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Original Article

Risk factors for death in patients with sepsis in an intensive care unit

Fatores de risco para morte em pacientes com sepse em uma unidade de terapia intensiva

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Objective: to determine the main risk factors for death in patients with sepsis in an intensive care unit. **Methods:** it is a retrospective cohort study, wich included 126 patient chorts lhat had clinical and clinical and laboratory diagnosis of sepsis were considered eligible. The conditional probability of death was calculated through the Kaplan-Meier method and the risk of death was estimated by the hazard ratio, using a Cox regression model with p<0.050. **Results:** a total of 124 patients were included in the study. The main focus of infection was the respiratory system. Regarding the outcome, 40.3% patients with sepsis, 73.9% with severe sepsis and 69.2% with septic shock died. Patients with abdominal sepsis and using vasopressors were at higher risk of death. **Conclusion:** septic patients with abdominal source of infection and using vasopressor agents had a higher risk of dying, while patients who were tracheostomized had a better chance of living.
Descriptors: Intensive Care Units; Sepsis; Risk Factors; Death; Nursing Care.

Objetivo: determinar os principais fatores de risco para a morte em pacientes com sepse em uma unidade de terapia intensiva. **Métodos**: trata-se de uma coorte retrospectiva, onde foram incluídos 124 prontuários de pacientes que tiveram diagnóstico clínico e laboratorial de sepse. A probabilidade condicional de morte foi calculada através do método de Kaplan-Meier; o risco de morte foi estimado pela razão de risco, utilizando modelo de regressão de Cox com p<0,050. **Resultados:** o foco principal da infecção foi o sistema respiratório. Em relação ao desfecho, morreram 40,3% pacientes com sepse, 73,9% com sepse grave e 69,2% com choque séptico. Os pacientes com sepse abdominal e que utilizaram vasopressores apresentaram maior risco de morte. **Conclusão:** pacientes sépticos com fonte abdominal de infecção e fazendo uso de agentes vasopressores apresentaram maior risco de morte, enquanto que pacientes traqueostomizados tiveram melhores chances de sobreviver.
Descritores: Unidades de Terapia Intensiva; Sepse; Fatores de Risco; Morte; Cuidados de Enfermagem.

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Introduction

Sepsis is the primary cause of death from infection. It is, thus, necessary to pay urgent attention to the detection of this condition. The epidemiology of sepsis in healthcare services of developing countries remains an area that needs further investigation[1].

According to the Third International Consensus Definitions for Sepsis and Septic Shock, sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection, while septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone[1].

Sepsis is a major public health problem, frequent, costly, and often fatal. Despite advances in treatment, the incidence of sepsis and the number of sepsis-related deaths has increased[2]. Mortality rates for sepsis in recent years have ranged from 18 to 40.0%; patients with severe sepsis receiving usual care have a 28-day mortality of 33.2%. It is, thus, necessary to pay urgent attention to prompt recognition and treatment of this condition[1,2-4]

Severe sepsis and septic shock are major causes of mortality in intensive care unit patients worldwide and it is unknown whether there was evidence has been to support the increase in mortality rates[5]. Most of the global burden of sepsis occurs in middle- and low-income countries and, although some centers have the resources to conduct appropriate diagnosis and follow-up of sepsis, the education and awareness about sepsis appear to be too low[2,6].

Many risk factors that contribute to sepsis and severe sepsis are related to the patient's ability to fight the infection and propensity to develop acute organ failure in response to infection. Advanced age, male sex, black race, and chronic health conditions are some examples. Severe sepsis is also related to the following sites of infection: abdomen, skin, soft tissue, urinary tract, lungs and the bloodstream[3]. In the intensive care unit studied, many patients die from abdominal septic focus, but we do not know to which extent this information corresponds to the reality and which are the causes of such deaths.

A number of studies has described the epidemiology, risk factors and outcome of severe sepsis and septic shock in different countries[5,7]. However, the incidence of severe sepsis outside modern intensive care units is unknown, especially in parts of the world where intensive care units are scarce, as in the North of Brazil[8].

