%) participated in the study (Fig. 1). The main characteristics of the participating EDs and the availability of resources are available in Supplemental Material Tables S1 and S2. There was a median of 13.8% (9.0–19.3%) of ICU beds per total hospital beds in the 74 institutions (public: 10.2 (6.4–14.3), private 17.6 (12.0–21.6), $p < 0.001$). On the 3 study days, the participating institutions collected data and reported the number of visits to the ED for 205 ED days (92.3% of the potential study days). The main reason for not collecting data was the unavailability of the study team. There were no significant differences between institutions with or without missing days (Supplemental Material Table S3).

Prevalence assessment and characteristics of the included patients

There were 33,902 visits to the 74 participating EDs on the study days. On these days, 183 patients presented to the EDs with acute sepsis, resulting in a prevalence of 5.4 per 1000 ED visits (95% CI 4.6–6.2%). In addition, among these patients, 145 also met the sepsis 3 criteria [145//176 (82.4%), SOFA data were not available for six patients], resulting in a prevalence of 4.3 per 1000 ED visits (95%CI 3.6–4.9%).

In addition to these 183 patients with acute sepsis admission, 148 patients were already in the ED with sepsis (previous sepsis admission: 108; sepsis after ED admission: 40), totaling ED admission of 331 patients. All 40 patients who developed sepsis after their ED stay were admitted to the ED with other diseases and had sepsis during their ED boarding time, with a mean time for sepsis development of 5.1 days (1.9–10.9). In public hospitals, the percentage of patients with prior admission with sepsis and sepsis after ED admission was higher than that in private institutions (prior admission: public, 77/193, [39.9%]; private, 31/138, [22.5%]; sepsis after admission: public: 34/193, [17.6%]; private: 6/138, [4.3%]; p < 0.001). The patients' main characteristics are shown in Table 1 and Supplemental Material Table S4.

Allocation patterns

Allocation within 24 h of the day of sepsis diagnosis was adequate in only 52.8% (170/322) of the patients (public hospitals: 42.4% [81/190] vs. private institutions: 67.4% [89/132], $p < 0.001$). In public institutions, only 15.8% of the patients were admitted to the ICU within 24 h of ED presentation, compared to 40.2% in private institutions ($p < 0.001$). For those admitted within the first 24 h, timing for ICU admission was also longer in public institutions (18.9 [7.2–67.7] hours vs. 6.3 [3.6–11.1] hours). The main reason for non-admission to the ICU was bed unavailability in public (77.4%) and private (60.5%) institutions. The second most common reason was the lack of healthcare insurance in private institutions (31.6%) (Table 2).

Regarding the immediate destination after ED, in public institutions, 39.2% (74/189) of the patients were treated in the ED during their entire hospitalization, compared with only 9.2% (12/130) in private institutions ($p < 0.001$). Among patients with sepsis who remained in the ED during their hospitalization in public institutions, 55.4% (41/74) died in the ED (median time to death, 2.7 (0.9–13.5) days) (Fig. 2). The main reasons for remaining in the ED in a public institution were the unavailability of ICU (27/68, 39.7%) or ward (20/68, 29.4%) beds, and of end-of-life care (10/68, 14.7%). In private institutions, the main reason for remaining in the ED was the absence of indications for ICU/ward admission (5/12, 41.7%) (Table 2).

In-hospital all-cause mortality

Vital status at hospital discharge was available for 322 (97.3%) of 331 patients. Altogether, 103 of the 322 admitted patients died in the hospital (32.0%; 95% CI 23.0–1.0), with a higher number of deaths in public hospitals (public: 78/192, 40.6% vs. private: 25/130, 19.2%; hazard ratio [HR], 1.73; 95% CI 1.09–2.73, $p = 0.02$, Fig. 3A). Among the patients with acute sepsis admission, the overall hospital mortality rate was 22.3% (39/175) and 37.4% (40/107) for those admitted prior to the first study day with a diagnosis of sepsis and 60.0% (24/40) for those with sepsis as a complication of their ED stay (previous sepsis admission vs. acute admission: HR = 1.23; 95% CI 0.79–1.93, $p = 0.354$; sepsis after ED admission vs. acute sepsis admission HR = 1.72; 95% CI 1.03–2.88, $p = 0.034$) (Fig. 3B). Using the sepsis 3 criteria, the overall hospital mortality rate was 36.2% (102/282; 95% CI 27.1–45.8) (Table 1). The mortality rate was higher in vasopressor-dependent sepsis (40/80, 50%) than in sepsis without vasopressors (63/249, 25%).

