Late recognition and illness severity are determinants of early death in severe septic patients

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OBJECTIVE: To identify the independent variables associated with death within 4 days after the first sepsis-induced organ dysfunction.

METHODS: In this prospective observational study, severe sepsis and septic shock patients were classified into 3 groups: Group 1, survivors; Group 2, late non-survivors; and Group 3, early non-survivors. Early death was defined as death occurring within 4 days after the first sepsis-induced organ dysfunction. Demographic, clinical and laboratory data were collected and submitted to univariate and multinomial analyses.

RESULTS: The study included 414 patients: 218 (52.7%) in Group 1, 165 (39.8%) in Group 2, and 31 (7.5%) in Group 3. A multinomial logistic regression analysis showed that age, Acute Physiology and Chronic Health Evaluation II score, Sepsis-related Organ Failure Assessment score after the first 24 hours, nosocomial infection, hepatic dysfunction, and the time elapsed between the onset of organ dysfunction and the sepsis diagnosis were associated with early mortality. In contrast, Black race and a source of infection other than the urinary tract were associated with late death. Among the non-survivors, early death was associated with Acute Physiology and Chronic Health Evaluation II score, chronic renal failure, hepatic dysfunction Sepsis-related Organ Failure Assessment score after 24 hours, and the duration of organ dysfunction.

CONCLUSION: Factors related to patients' intrinsic characteristics and disease severity as well as the promptness of sepsis recognition are associated with early death among severe septic patients.

KEYWORDS: Prognosis; Mortality; Sepsis.

INTRODUCTION

Severe sepsis remains a challenge for healthcare providers because it carries a high mortality rate despite increased resource allocation from both health institutions and governments (1–5). For these reasons, many researchers have devoted their efforts to finding efficient interventions (6,7).

There are few published data regarding the potential risk factors associated with early death in sepsis patients, and the concept of ''early'' is inconsistent (8–10). Some authors have attempted to construct models, which included patients' general characteristics (11) or only coagulation factors (12), to predict short-term mortality in sepsis.

However, these authors used either 7 days or 14 days as the definition of short term. Another study only analyzed patients who were admitted to the emergency department without shock and reported a progression to shock in 17.8% of patients in the first 48 hours. However, they did not address early mortality (13).

Therefore, we hypothesized that some factors are linked to early death and that patients at risk for early death could be identified using clinical and laboratory data collected in the first days after intensive care unit (ICU) admission. Thus, the purpose of this study was to identify the variables that were independently associated with death within 4 days after the first sepsis-induced organ dysfunction.

METHODS AND MATERIALS

Design and setting

This prospective cohort study was conducted at 3 mixed medical/surgical Brazilian intensive care units (1 public, 2 private; 87 total beds) from January 2007 through March 2009. All the study procedures were in accordance with the

ethical standards of the revised Helsinki Declaration (1983). The Research and Ethics Committee from each institution approved the study (Federal University of Sao Paulo: 1477/06; Sirio Libanes Hospital: HSL2006/27; Hospital Israelita Albert Einstein: 07/549). All patients or their closest relatives signed informed consent forms allowing data collection.

Inclusion/exclusion criteria and definitions

All patients older than 18 years of age diagnosed with severe sepsis or septic shock, as previously defined (14), were prospectively included. Briefly, patients were eligible for inclusion if they had 2 or more signs of systemic inflammatory response syndrome secondary to a known or suspected infection and at least 1 sepsis-induced organ dysfunction. Patients were excluded if they were pregnant or if their physicians were not committed to full life support.

