**Revista da Sociedade Brasileira de Medicina Tropical**
*Journal of the Brazilian Society of Tropical Medicine*
**Vol.:52:e20180121: 2019**
doi: 10.1590/0037-8682-0121-2018

# Short Communication

# Survival analysis of patients with sepsis in Brazil

***Eliane Pereira da Silva*[1], *Vinícius da Costa Duarte*[2], *Miguel Maia Soares*[2], *Alexia Tayane Menezes de Melo*[2], *Emily Ramos Calife*[2], *Gilmar da Silva Rebouças*[2] *and Dyego Leandro Bezerra de Souza*[3]**

[1]. Departamento de Medicina Clínica, Unidade de Terapia Intensiva, Hospital Universitário Onofre Lopes, Universidade Federal do Rio Grande do Norte, Natal, RN, Brasil.
[2]. Faculdade de Medicina, Universidade Federal do Rio Grande do Norte, Natal, RN, Brasil.
[3]. Departamento de Saúde Coletiva, Programa de Pós-graduação em Saúde Coletiva e Programa de Pós-graduação em Ciências da Saúde, Universidade Federal do Rio Grande do Norte, Natal, RN, Brasil.

## Abstract

**Introduction:** This study aimed to analyze the survival of septic patients and to assess prognostic factors. **Methods:** Patients with sepsis, severe sepsis, and septic shock were followed up and clinical and laboratory data were collected. The sepsis-related organ failure assessment (SOFA) score was calculated. **Results:** The overall 30-day survival rates of patients with sepsis, severe sepsis, and septic shock were 86.3%, 72.5%, and 20%, respectively. Mortality was related to old age, septic shock, coagulopathy, lactate level, and high SOFA score among other factors. **Conclusions:** Identification of prognostic variables may reduce sepsis-related mortality.

**Keywords:** Sepsis. Severe sepsis. Septic shock. Mortality. Survival.

Sepsis was defined as the concomitant presence of a presumptive infection and two of the four criteria for systemic inflammatory response syndrome (SIRS). The progression of a septic condition to dysfunction of one or more organs was previously called severe sepsis, whereas the progression to hypotension that was unresponsive to volume replacement was considered septic shock[1].

Nonetheless, new definitions have been proposed by *The Third International Consensus on the Definition for Sepsis and Septic Shock* (Sepsis-3), in which sepsis is defined as a potentially fatal organic dysfunction caused by a deregulated host response to infection. Furthermore, septic shock is defined as sepsis associated with cellular and metabolic alterations that significantly increase mortality. Nevertheless, the *Latin American Sepsis Institute (ILAS)* has not endorsed these new definitions, justifying that they do not correspond to the Latin American reality[2].

***Corresponding author:*** Eliane Pereira da Silva.
**e-mail:** elilips@hotmail.com
**Orcid:** 0000-0002-3364-5046
**Received** 29 March 2018
**Accepted** 17 December 2018

Analysis of patient statistics in five intensive care units (ICUs) as part of the Brazilian Sepsis Epidemiological Study (BASES) revealed that severe sepsis and septic shock occurred in 27% and 23%, respectively, of patients with a hospital stay of more than 24 hours[1].

Although sepsis poses a major challenge for physicians worldwide and presents one of the main causes of mortality in the ICU, the number of studies investigating epidemiological data on sepsis in hospitals in Brazil is limited[3]. Identification of variables that may influence the prognosis of sepsis patients is fundamental for reduction of the mortality rates and more effective prevention, diagnosis, and treatment of sepsis[4]. Therefore, the present study aimed to analyze the survival of sepsis patients and to determine prognostic factors that may alter the outcome of these patients.

We conducted an observational, longitudinal, prospective study in the wards and ICU of the Onofre Lopes University Hospital (HUOL) in Natal, Rio Grande do Norte state, Brazil, between September 1, 2015 and November 30, 2015. Patients with a suspected infection were initially selected by analyzing their antimicrobial prescription files. Participants were finally selected based on their admittance to the ward and ICU with the respective authorization for hospital internment (AHI) that met the classification norms for sepsis, severe sepsis, and septic

shock. Patients who were under 18 years old and those using antimicrobial prophylaxis were excluded.