Table 1 Main characteristics of the whole population and according to survival status

Variable	All patients[a] ($n=331$)	Survivors[a] ($n=219$)	Non-survivors[a] ($n=103$)	p value[a]
Patients' characteristics				
Age (years)[b]	69 (50–80)	64 (43–79)	73 (60–80.2)	0.002
Sex (male)	171/331 (51.7)			
SOFA score at admission (points)[b]	4(2–7)	3 (2–5)	7 (4–11)	< 0.001
SOFA score 24 h (points) [b]	5(2–8)	3 (2–6)	9 (6–12)	< 0.001
Type of patient				
Sepsis acute admission	183/331 (55.3)	136/219 (77.7)	39/103 (22.3)	< 0.001
Previous sepsis admission	108/331 (32.6)	67/219 (62.6)	40/103 (37.4)	
Sepsis after ED admission	40/331 (12.1)	16/219 (40.0)	24/103 (60.0)	
Severity of illness				< 0.001
Sepsis without vasopressors	249/331 (75.7)	179/218 (74.0)	63/103 (26.0)	
Vasopressor dependent sepsis	80/331 (24.3)	39/218 (49.4)	40/103 (50.6)	
End-of-life care (< 48 h)				
Yes	19/299 (6.4)	3/198 (11.1)	16/99 (88.9)	< 0.001
No	280/299 (93.6)	195/198 (70.1)	83/99 (29.9)	
Public hospitals				
Yes	16/173 (9.2)	2/99 (12.5)	14/74 (87.5)	< 0.001
No	157/173 (90.8)	97/99 (61.8)	60/74 (38.2)	
Private hospitals				
Yes	3/126 (2.4)	1/99 (33.3)	2/25 (66.7)	< 0.001
No	123/126 (97.6)	98/99 (81.0)	23/25 (19.0)	
Type of infection[c]				0.005
Community	231/329 (70.2)	165/219 (73.0)	61/102 (27.0)	
Healthcare-associated infections	98/329 (29.8)	54/219 (56.8)	41/102 (43.2)	
Time to sepsis diagnosis (min) [b]	30 (4–210)	23 (6–148)	47 (3.5–324)	0.070
Adequate allocation[d]				0.053
Yes	170/322 (52.8)	123/217 (72.8)	46/102 (27.2)	
No	152/322 (47.2)	94/217 (62.7)	56/102 (37.3)	
Time to ICU admission (hours)[b]	9.8 (3.9–29)	7.7 (3.7–19.0)	11.2 (5.2–30.2)	0.180

Missing data not provided by the sites is indicated by the denominators in each variable. Results expressed in number (%) or median (25–75%)

SOFA Sequential Organ Failure Assessment, *ED* emergency department, *ICU* intensive care unit

[a]Chi-square and Mann Whitney. For the whole population, the 100% refers to the columns and for the survival status it refers to the line

[b]Data available for: age—323 patients, SOFA at admission—324 patients, SOFA 24 h—323 patients, number of organ dysfunction: 329 patients; time to sepsis diagnosis—325 patients, time to ICU admission: 104 patients

[c]Healthcare-associated infections include those infections acquired by out-clinic, hospice and homecare patients manifested at the community as well as those started after 48 h of hospital stay and not present at hospital admission

[d]Defined as admission in the ICU within the first 24 h or, if not admitted, those with no request for ICU and no indication for ICU admission in the judgement of the principal investigator, under end-of-life care and with immediate death after ED admission

End-of-life measures within 48 h of sepsis diagnosis were applied in 19/299 (6.4%) patients. The percentage of patients receiving end-of-life care was higher in public (16/173, 9.2%) than in private hospitals (3/126, 2.4%) ($p=0.02$). (Table 1).