Sepsis-induced organ dysfunction was defined by one of the following symptoms: hypotension, arterial oxygen partial pressure/oxygen inspiratory fraction (PaO_2/FiO_2) ratio ≤ 300, lactate level ≥ 1.5 times the reference value and base deficit >5, bilirubin level >2 times the reference value, urine output ≤ 0.5 ml/kg/hour after an adequate volume replacement or the need for renal replacement therapy, platelet count $\leq 100,000$ mm^3 or a 50% decrease from the last 3 days' values, and a reduced level of consciousness. Septic shock was defined as volume-refractory hypotension with a need for vasopressors. The time for sepsis diagnosis was defined as the number of hours elapsed between the onset of the first dysfunction and its recognition or management by the healthcare provider. We defined sepsis recognition as the record of a sepsis hypothesis in the patient's chart. To identify the moment of organ dysfunction, the patient's chart was carefully reviewed to determine the first record of hypotension, reduced level of consciousness or low urine output as well as the first laboratory sampling time whose results fulfilled the respiratory, metabolic, coagulation or hepatic criteria for organ dysfunction. For patients admitted from the emergency department who already had severe sepsis criteria, we used the time of triage.

Patients were classified into 3 groups according to their outcomes: survivors (Group 1), late death (Group 2), and early death (Group 3). Early death was defined as death occurring within 4 days after the onset of the first sepsis-induced organ dysfunction.

Data collection

Demographic data were collected at inclusion, as were the Acute Physiological and Chronic Health Evaluation (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores (SOFA D0). SOFA scores were also determined on Day 1 (SOFA D1) and Day 3 (SOFA D3). The change in SOFA score was calculated by subtracting SOFA D0 from SOFA D3 (ΔSOFA D3) and SOFA D1 (ΔSOFA D1). Clinical and outcome features, including compliance to the 6-hour and 24-hour Surviving Sepsis Campaign (SSC) bundles, were registered as proposed by the Campaign (15). We did not record data on activated protein C or low-dose steroid adherence because of the controversial aspects related to their use. The patients were followed until hospital discharge or for 60 days, and ICU and hospital outcomes were recorded.

Statistics

Continuous data were presented as medians and inter-quartile ranges, and categorical variables were reported as the number (%). The normality of continuous variables was determined with the Kolmogorov-Smirnov test. The 3 groups were compared regarding the mortality risk factors. The non-parametric Kruskal-Wallis test, with the Muller-Dunn post-test, were used for non-normally distributed variables. The chi-squared likelihood ratio test or Pearson's chi-squared test was used, as appropriate, and partitioning of chi-square was performed if needed.

We performed a multinomial logistic regression analysis to allow for simultaneous comparisons among the 3 studied groups. For a variable to be included in the model, we transformed all the continuous variables into categorical variables according to the best cut-off point for early mortality prediction in the receiver operating characteristic (ROC) curve. For all the SOFA scores, we used the same cut-off value based on the ROC curve of SOFA scores at admission. For ΔSOFA D3 and ΔSOFA D1, any negative value was considered an improvement, while all positive or zero values were considered a worsening outcome. Variables associated with early death at the 0.2 level in the univariate analysis were included in the model, except for those with more than 50 missing cases or those not applicable for all patients. A step-by-step method was used to select the significant variables. To identify the risks factors for early and late death compared with the survivors, Group 1 was considered the reference group. To identify the risk factors related to early death among non-survivors, Group 2 (late death) was the reference group. A p-value <0.05 for any of the groups being compared was considered to retain a specific variable in the analysis. After the selection, the results were presented as odds ratios and 95% confidence intervals (CI).

Statistical analyses were performed using PASW Statistics 18 for Windows (SPSS Inc., Chicago, USA), and all the tests were two tailed.

■ RESULTS

Basic characteristics of septic patients

A total 414 septic patients were included in the study: 218 (52.7%) in Group 1, 165 (39.8%) in Group 2, and 31 (7.5%) in Group 3. We followed all the patients until hospital discharge or death. Among the deaths, 15.8% occurred in the first 4 days. All demographic and baseline character-istics are shown in Table 1.