Data was collected using a form adapted from ILAS[2], which initially addresses general patient characteristics (first name, age, sex, and hospitalization record, respecting ethical standards in research) followed by information on the suggestive record of infection (signs and symptoms of SIRS, infectious focus, organic dysfunctions) and classification of sepsis based on the definitions currently accepted by ILAS (sepsis, severe sepsis, or septic shock). The organ dysfunctions considered were systolic blood pressure (SBP) <90 mmHg or mean arterial pressure (MAP) <65 mmHg, a decrease in blood pressure (BP <40 mmHg), creatinine levels >2.0 mg/dL or diuresis <0.5 mL/kg/h in the last 2 hours, bilirubin >2 mg/dL, platelet count <100,000, serum lactate >2 mmol/dL, coagulopathy (international normalized ratio/INR >1.5 or prothrombin time/PTT >60 sec), $PaO_2/FiO_2$ ratio <300, and a recent or increased need to maintain oxygen ($O_2$) for peripheral oxygen saturation ($SpO_2$) >90%.

The sequential organ failure assessment (SOFA) score is used for the evaluation and prognosis of sepsis by assessing the degree of dysfunction of several organs. This score should be determined daily because it descriptively evaluates organ failure with a formula that considers its frequency, interventions/treatment, and impact on survival[5]. In this study, we determined the SOFA score and its prognostic indicators (hemodynamic, neurological, respiratory, hepatic, hematological, and renal), the daily condition of the patient, and the outcome of the patient, which was followed up until hospital discharge, death, or the 30th day after admission into the study. Patients who were discharged or remained alive at the end of the 30th day were right censored for statistical analysis.

Data were statistically analyzed using the Kaplan-Meier method to estimate the median of survival times and corresponding confidence intervals (95% CI) for the subgroups of patients classified by the variables of interest. Kaplan-Meier curves were constructed for the main categorical variables that were compared using the log-rank, Tarone-Ware, or Breslow tests. Data were processed and analyzed using the Statistical Package for the Social Sciences (SPSS) software version 20.0.

The study was submitted to the Ethics and Research Council of the Onofre Lopes University Hospital and approved (study number: 1.085.985) along with the informed consent terms.

The study was conducted with 102 septic patients who met the inclusion criteria and provided informed consent. The mean age of the patients was 55±17.2, and 58.82% were women. Of these patients, 22 (21.56%) died and 51 (50%) were discharged during the study. Twenty-nine patients (28.43%) remained hospitalized after 30 days, of which 23.53% had been referred by another institution with the diagnosis of sepsis.

The overall survival rate was 71.8% 30 days after hospital admission. Septic patients without any organ dysfunction comprised 55% of all patients and had a survival rate of 86.3% after 30 days. In contrast, 35% of all patients developed severe sepsis and their survival rate was 72.5% 30 after admission to the hospital. Patients who progressed to septic shock accounted for only 10% of all patients, with a 30-day survival rate of 20% ($p<0.001$, **Table 1**).

A pulmonary origin of sepsis was detected in 30.39% of cases (n=31), a urinary origin in 25.49% (n=26), and a gastrointestinal origin in 18.63% (n=19). Other foci such as neurological, skin and soft parts, bone and joint, surgical wound infection, catheter, endocarditis, and prosthesis infections were responsible for 25.49% of sepsis cases (n=26). Patients with pneumonia, urinary infection, and abdominal infection had a 30-day survival rate of 71.9%, 68.0%, and 48.2%, respectively. There were no statistically significant differences detected between foci ($p<0.191$).

Possible prognostic clinical and laboratory factors were analyzed for their influence on mortality (**Table 1**).

SOFA scores were calculated at the beginning of the study within the first 24 hours of antibiotic therapy. The overall mean score was 3.19±3.56 and 6.40±4.13 in the patients who died during the study. Patients with a SOFA score of ≤2 points had a 30-day survival rate of 86.17%, which was much higher than that of patients with a score of ≥3 points (57.73%, **Table 1**).