Clinical characteristics, organizational factors, and mortality

Variables associated with mortality in the univariate analyses are shown in Table 1 and Supplementary Table S4. In

Table 2 Main outcomes and allocation patterns according to the type of institution

Variable	Patients at public hospitals ($n=193$)	Patients at private hospitals ($n=138$)	p value[a]
Mortality	78/192 (40.6)	25/130 (19.2)	< 0.001
Time to ICU admission (hours)[b]	18.9 (7.2–67.7)	6.3 (3.6–11.1)	< 0.001
First 24 h			
Admission in the ICU within 24 h	30/190 (15.8)	53/132 (40.2)	< 0.001
Adequate location	81/190 (42.4)	89/132 (67.4)	< 0.001
Reason for non-admission within 24 h			< 0.001
No ICU bed available	89 /115 (77.4)	23/38 (60.5)	
No insurance coverage	–	12/38 (31.6)	
End-of-life care	20/115 (17.4)	3/38 (7.9)	
Death before ICU request	3/115 (2.6)	0	
Early death (6 h)	1/115 (0.9)	0	
Admission denied by intensivist	2/115 (1.7)	0	
Whole hospital stay			
Allocation after ED stay			< 0.001
Ward	51/189 (27.0)	57/130 (43.8)	
ICU	52/189 (27.5)	57/130 (43.8)	
Transfer to other hospital	12/189 (6.3)	3/130 (3.1)	
Stay in the ED up to hospital discharge	74/189 (39.2)	12/130 (9.2)	
Status at discharge			0.156
Dead	41/74 (55.4)	4/12 (33.3)	
Alive	33/74 (44.6)	8/12 (66.7)	
End of life care	13/62 (21.0)	2/10 (30)	0.524
Reason to remain in the ED			
No ICU bed available	27/68 (39.7)	2/12 (16.7)	< 0.001
No ward bed available	20/68 (29.4)	1/12 (8.3)	
End-of-life care	10/68 (14.7)	0	
No indication for ICU/ward admission	6/68 (8.8)	5/12 (41.7)	
Death before ICU request	5/68 (7.4)	0	
No insurance coverage	0	3/12 (25)	
Early death (6 h)	0	1/12 (8.3)	

Missing data not provided by the sites is indicated by the denominators in each variable

ICU intensive care unit, *ED* emergency department

[a]Chi-square and Mann Whitney; [b] Data available for time for ICU admission—104 patients

the logistic regression model adjusted for the SOFA score (OR 1.41 [95% CI 1.28–1.57]) and age (OR 1.22 [95% CI 1.10–1.37]), having a healthcare-associated infection (OR 2.59 [95% CI 1.24–5.50]) and being admitted to an institution with low availability of resources (OR 2.65 [95% CI 1.07–6.90]) were associated with higher mortality. Conversely, admission to an accredited institution (OR, 0.42 [95% CI 0.21–0.86]) was associated with lower mortality. Compliance with antibiotics within 1 h, including the time needed for sepsis recognition, did not reach significance (OR 0.57 (0.29–1.13), $p=0.111$ (Fig. 4 and Supplemental Table S5). Type of hospital, allocation adequacy, and type of patients did not remain in the model adjusted for accreditation status.

The results of our multivariate analysis were further explored by analyzing resource availability. Lower resource availability was more common in public institutions, with a higher frequency of inadequate patient allocation and of patients with sepsis after ED admission. (Supplemental Material Table S6).

Discussion

In this national study of patients with sepsis in Brazilian ED, we found a high disease burden, represented not only by patients presenting to the ED but also by patients who remained in the ED until discharge from the hospital, mainly