Although studies on this theme have increased in the last 10 years, information about sepsis in Brazilian intensive care units remains sparse and incomplete. Sepsis is a common event among critically ill patients. Data underscoring the regional variability of the epidemiology and outcome of sepsis may be useful to guide an appropriate allocation of resources[9]. However, to our knowledge, no studies have addressed this issue in developing countries. In this sense, in was observed many deaths among septic patients in intensive care unit studied, mainly from abdominal septic focus, but it is not know yet which are the risk factors for these deaths, valuable information to direct interventions based on scientific evidence.

Therefore, the aim was to determine the main risk factors for death in patients with sepsis in an intensive care unit.

Methods

A retrospective cohort study was conducted in an intensive care unit of a Brazilian Hospital in Acre, from September 2012 to July 2014. This intensive care unit was founded in 2003 and serves the public health system. It has 18 beds and receives all patients coming from the emergency departments of the State of Acre and from some the cities of Rondônia and Amazonas, Brazil. Only emergency surgeries are performed in this hospital.

During the study period, a total of 792 patients were admitted to the intensive care unit and 170 were diagnosed with sepsis; among the septic patients, 46

were excluded from the study for lack of clinical and laboratory evidence of sepsis. Medical records were analyzed and patients were considered eligible when they had clinical and laboratorial diagnosis of sepsis. Thus, 124 patients were included in this study.

Data were collected from the intensive care unit information system, the Epimed Solutions®. This system has been designed for the management of clinical information and aims to improve the quality and efficiency of hospital care. It was created in 2007 by intensive care physicians with extensive experience in risk and prognostic studies. The Epimed Monitor system is used in more than 400 hospitals in Brazil, 750 intensive care units, and 11,000 monitored beds, gathering information from over 1,000,000 patients. It is the largest clinical and epidemiological database in Latin America.

Information is fed into the system daily by the head nurse of the intensive care unit, using the patients' records. The data collection tool used in this study was developed by the research team and assessed for face and content validity by a panel of experts. The main nurse researcher collected the data in a daily basis in this intensive care unit.

The independent variables analyzed were: age, gender, type of admission (clinical, clinical emergency, postoperative), diagnosis for admission to the intensive care unit (clinical emergency, trauma, surgery), type of sepsis (sepsis, severe sepsis, septic shock), length of stay in the intensive care unit, presence of multidrug-resistant microorganisms, systolic blood pressure in the first hour of admission to the intensive care unit, serum lactate level, presence of mechanical ventilation, use of vasopressors, presence of tracheostomy, Simplified Acute Physiology Score III (SAPS III) prognosis, and patient outcome (discharge, death). The Simplified Acute Physiology Score III is a generic prognostic index used in intensive care units and it was developed based on prospective multiinstitutional studies. It is calculated from the data available within the first hour of admission to the intensive care unit and reflects the severity of the disease at admission[10].

The diagnosis of sepsis was made by a physician and a nurse through the investigation of the presence of infection and at least two or more of the following signs and symptoms: fever or hypothermia, heart rate greater than 90 beats per minute, tachypnea, hyperglycemia, hypotension, altered mental status and edema. In addition to the clinical findings, the diagnosis was also based on laboratory data findings of leukocytosis or leukopenia (leukocytes >12000 cells/mm^3 or <4000 cells/mm^3 or the presence of >10% immature forms). Finally, sepsis was categorized into one of three types: sepsis, severe sepsis, or septic shock[11].

The concepts for classification of sepsis used herein were based on the criteria proposed by the consensus of the American College of Chest Physicians/Society of Critical Care Medicine[11]. The dependent variable was death from sepsis in a Brazilian Amazon intensive care unit.

The time zero (T0) for this cohort was the date of clinical and laboratory diagnosis of sepsis, and the follow-up time (ΔT) was the period between the diagnosis and the outcome (discharge or death).

Data were entered in an Excel 2010 (Microsoft, USA) spreadsheet and were imported into the Statistical Package for the Social Sciences® version 17.0. The Kaplan-Meier method was used to estimate the conditional probability of death after 12 and 24 days of monitoring. The 95% log-rank test was used to assess the differences between the curves.