The 30-day survival rate of septic patients without organ dysfunction was 83.6%, while 27.5% of patients with severe sepsis died in this period. Nonetheless, mortality rates of severe sepsis declined from 46.9% between 1991 and 1995 to 29% between 2006 and 2009[6]. Patients with septic shock had a 30-day survival rate of 20%, which is in contrast to that of 72.6% observed in a previous study[4]. According to a multicenter cohort study in 65 hospitals in different regions across Brazil, the overall 28-day mortality of septic patients was 46.6%, with survival rates of 16.7%, 34.4%, and 65.3% for patients with sepsis, severe sepsis, and septic shock, respectively. The results on sepsis and severe sepsis are similar to those obtained in our study[7]. Nonetheless, our results differ from data obtained in the BASES, in which the mortality rates for sepsis, severe sepsis, and septic shock were 33.9%, 46.9%, and 52.2%, respectively[1].

Older age represents a risk factor for higher sepsis mortality according to previous studies[4]. Furthermore, we found a correlation between a body temperature <35ºC and higher mortality in septic patients, which is in agreement with previous observational studies reporting that a low body temperature in critically ill ICU patients with infection is associated with an increased mortality, as is hypothermia in patients with bacteremia[8].

Our study revealed that a $PaO_2/FiO_2$ ratio of <300 had a negative impact on the survival of septic patients. In line with these observations, a recent study showed that that acute respiratory distress syndrome (ARDS), which is characterized by a $PaO_2/FiO_2$ ratio of <200, induced by sepsis rapidly progresses and is associated with high hospital mortality rates in critically ill patients, although the incidence of this syndrome is relatively low. Oxygen supply increases survival rates of these patients and those of patients with non-sepsis-induced ARDS[9].

We observed a clear relationship between hyperbilirubinemia (>2 mg/dL) and lower survival rates of the septic patients. This relationship is corroborated by other studies and seems to be associated with longer hospital stay, use of mechanical ventilation, and support with vasopressors[10].

**TABLE 1:** Survival rates relative to prognostic variables.

| | N | Incidence (%) | 15-day survival rate (%) | Confidence interval (%) | 30-day survival rate (%) | Confidence interval (%) | P-value |
|---|---|---|---|---|---|---|---|
| Sepsis (without any organ dysfunction) | 56 | 54.90 | 97.4 | 94.80-100.00 | 0.836 | 76.70-90.50 | <0.001 |
| Severe sepsis | 36 | 35.29 | 82.2 | 75.50-88.90 | 0.725 | 63.80-81.20 | |
| Septic shock | 10 | 9.80 | 30.0 | 15.50-44.5 | 0.2 | 7.40-32.60 | |
| Male | 42 | 41.18 | 85.20 | 79.60-90.80 | 68.30 | 59.10-77.50 | <0.708 |
| Female | 60 | 58.82 | 84.00 | 78.70-89.30 | 74.50 | 67.50-81.50 | |
| Age ≤49 years | 35 | 34.31 | 100.00 | 100.00 | 87.00 | 77.90-96.10 | <0.014 |
| Age >49 years | 67 | 65.69 | 76.80 | 71.30-82.30 | 64.70 | 57.80-71.60 | |
| SOFA score ≤2 | 55 | 53.92 | 97.14 | 94.32-99.95 | 86.17 | 79.66-92.68 | <0.001 |
| SOFA score >2 | 47 | 46.08 | 68.15 | 61.04-75.26 | 57.73 | 49.48-65.97 | |
| Hyperthermia >38.3ºC | 15 | 14.71 | 92.90 | 86.00-99.80 | 82.50 | 71.00-94.00 | <0.591 |
| Hypothermia <35ºC | 9 | 8.82 | 77.80 | 63.90-91.70 | 43.20 | 22.40-64. 00 | <0.035 |
| Tachycardia >90 bpm | 79 | 77.45 | 83.60 | 79.00-88.20 | 69.70 | 63.20-76.20 | <0.632 |
| Tachypnea >20 rpim | 68 | 66.67 | 83.80 | 79.10-88.50 | 68.60 | 61.60-75.60 | <0.352 |
| Leukocytosis >12,000 | 75 | 73.53 | 84.00 | 79.50-88.50 | 69.40 | 62.80-76.00 | <0.802 |
| Leukopenia <4,000 | 4 | 3.92 | 83.80 | 79.80-87.80 | 70.80 | 65.8-75.88 | <0.382 |
| Recent or increased need of $SpO_2$ >90% | 16 | 15.69 | 43.80 | 30.20-57.40 | 43.80 | 30.20-57.40 | <0.001 |
| $PaO_2/FiO_2$ <300 | 13 | 12.75 | 61.50 | 48.00-75.00 | 51.30 | 36.70-65.90 | <0.038 |
| Coagulopathy (INR >1.5 or PTT >60 seconds) | 4 | 3.92 | 25.00 | 3.35-46.65 | 25.00 | 3.35-46.65 | <0.001 |
| Lactate >2 mmol/dL | 14 | 13.73 | 61.90 | 48.26-75.49 | 42.42 | 27.59-57,25 | <0.001 |
| Platelet count <100,000 | 8 | 7.84 | 75.00 | 59.69-90.30 | 60.00 | 41.83-78.16 | <0.273 |
| SBP <90 or MAP <65 mmHg | 18 | 17.65 | 57.43 | 45.12-69.73 | 57.43 | 45.12-69.73 | <0.034 |
| Drop in BP >40 mmHg | 9 | 8.82 | 66.66 | 51.49-82.37 | 66.66 | 51.49-82.37 | <0.568 |
| Creatinine >2 mg/dL or diuresis <0.5 mL/kg/h | 19 | 18.63 | 59.23 | 40.02-71.44 | 50.77 | 37.70-63.84 | <0.002 |
| Bilirubin >2 mg/dL | 7 | 6.86 | 68.57 | 49.94-87.19 | 0.00 | 0.00 | <0.035 |
| Referred with sepsis from another institution | 24 | 23.53 | 78.70 | 70.23-87.18 | 63.94 | 51.99-75.90 | <0.278 |