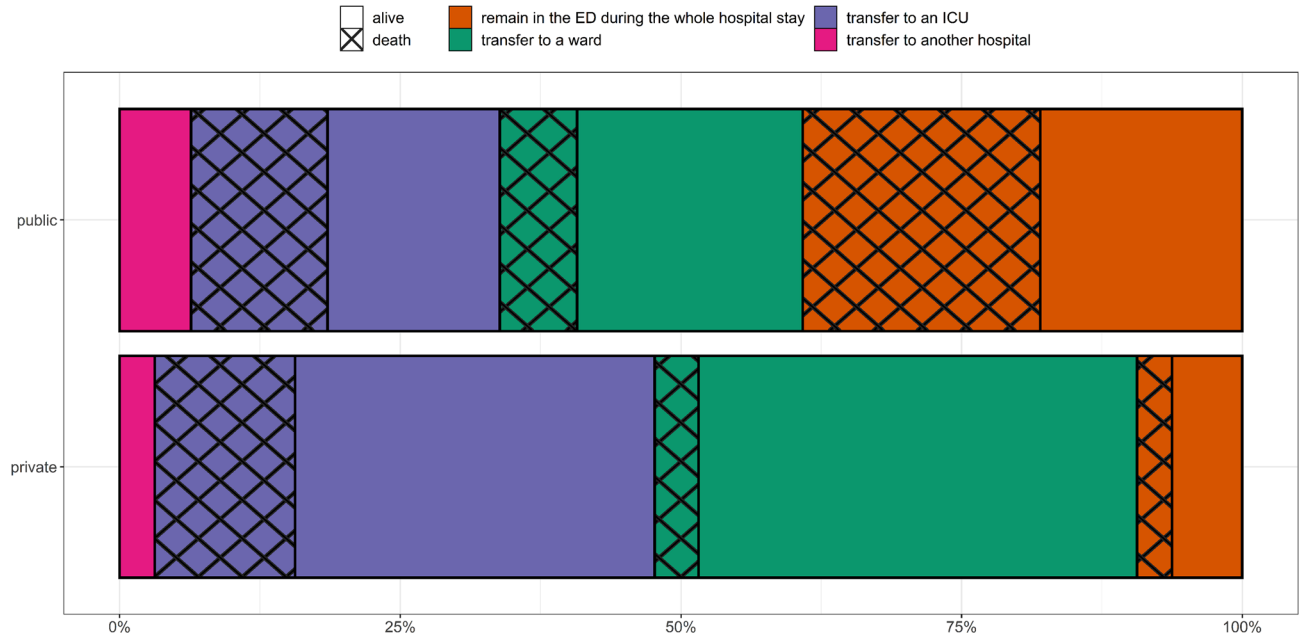

Fig. 2 Immediate location after emergency department and survival status in public and private institution. The area of rectangles represents the proportion of patients in each location (orange: patients who remain in the ED for the entire duration of their hospitalization; green: patients transferred to wards; blue: patients transferred to an ICU and pink: transferred to another hospital). In addition, we represent for each of these locations the proportion of patients who were discharge alive from hospital (smooth rectangles) or those who died (dashed rectangles). As can be depicted from this figure, in public institutions (upper figure) a larger proportion of patients remained in the ED for the entire duration of their hospitalization as compared with private institutions (lower figure) and a larger proportion of them died in the ED

due to a shortage of ICU beds. Mortality rates were high, and modifiable factors, such as being admitted to an accredited institution, were associated with lower mortality rates, while hospitalization in an institution with low availability of resources and having a nosocomial infection were associated with a higher chance of death.

There is substantial variation in the prevalence rates of sepsis in the ED, even among HICs [10, 11, 23]. Our prevalence was similar to that in other reports, with < 10 patients with sepsis per 1000 ED visits. However, the ED sepsis burden noted in our study accounted for patients who remained in the ED due to inadequate allocation. In public hospitals, only 16% of patients were admitted to an ICU within 24 h, with a median time of 19 h for ICU admission. We could not identify a difference in the time to ICU admission between survivors and non-survivors; however, this might be due to our sample size. Patients who were never transferred to the ICU or ward contributed to the high burden due to sepsis; this occurred primarily in public hospitals where 40% of the patients were treated in the ED for the entire duration of their hospitalization. It is important to highlight that access to the public healthcare system in Brazil is universal and free; thus, patients were not discharged for their personal lack of funds. The main reason for the inadequate allocation in public institutions was the shortage of ICU beds. The limited number of ICU beds is a well-known issue in low-resource settings [24]. In Brazil, disparity is present, with a difference in the availability of ICU beds between the public and private systems [25], and a scarcity of total public hospital beds. Although disparities have also been reported in HICs [26], in these countries, most patients are promptly transferred to the ICU, and even short delays of 3–6 h may have an impact on patient outcomes [19, 20]. Although there are many studies on ED boarding time [15–21], we are unaware of previous studies focusing on sepsis burden secondary to patients who were never transferred to the ward or ICU and thus remained treated in the ED during their entire hospitalization. Our findings highlight the importance of this additional burden and the need for future studies to better understand the reasons for delayed ED boarding and strategies to reduce ED stays and improve patient allocation, as the ED is neither designed nor staffed to provide extended care to critically ill patients.