A Cox regression model was used to estimate *crude and adjusted* relative hazards, with a confidence interval of 95%, to assess the risk factors for death in these patients. The final model was built to evaluate prognostic factors of death in patients with sepsis in the intensive care units. Independent variables that showed statistical significance in the univariate analysis were included in the multivariate Cox regression model, with p-value set at 5% ($p<0.050$); p-values >10% were adopted as criterion for exclusion of va-

riables from the model.

The study respected the formal requirements of national and international regulatory standards for research involving human subjects.

Results

A total of 62 patients (50.0%) had sepsis, 23 (18.5%) had severe sepsis, and 39 (31.5%) had septic shock. Among patients, the mean age was 47.5±20.3 years old in the case of septic patients, 47.9 ±19.1 in cases of severe sepsis, and 49.9 ±22.4 in cases of septic shock. Males predominated among patients (62.9%). The patients had a mean length of stay in the intensive care units of 23.6 ±15.6, 23.3 ±15.5 and 19.5 ±19 days, respectively and the reason for admission was clinical emergency (50.0%).

The main focus of infection was the respiratory system (72.6%); 51.6% of the cases had been caused by multidrug-resistant microorganisms; the majority had systolic blood pressure > 90 mmHg (82.3%) and serum lactate > 4 mmol/L (54.2%). It is noteworthy that most of the patients, regardless of sepsis classification, were using mechanical ventilation (90.3%), while a minority was tracheostomized (31.5). A total of 50.3% of patients with septic shock used vasopressors. Regarding the final outcome, 40.3%, 73.9% and 69.2% of sepsis, severe sepsis or septic shock patients died (Table 1).

The conditional probability of death at the first 12 and 24 days after admission to the intensive care unit were compared. The patients had a higher probability of death in the end of the 24 days of stay. Other factors associated with an increased probability of death in the first 24 days after admission to the intensive care unit were: abdominal focus of infection (43.4% respiratory focus *versus* 100.0% abdominal focus; p=0.038) and use of vasopressors (30.7% *versus* 51.3%; p=0.004). However, tracheostomized patients presented lower probability of death when compared to non-tracheostomized patients (19.8% *versus* 59.9%, p=0.050) (Table 2).

Table 1 – Characteristics and outcomes of patients with sepsis, severe sepsis and septic shock

Independent variable	Sepsis	Severe Sepsis	Septic shock
	n (%)	n (%)	n (%)
Frequency	62 (50.0)	23 (18.5)	39 (31.5)
Sex			
Female	23 (37.1)	9 (39.1)	17 (43.6)
Male	39 (62.9)	14 (60.9)	22 (56.4)
Diagnosis for admission			
Clinical emergency	31 (50.0)	16 (69.6)	24 (61.5)
Trauma	16 (25.8)	1 (4.3)	4 (10.3)
Surgery	15 (24.2)	6 (26.1)	11 (28.2)
Site of infection			
Respiratory	45 (72.6)	19 (82.6)	24 (61.5)
Abdominal	3 (4.8)	1 (4.4)	4 (10.3)
Urinary	3 (4.8)	-	-
Vascular catheter	7 (11.3)	1 (4.4)	1 (2.6)
Other	4 (6.5)	2 (8.6)	10 (25.6)
Multiresistant microorganisms			
Yes	32 (51.6)	11 (47.8)	8 (20.5)
Systolic blood pressure in the first hour of admission			
< 90mmHg	11 (17.7)	5 (21.7)	14 (36.8)
Serum lactate			
≥ 4mmol/L	32 (54.2)	11 (57.9)	24 (70.6)
Mechanical ventilation			
Yes	56 (90.3)	21 (91.3)	38 (97.4)
Vasopressors			
Yes	41 (66.1)	13 (56.5)	28 (71.8)
Tracheostomy			
Yes	21 (33.9)	9 (39.1)	9 (23.1)
Prognostics scores (SAPS III)	34.7	39.5	47.6
Outcome			
Death	25 (40.3)	17 (73.9)	27 (69.2)