**BP:** blood pressure; **bpm:** beats per minute; **$FiO_2$:** inspired fraction of oxygen; **INR:** international normalized ratio; **MAP:** mean arterial pressure; **$O_2$:** oxygen; **$PaO_2$:** partial pressure of oxygen; **PTT:** prothrombin time; **RPIM:** respiratory incursions per minute; **SBP:** systolic blood pressure; **SOFA:** sequential organ failure assessment; **$SpO_2$:** peripheral oxygen saturation.

In addition to liver dysfunction, the occurrence of acute kidney injury (AKI), defined as creatinine levels >2 mg/dL or diuresis <0.5 mL/kg/h, was also related to an adverse prognosis in septic patients. AKI in septic patients appears to be linked to hemodynamic parameters, endothelial dysfunction, intraglomerular thrombosis, and tubular obstruction. Therefore, early identification and treatment of AKI can improve the chances of survival of septic patients[11].

Sepsis-induced coagulopathy is a risk factor for mortality with an incremental threat of poor outcomes with increasing severity of this pathology[12]. We identified a relationship between this condition and septic patients hospitalized with coagulation disorders (INR >1.5 or PTT >60 seconds).

Although we observed a statistically significant association between hypotension (SBP <90 mmHg or MAP <65 mmHg) and higher mortality rates, this relationship is not corroborated by any previous data. A significant correlation between SBP levels <110 mmHg in septic patients undergoing surgery and higher mortality has been demonstrated[13], but it remains unclear whether this association applies to non-surgically treated septic patients.

In our study, patients with lactate levels >2 mmol/dL had lower survival rates in comparison to patients with lower serum lactate levels and this relationship was independent of blood pressure levels or presence of other organic dysfunction[14].

The SOFA score is used in hospitals as a prognostic factor for patients with sepsis[7], with a high score upon admission or an increasing score in the first 3 days in the ICU correlating with high mortality rates[15]. Patients with SOFA scores ≥3 were associated with lower survival compared to those scoring ≤2 points in our study.

Certain limitations of our study should be acknowledged. First, the survival analysis was performed in a single hospital center. Second, the short follow-up period of 30 days limits the understanding of how certain clinical factors may influence the long-term survival of patients with sepsis. Third, multivariate analysis by Cox regression could not be performed due to the small number of outcomes (22 deaths).