We found a high mortality rate in institutions with low resource availability, even after adjusting for illness severity and quality of care. Previous Brazilian studies on ICU sepsis have already shown that low availability of resources was more frequent in public institutions [27] and was associated with a higher mortality rate [5]. Our study was not designed to assess the potential reasons for this association. However,

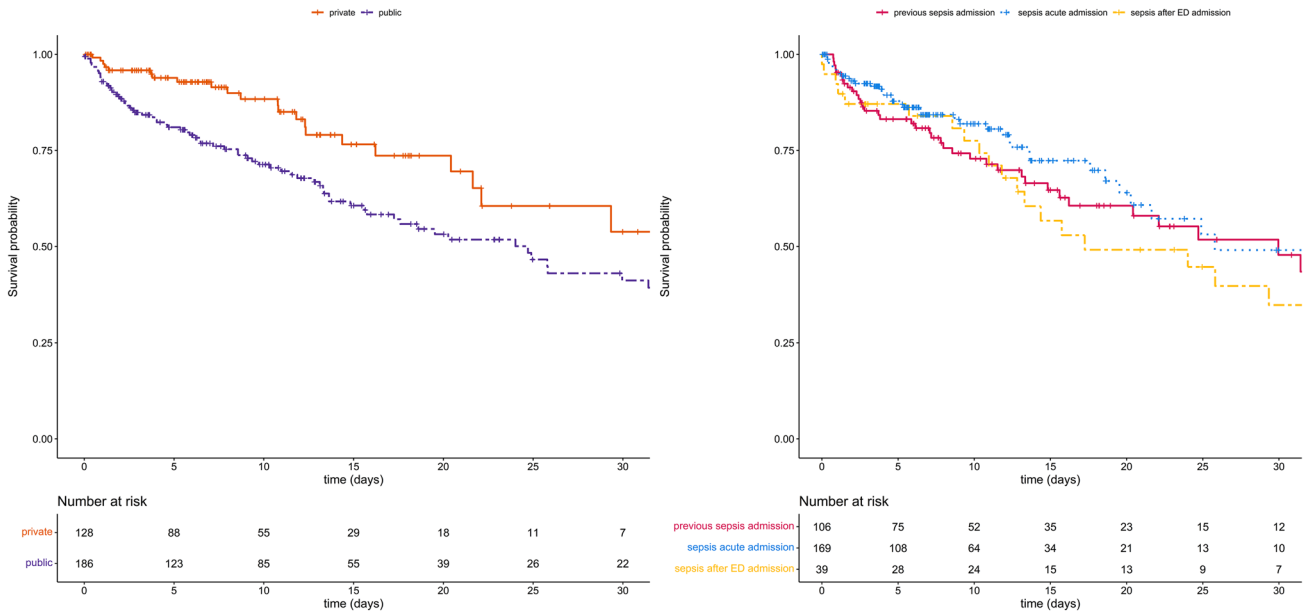

Fig. 3 Survival within 30 days among emergency department patients with sepsis. **A** According to the type of hospital—public or private. [hazard ratio (HR), 1.73; 95% CI 1.09 to 2.73, $p=0.019$] Curves were plotted with the Kaplan–Meier method. Hazard ratio, 95% confidence interval and P-value calculated from a Cox proportional hazards model. **B** According to the type of patient—acute sepsis admission, previous sepsis admission or sepsis acquired after admission. Acute admissions are those who presented to the ED during the 3 study days with sepsis; previous sepsis admissions are those with sepsis as the primary cause of their ED who were admitted and retained in the ED during the study days without transfer to the ward or ICU; sepsis after ED admission denotes patients who had been admitted for other diseases and subsequently acquired sepsis as a complication of their ED stay. Previous sepsis admission vs acute admission: HR = 1.23; 95%CI 0.79 to 1.93, $p=0.354$; sepsis after ED admission vs acute sepsis admission HR = 1.72; 95%CI 1.03 to 2.88, $p=0.034$. Curves were plotted with the Kaplan–Meier method. Hazard ratio, 95% confidence interval and P-value calculated from a Cox proportional hazards model

we can hypothesize that the low availability of resources might compromise the adequacy of treatment and also be a proxy of other issues, such a shortage of ICU beds and healthcare professionals.