Table 2 – Conditional probability of death in septic patients within 12 and 24 days of stay in the intensive care unit

Variable	Total n(%)	% of death (days)		Log-Rank
		12	24	p-value
Diagnosis for admission				
Clinical emergency	71 (57.3)	20.3	49.7	
Trauma	21 (16.9)	0.9	24.4	0.224
Surgery	32 (25.8)	26.2	49.8	
Site of infection				
Respiratory	88 (70.9)	16.4	43.4	
Abdominal	8 (6.6)	47.5	100.0	
Urinary	3 (2.4)	-	-	0.038
Vascular catheter	9 (7.2)	11.1	11.1	
Other	16 (12.9)	40.2	70.1	
Multiresistant microorganisms				
No	73 (58.9)	29.0	56.2	0.195
Yes	51 (41.1)	0.8	32.1	
Systolic blood pressure in the first hour (mmHg) of admission				
< 90	93 (24.4)	20.8	57.4	0.616
≥ 90	30 (75.6)	20.0	42.1	
Serum lactate (mmol/L)				
< 4	45 (40.2)	19.3	41.5	0.229
≥ 4	67 (59.8)	20.6	48.8	
Mechanical ventilation				
No	9 (7.3)	20.0	20.0	0.725
Yes	115 (92.7)	20.1	45.8	
Vasopressors				
No	42 (33.9)	10.8	30.7	0.004
Yes	82 (66.1)	24.2	51.3	
Tracheostomy				
No	85 (68.5)	27.6	59.9	0.050
Yes	39 (31.5)	0.5	19.8	

In the final analysis, the main risk factors for death in septic patients were estimated by the Cox regression model. Patients with abdominal infection (hazard ratio: 3.71; 95% confidence interval: 1.31 to 10.49) and using vasopressors (hazard ratio: 4.29; 95% confidence interval: 2.16 to 8.50) had a higher risk for death. However, tracheostomized patients had a lower risk for death (hazard ratio: 0.43; 95% confidence interval: 0.22 to 0.83), when compared with non-tracheostomized patients (Table 3).

Table 3 – Risk factors for death in septic patients in a Brazilian intensive care unit

Variable	Hazard ratio $_{crude}$ (CI 95%)	Hazard ratio $_{adjusted}$ (CI 95%)*
Site of infection		
Respiratory	1	1
Abdominal	3.1 (1.2-8.0)	3.71 (1.3-10.4)
Urinary	0.5 (0.1-2.3)	2.23(0.4-11.6)
Vascular Vascular catheter	0.7 (0.2-2.0)	1.39(0.4-4.2)
Other	1.7 (0.8-3.4)	1.42(0.6-3.3)
Vasopressors		
No	1	1
Yes	2.3 (1.2-4.3)	4.2 (2.1-8.5)
Tracheostomy		
No	1	1
Yes	0.6 (0.3-1.0)	0.4 (0.2-0.8)

*CI=Confidence interval, Adjusted for gender and age

Discussion

Among the limitations of this study is the retrospective design and use of information from medical records, whose credibility depends on the quality of the data recorded therein. However, we believe that the data had a good quality level because they were fed into the Epimed's system database in a daily basis by the head nurse of the intensive care unit. Another limitation of the present study is the relatively small sample size taken from a single intensive care unit in Brazil, what hinders the generalizability of the findings. A multicenter study is needed to confirm the findings on mortality of critically ill patients with sepsis.

In this sense, efforts should be made to diagnose and treat septic patients as soon as possible, as well as to perform tracheostomy and provide evidence-based nursing care in a timely manner in this unit. We also suggest the realization of a study to investigate the reasons for death from abdominal sepsis among patients in the studied unit.

Similar high mortality rates to that found in the currently studied intensive care unit have also been reported in several intensive care unit patients with sepsis[12]. The implementation and training for early

identification of sepsis and the use of Sequential Organ Failure Assessment (SOFA) along with a patient flow chart has improved the thorough monitoring of vital signs in patients with and without organ failure[13].