Factors associated with early and late hospital mortality – univariate analysis

In the univariate analysis, the APACHE II and SOFA scores at admission were associated with both early and late mortality. However, more patients had high scores in the early mortality group compared to those with late mortality. The severity of organ dysfunction was higher in non-survivors, and the percentage of higher scores at Day 1 and Day 3 clearly distinguished between early and late death. The worsening of dysfunction, as measured by both ΔSOFA D1 and ΔSOFA D3, occurred more frequently in the non-survivors, regardless of the time of death (Table 1). Respiratory dysfunction was a marker of early and late death, while hepatic dysfunction was more prevalent only in the early death group. We found higher lactate levels in the patients with hepatic dysfunction (17.4, 11.1–29.0 *vs*. 23.5, 14.2–47.3, $p = 0.013$). Late recognition of organ dysfunction (>1 hour) was more prevalent in non-survivors. There

Table 1 - Patient demographics and infection characteristics according to the survival group.

Variable	Group 1 (n = 218)	Group 2 (n = 165)	Group 3 (n = 31)	p-value[+]
Age (years)	62.0 (46.0–77.0)	69.0 (54.0–78.0)***	69.0 (54.0–77.0)*	0.069
Age ≥52	150 (68.8),	137 (83.0)***	27 (87.1)*	0.001
Gender				
Female	94 (43.1)	67 (40.6)	9 (29.0)	0.324
Male	124 (56.9)	98 (59.4)	22 (71.0)	
Race				
Black	22 (10.1)	35 (21.2)**	7 (22.6)	0.030
White	187 (85.8)	124 (75.2)	22 (71.0)	
Other				
APACHE II score	17.0 (13.0–21.0)	19.0 (15.0–24.0)*	22.0 (15.0–26.0)*	0.0002
APACHE ≥22	52 (23.9)	54 (32.7)	16 (51.6)*[†]	0.004
SOFA score				
SOFA D0	6.0 (4.0–9.0)	8.0 (5.0–10.0)*	9.0 (8.0–11.0)*	<0.00001
SOFA D0 ≥8	81 (37.5)	90 (54.5)***	25 (80.6)*** [††]	<0.00001
SOFA D1	6.0 (4.0–8.0)	8.0 (6.0–11.0)*	10.0 (8.0–12.0)*	<0.0001
SOFA D1 ≥8	73 (34.3)	101 (61.2)***	23 (85.2)*** [††]	<0.0001
SOFA D3	5.0 (2.0–8.0)	8.0 (6.0–11.0)*	9.0 (8.0–12.0)*	<0.0001
SOFA D3 ≥8	50 (26.5)	92 (56.8)***	11 (84.6)*** [†]	<0.0001
ΔSOFA D1	0.0 (−2.0–1.0)	0.0 (−1.0–2.0)*	1.0 (0.0–2.0)*	<0.0001
Worsening ΔSOFA D1	123 (57.7)	117 (70.9)**	21 (77.8)*	<0.009
ΔSOFA D3	−1.0 (−3.0–0.0)	0.0 (−1.0–2.0)*	2.0 (0.0–4.0)*	<0.0001
Worsening ΔSOFA D3	68 (36.0)	92 (56.8)***	10 (76.9)**	<0.0001
Lactate at admission	17.0 (11.0–30.0)	17.0 (11.9–28.8)	24.0 (16.0–55.0)*[†]	0.035
Lactate ≥20 mg/dL	71 (47.7)	55 (49.1)	18 (66.7)	0.181
Comorbidities	158 (72.5)	134 (81.2)	25 (80.6)	0.116
COPD	32 (14.7)	23 (13.9)	5 (16.1)	0,944
Arterial hypertension	85 (39.0)	70 (42.4)	13 (41.9)	0.784
CRF	24 (11.00)	31 (18.8)*	2 (6.5)	0.043
Immunosuppression	40 (18.3)	42 (25.5)	10 (32.3)	0.100
Diabetes mellitus	50 (22.9)	47 (28.5)	8 (25.8)	0.465
Alcoholism	14 (6.5)	11 (6.7)	1 (3.2)	0.759
Admission category				
Clinical	141 (64.7)	116 (70.3)	20 (64.5)	0.490
Surgical	77 (35.3)	49 (29.7)	11 (35.5)	
Sepsis category				
Severe sepsis	70 (32.1)	54 (32.7)	5 (16.1)	0.138
Septic shock	148 (67.9)	111 (67.3)	26 (83.9)	
Infection category				
Community acquired	137 (62.8)	56 (33.9)***	12 (38.7)*	<0.0001
Hospital acquired	81 (37.2)	109 (66.1)	19 (61.3)	
Source of infection				
Pulmonary	100 (45.9)	95 (57.6)*	13 (41.9)	0.048
Abdominal	49 (22.5)	38 (23.0)	10 (32.3)	0.503
UTI	32 (14.7)	8 (4.8) ***	2 (6.5)	0.005
Organ dysfunction (n)	3.0 (2.0–3.0)	3.0 (2.0–3.0)	3.0 (2.0–4.0)	0.369
Dysfunction >2	113 (51.8)	91 (55.2)	20 (64.5)	0.386
Type of dysfunction				
Cardiovascular	198 (90.8)	148 (89.7)	29 (93.5)	0.784
Respiratory	97 (44.5)	95 (57.6)*	21 (67.7)*	0.006
Renal	87 (39.9)	78 (47.3)	15 (48.4)	0.301
Metabolic	46 (21.1)	32 (19.4)	12 (38.7)	0.076
Hematologic	43 (19.7)	38 (23.0)	8 (25.8)	0.617
Hepatic	25 (11.5)	25 (15.2)	12 (38.7)*** [††]	<0.0001
Neurologic	59 (27.1)	60 (36.4)	10 (32.3)	0.150