There were several strengths of our study. First, this was a multicenter study comprising institutions from all Brazilian regions, with the majority being public hospitals located in the countryside. Although our sampling cannot be considered a proportional representation of Brazilian ED, we believe we have achieved a reasonable representative sampling of Brazilian ED. We captured a broad amount of relevant data, including the availability of resources, infrastructure, practices, time to sepsis diagnosis, compliance with bundles, and severity scores, with a low rate of missing data regarding the primary outcome. Third, this study is the first to assess the sepsis burden in the ED setting in Brazil and among the few to assess the burden of sepsis in a LMIC. Finally, we assessed end-of-life care, as this is an important factor related to allocation adequacy and mortality.

Our study had some limitations. First, despite our efforts to reduce the burden of data collection, many of our participating hospitals did not collect clinical data. As the incapacity to deal with the data collection burden might be linked to ED overcrowding and understaffing, we cannot rule out a selection bias toward better structured hospitals. However, this bias would mean that our data underestimated the severity of the sepsis burden and its associated mortality. In addition, hospitals that could not be contacted might also have different characteristics, which could lead to bias. Although we tried to include patients from all Brazilian regions, substantial differences among Brazilian geographic regions in socioeconomic respects might have compromised our representativeness. Second, we generated data on 3 days, leading to limitations such as seasonal variability. Third, we did not collect patients' socioeconomic data; this is a known risk factor influencing sepsis incidence and mortality. Fourth, our resource availability considered only the core elements of the first 6 h of care, as recommended by the SSC guidelines. Fifth, we did not monitor the quality of data collection with on-site verification of source documents, although we implemented central data monitoring for completeness and consistency. Finally, we analyzed patients with healthcare-associated infections, community-manifested healthcare-associated infections, and nosocomial infections. Although this approach is based on the current concept of HAI, its impact on sepsis mortality might differ between the two