We succeeded in analyzing the survival rates of hospitalized sepsis patients in Brazil. Furthermore, we identified variables that influence mortality rates of septic patients, namely age, diagnosis of septic shock, hypothermia, recent or increased need to maintain $O_2$ to achieve $SpO_2$ >90%, $PaO_2/FiO_2$ ratio <300, coagulopathy, serum lactate >2 mmol/dL, hypotension, AKI related to sepsis, hyperbilirubinemia, and a SOFA score >2. We revealed high hospital mortality rates due to sepsis, particularly of patients with septic shock, which is in accordance with other studies from Brazil.

**Conflict of Interest:** The authors declare that there is no conflict of interest.

## REFERENCES

1. Silva E, Pinheiro C, Michels Jr. V. Epidemiologia. Consenso Brasileiro de Sepse. Rev Bras Ter Intensiva. 2004;16(2):97-101.
2. Instituto Latino Americano de Sepse (ILAS). Roteiro de Implementação de Protocolo Assistencial Gerenciado. 4ª edição. São Paulo: ILAS; 2016. 36p. Citado: 12 jan 2017. Disponível em: http://www.ilas.org.br/assets/arquivos/ferramentas/roteiro-de-implementacao.pdf
3. Zanon F, Caovilla JJ, Michel RS, Cabeda EV, Ceretta DF, Luckemeyer GD, et al. Sepse na Unidade de Terapia Intensiva: etiologias, fatores prognósticos e mortalidade. Rev Bras Ter Intensiva. 2008;20(2):128-34.
4. Drumheller BC, Agarwal A, Mikkelsen ME, Sante SC, Weber AL, Goyal M, et al. Risk factors for mortality despite early protocolized resuscitation for severe sepsis and septic shock in the emergency department. J Crit Care. 2016;31(1):13-20.
5. Bueno LO, Guimarães HP, Lopes RD, Schneider AP, Leal PHR, Senna APR, et al. Avaliação dos indices prognósticos SOFA e MODS em pacientes após prada cardiorrespiratória em Unidade de Terapia Intensiva Geral. Rev Bras Ter Intensiva. 2005;17(3):162-4.
6. Stevenson EK, Rubenstein AR, Radin GT, Wener RS, Walkey AJ. Two decades of mortality trends among patients with severe sepsis: a comparative meta-analysis. Crit Care Med. 2014;42(3):625-31.
7. Sales Júnior JAL, David CM, Hatum R, Souza PCSP, Japiassú A, Pinheiro CTS, et al. Sepse Brasil: estudo epidemiológico da sepse em Unidades de Terapia Intensiva brasileiras. Rev Bras Ter Intensiva. 2006;18(1):9-17.
8. Yamamoto S, Yamazaki S, Shimizu T, Takeshima T, Fukuma S, Yamamoto Y, et al. Body temperature at the emergency department as a predictor of mortality in patients with bacterial infection. Medicine (Baltimore). 2016;95(21):e3628.
9. Kim WY, Hong SB. Sepsis and Acute Respiratory Distress Syndrome: Recent Update. Tuberc Respir Dis (Seoul). 2016;79(2):53-7.
10. Patel JJ, Taneja A, Niccum D, Kumar G, Jacobs E, Nanchal R. The association of serum bilirubin levels on the outcomes of severe sepsis. J Intensive Care Med. 2015;30(1):23-9.
11. Zarjou A, Agarwal A. Sepsis and acute kidney injury. J Am Soc Nephrol. 2011;22(6):999-1006.
12. Lyons PG, Micek ST, Hampton N, Kollef MH. Sepsis-associated coagulopathy severity predicts hospital mortality. Crit Care Med. 2018;46(5):736-42.
13. Clarke DL, Chipps JA, Sartorius B, Bruce J, Laing GL, Brysiewicz P. Mortality rates increase dramatically below a systolic blood pressure of 105-mm Hg in septic surgical patients. Am J Surg. 2016;212(5):941-45.
14. Puskarich MA, Illich BM, Jones AE. Prognosis of emergency department patients with suspected infection and intermediate lactate levels: a systematic review. J Crit Care. 2014;29(3):334-9.
15. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med. 2003;31(12):2742-51.