APACHE: Acute Physiological and Chronic Health Evaluation; SOFA D0: Sequential Organ Failure Assessment at admission; ICU: intensive care unit; COPD: chronic obstructive pulmonary disease; CRF: chronic renal failure; UTI: urinary tract infection. The results are expressed as the number (%) or median (25%–75% percentile). [+]Chi-squared and Kruskal-Wallis tests. Chi-squared partition or Muller-Dunn post-test: * $p \leq 0.05$ *vs.* Group 1; ** $p \leq 0.01$ *vs.* Group 1; *** $p \leq 0.001$ *vs.* Group 1; † $p \leq 0.05$ *vs.* Group 2; †† $p \leq 0.01$ *vs.* Group 2; ††† $p \leq 0.001$ *vs.* Group 2.

were no differences between groups in compliance with any indicator of the SSC-6 h bundle or glycemic control (Table 2).

Factors associated with early and late hospital mortality – multinomial analysis

The covariance analysis using the Jaccard test detected a high degree of colinearity between the presence of shock and SOFA D1 (r = 0.764), as well as between respiratory dysfunction and a pulmonary source of infection (r = 0.724). Thus, on the basis of their p values in the univariate analysis, we excluded both septic shock ($p = 0.138$) and a pulmonary source of infection ($p = 0.048$) from the multinomial analysis.

The multinomial analysis revealed that the patient age, SOFA score after the first 24 hours, nosocomial infection, and duration of organ dysfunction were associated with both early and late mortality. However, the odds ratios were

Table 2 - Characteristics related to adequate treatment and organ dysfunction evolution according to the survival group.