As for length of stay, patients with sepsis, severe sepsis and septic shock stayed for 19.5 to 23.6 days in the intensive care unit. These results differ from other national[14] and international[5,7] data that identified lengths of stay varying from 3.2 to 15.4 days.

Lengths of stay and sepsis severity are associated with high costs of hospitalization. Therefore, training in diagnosis and effective treatment of sepsis and the institutionalization of protocols for provision of care by intensive care unit teams are important to decrease the days of hospitalization, by means of earlier and more effective diagnosis and treatment[15].

Regarding the infection sites, the main source of infection was the respiratory system, with 72.6% of the cases. Respiratory infections are the most common cause of sepsis, accounting for approximately half of all cases of sepsis. One of the main factors associated with pulmonary focus of sepsis is ventilation-associated pneumonia, which occurs 48–72 hours after intubation and is associated with a higher mortality rate and significantly longer stay in intensive care units and higher hospital costs[16].

The invasion and proliferation of infectious agents in the abdominal cavity provoke an intense inflammatory process: release of cytokines; formation of free radicals and oxygen; reduction of cellular production of adenosine triphosphate, translocation of intestinal bacteria, and intestinal edema. These responses predispose the patients to multiple organ dysfunction syndrome, which leads to high rates of morbidity and mortality[17].

The vast majority of patients were under mechanical ventilation regardless the level of sepsis. However, a minority was tracheostomized. Tracheostomy is indicated to relieve upper airway obstruction, provide prolonged ventilatory support, reduce dead space, facilitate clean bronchial aspiration, allow faster weaning, reduce risks of laryngeal infection, and mitigate the risk of sequelae from tracheal stenosis. In this aspect, daily assessment of the patient is important to identify indication for tracheostomy and to plan this procedure[13].

Most patients in this cohort had used vasopressors (inotropes). Evidence suggests a survival benefit, improved hemodynamic profile, and reduced rate of adverse events with the use of vasoactive agents[18].

The use of vasopressors begins when patients with severe sepsis and septic shock maintain a systolic blood pressure ≤90mmHg or a mean blood pressure ≤ 65mmHg, even after volume replacement. The use of vasopressors it is considered a protective factor for mortality[19].

The observed mortality rate in the intensive care unit during the study period was high; the majority of patients with severe sepsis (73.9%) or septic shock (69.2%) died during hospitalization; thus, patients with severe sepsis had an increased chance of dying. Mortality rates from severe sepsis have been reported to vary from 17.3 to 22.2 in U.S. hospitals in the period of 2008 and 2012[20]. These results differ from those found in the present study, probably because of the profile of the patients (trauma and abdominal trauma) and the developing the two countries.

Another fundamental point is the importance of the early diagnosis of sepsis by the whole intensive care team. This team must perform a good physical examination and start the treatment within the first 3 hours after detection of sepsis, which are called the "golden hours"[11].

The conditional probability of death in patients with sepsis, severe sepsis and septic shock was higher after 24 days of admission to the intensive care unit, when compared to the first 12 days (p=0.030). The results revealed that despite the improvements in patient care and sepsis management, the issue remains a challenge in intensive care environments, especially in developing countries. One of the factors that may

explain the result is the delay to administrate vasopressors in patients with septic shock, which further worsens the condition clinical decompensation of the patient, thus increasing mortality. The use of norepinephrine consistently reduced all-cause mortality at 28 days with supporting hemodynamic data and lower rate of major arrhythmias[18].

Conclusion

This study demonstrated that septic patients with an abdominal source of infection and using vasopressor agents had a higher risk for death during stay in the intensive care unit, while patients who were tracheostomized had a better chance of living.

Collaborations

Prado PR, Volpáti NV, Gimenes FRE and Amaral TLM contributed to the design of the project, analysis and interpretation of the data, writing of the paper, relevant critical review of the intellectual content and final approval of the version to be published. Atila E and Maggi LE contributed to the writing of the paper, relevant critical review of the intellectual content and final approval of the version to be published.

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