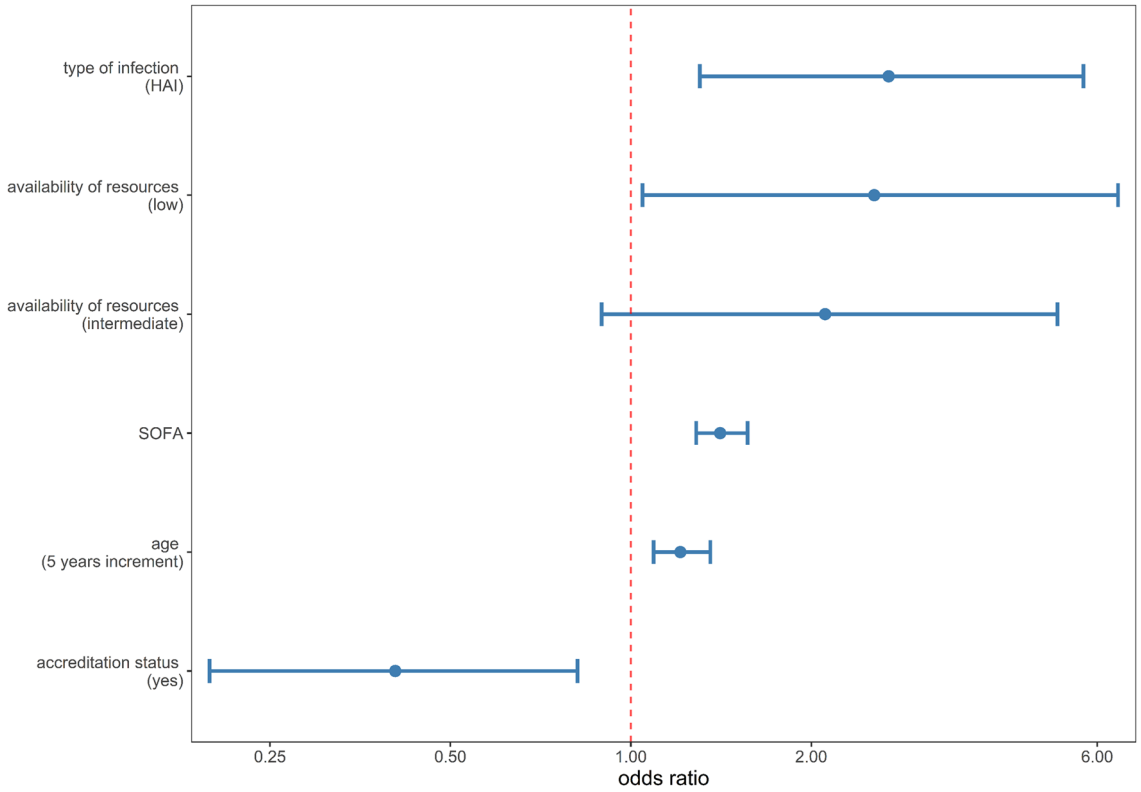

Fig. 4 Multivariate analysis of factors associated with mortality *HAI* healthcare-associated infection, *SOFA* Sepsis-Related Organ Failure Assessment score. We included in the multivariate analysis teaching status, resource availability, accreditation status, age, chronic obstructive pulmonary disease, immunosuppression, chronic renal failure, type of patient, type of infection, severity of illness, time to sepsis diagnosis, compliance with antibiotics and with 6-h bundle and allocation adequacy. Only patients without an end-of life care directive within the first 48 h were included in the model. Logistic regression analysis with random effects for the intercept. The central dot represents the odds ratio and the bars represent the 95% confidence interval

populations. We also did not collect data on the causative pathogens and multidrug resistance phenotypes for pragmatic reasons; this is a significant risk factor that may influence the outcome [28].

Conclusion

In conclusion, in a convenience sample of Brazilian ED, sepsis prevalence and in-hospital mortality were high, and inadequate allocation was frequent mainly in public institutions. Mortality is associated with modifiable factors, such as the prevalence of healthcare-associated infections, availability of resources, and quality of care.

Participating sites

Complexo Hospitalar de Niterói: SZSP Alves, CB Velasco; Fundação Centro Médico de Campinas: GF Sanches, LN Azevedo; Hospital Adventista de Belém: EB Sobrinho, AOL Veríssimo; Hospital Adventista de Manaus: AG Macedo; Hospital Alemão Oswaldo Cruz: AP Borges, F Colombari; Hospital Alvorada Moema: A Habitante, GS Oliveira; Hospital Ana Costa: RM Filho, NM Gambero; Hospital Brasília: LC Machado; Hospital Copa D'Or: JAL Albuquerque, SFM Fernandes; Hospital da Luz Vila Mariana: BAMP Bessen, EVN Martins; Hospital de Clínicas da Unicamp: MR da Silva, EF de Paula; Hospital de Clínicas de Uberlândia: MMC Silva; Hospital De Clínicas Mário Lioni: AF Pereira, PA Quesado; Hospital de Clínicas Nossa Senhora da Conceição/Associação Congregação de Santa Catarina: G Fernandes; Hospital de Doenças Tropicais Dr. Anuar Auad HDT/HAA: W Ayrão, N Kondratievans; Hospital de Emergência e Trauma Dom Luiz Gonzaga Fernandes: IR Leite, PKO Sá; Hospital de Pronto Socorro de Porto Alegre: EA de Oliveira, IO de Freitas; Hospital de Urgências de Goiânia: D Pedroso, A Bonifácio; Hospital Divina Providência: SA dos Santos Junior, MB do Amaral; Hospital Djalma Marques: AAG Alves, SHCA Carvalho; Hospital Ernesto Dorneles: JC Fernandes, CR Duarte; Hospital Estadual Jayme Santos Neves: GR Fonseca, LG Almeida; Hospital Geral Clériston Andrade:

LC de Oliveira Junior, RN de Oliveira; Hospital Geral De Juiz De Fora- M Damos; Hospital Geral de Palmas Dr. Francisco Ayres: RNDM de Souza, VS dos Santos; Hospital Geral Roberto Santos: AR Durães, YSL Bitar; Hospital Metropolitano De Várzea Grande: F Liberali; Hospital Miguel Arraes: CA Branco; Hospital Moinhos De Vento- LFS Varela; Hospital Municipal Dr. José Soares Hungria: KAP Conde; Hospital Municipal Santa Isabel: EA Peixoto; Hospital Municipal Vereador José Storopolli: RB Pardo, L Delgatto; Hospital Next Santo Amaro: CGC Jacob, A Silva; Hospital Next São Bernardo: LMB Vinãs, KDA Coqueti; Hospital Oeste D'Or: MCG Ribeiro, GBA Faria; Hospital Pasteur: DASF da Silva, JS Jardim; Hospital Português da Bahia: A Farias, AP Amorin; Hospital Pronto Socorro João Lucio Pereira Machado: ZE Sakamoto, VHC Barros; Hospital Quinta D'Or: ALM Filho, DP de Oliveira; Hospital Regional de Presidente Prudente: R Guimarães, LF Pires; Hospital Rio Grande: MA Sicolo; Hospital Santa Catarina de Blumenau: BBK Boettger, FA de Castro; Hospital Santa Cruz SP: JS Yamano, AR da Silva; Hospital Santa Cruz: CFD Dornelles; Hospital Santa Isabel: GP Alba, AP Correa; Hospital Santo Antônio: N de Alcantara; Departamento de Pesquisa Imed, Hospital São Camilo Pompéia: A Martins, NB Gouveia; Departamento de Pesquisa Imed, Hospital São Camilo Ipiranga: RL Coelho, AT Maciel; Departamento de Pesquisa Imed, Hospital São Camilo Santana: CSS Matos, EGL Guadalupe; Hospital São José/Associação Congregação Santa Catarina: M Pereira, R Rabe; Hospital São Lucas: T Smith, R Oliveira; Hospital São Lucas da PUC RS: C Toscan, MR e Karnikowski; Hospital Sepaco: FGR Freitas AT Bafi; Hospital Tacchini: J Giacomazzi; Hospital TotalCor: PGMB e Silva, AN Rabaça; Hospital Unimed Petrópolis: LES Fontes, AB Simões; Hospital Universitário de Londrina: C Grion, J Festti; Hospital Universitário de Petrolina: KR de Oliveira, S Xavier; Hospital Universitário do Oeste do Paraná: TS Giancursi, DF Maccari; Hospital Vera Cruz: BGC Araujo, JF Ferreira; Hospital Vitória Curitiba: G Borges, A Dino; Hospital Vitória Anália Franco: AH Soares, LF Vieira; Instituto Do Coração: InCor/HCFMUSP- AM Soeiro, MT de Oliveira Junior; O.S.S. Santa Marcelina Hospital Cidade Tiradentes: RS Lopes, F Moulin; Santa Casa de Misericórdia de Juiz de Fora: GC Fernandes, DA de Mattos; Santa Casa de Misericórdia de Passos: FM Araujo, VOS Pereira; Santa Casa de São Paulo: MV Arnoni, SP Santana; São Lucas Hospital das Clínicas: E Zukeran, SRSA Velihovetchi; Seisa Serviços Integrados de Saúde Ltda: Hospital Next Guarulhos: MAP Bronchtein, MT de Araújo; Unidade de Pronto Atendimento UAI Pampulha: R Borges, MT Ferreira; Unidade de Pronto Atendimento UAI São Jorge (UPA Sul): R Borges, MT Ferreira; Unidade de Pronto Atendimento de Varginha: EY Hamada; UPA Região Norte: G Marcatto; Vitória Apart Hospital: C Piras, TR Pancini.

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Author contributions FRM: had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. FRM: assumes full responsibility for the integrity of the submission as a whole, from inception to the published article. FRM, ABC, AB, FDP, FST, JL, MAB, MBM, TL, LCPA: contributed substantially to the study design. FRM, ABC, AB, FDP, FST, JL, MAB, MBM, TL, LCPA: contributed substantially to data collection. FRM, ABC, AB, FDP, FST, JL, MAB, MBM, TL, LCPA: contributed substantially to the data analysis and interpretation, and the writing of the manuscript. All authors read and approved this manuscript before submission.

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Availability of data and materials The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interests We declare that we have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants 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. The study was approved by the Research Ethics Committee (ERB) at the coordinating center (Federal University of São Paulo) under the number CAAE: 60953816.4.1001.5505.

Consent to participate Informed consent was waived because of its observational nature and no direct involvement of patients beyond data collection from patients' charter.

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