Variable	Group 1 (n = 218)	Group 2 (n = 165)	Group 3 (n = 31)	*p*-value[+]
Duration of organ dysfunction (hours)	2.2 (0.0–9.6)	6.0 (0.0–15.0)*	6.0 (1.6–9.0)	0.019
Duration of organ dysfunction >1 hour	128 (59.3)	115 (70.1)*	26 (83.9)**	0.005
6-hour bundle compliance				
Lactate sampling	137 (62.8)	106 (64.2)	24 (77.4)	0.283
Blood culture sampling	117 (53.9)	76 (46.1)	14 (45.2)	0.266
Antibiotics				
Up to 1 hour	129 (59.2)	87 (52.7)	19 (61.3)	0.392
Time to antibiotics (h)	2.0 (0.62–6.0)	2.64 (1.0–6.0)	1.25 (0.5–5.0)	0.319
Volume/vasopressors	191 (97.0)	143 (96.6)	29 (96.7)	0.981
CVP achievement	67 (45.9)	51 (45.1)	17 (65.4)	0.154
SvcO$_2$ achievement	76 (52.1)	57 (50.4)	15 (57.7)	0.799
Compliance with all 6 h items	0	0	0	–
24 h bundle compliance				
Glycemic control				
Median <180 mg/dL	160 (73.4)	121 (73.3)	20 (64.5)	0.567
Glycemia*	140.0 (120.0–162.0)	143.0 (120.0–167.0)	128.0 (119.0–169.0)	0.648
Hypoglycemia**	15 (6.9)	11 (6.7)	4 (12.9)	0.457
Plato pressure				
Median <30 cmH$_2$O	117 (89.3)	112 (91.1)	21 (87.5)	0.825
Median	24.0 (20.0–27.0)	25.5 (22.0–28.0)*	25.0 (22.0–28.0)	0.020
Median >24 cmH$_2$O	67 (51.1)	82 (66.1)*	16 (69.6)	0.030

CVP: central venous pressure; SvcO$_2$: central venous oxygen saturation; SOFA: Sequential Organ Failure Assessment; D: day; *median value between the 6th and 24th hours; ** patients with at least 1 episode of hypoglycemia. The results are expressed as the number (%) or median (25%–75% percentile). [+]Chi-squared and Kruskal-Wallis tests. Chi-squared partition or Muller-Dunn post-test: *$p \leq 0.05$ *vs.* Group 1; **$p \leq 0.01$ *vs.* Group 1; ***$p \leq 0.001$ *vs.* Group 1; †$p \leq 0.05$ *vs.* Group 2; ††$p \leq 0.01$ *vs.* Group 2; †††$p \leq 0.001$ *vs.* Group 2.

higher for early death. The illness severity at admission (APACHE II) and hepatic dysfunction were only correlated with early death, while Black race and a source of infection other than the urinary tract were only correlated with late death. When the risk factors for early death were analyzed among the non-survivors, APACHE II, chronic renal failure, hepatic dysfunction, and the SOFA score after 24 hours and duration of organ dysfunction were identified. The results of the multinomial analysis are shown in Table 3. The lactate level was not included in the primary multinomial analysis, as there were too many missing values (n = 55). A secondary multinomial analysis that included the lactate levels categorized according to the ROC curve did not change the results (data not shown).

Table 3 - Risk factors related to early and late death – multinomial analysis.

Variable	*p*-value	OR (95% CI)
Factors related to early death (Group 1 *vs.* Group 3)		
Duration of organ dysfunction >1 hour	0.003	6.289 (1.886–20.833)
SOFA D1 ≥ 8	<0.0001	8.333 (2.610–26.315)
Age ≥52 years	0.058	3.225 (0.961–45.933)
Hospital-acquired infection	0.030	2.808 (1.102–7.142)
APACHE ≥22	0.013	3.389 (1.292–8.850)
Hepatic dysfunction	0.001	5.988 (2.164–16.666)
Factors related to late death (Group 1 *vs.* Group 2)		
Duration of organ dysfunction > 1 hour	0.025	1.764 (1.075–2.899)
SOFA D1 ≥8	<0.0001	2.632 (1.639–4.219)
Age ≥52 years	0.003	2.370(1.345–4.184)
Hospital-acquired infection	<0.0001	2.950 (1.851–4.695)
Urinary tract infection	0.024	0.362 (0.150–0.8741)
Black race	0.013	2.304 (1.191–4.464)
Factors related to early death among non-survivors (Group 2 *vs.* Group 3)		
Duration of organ dysfunction >1 hour	0.024	3.953 (1.195–13.080)
SOFA D1 ≥8	0.037	3.406 (1.077–10.771)
APACHE ≥22	0.043	2.610 (1.030–6.615)
Hepatic dysfunction	0.001	4.776 (1.833–12.445)
Chronic renal failure	0.040	0.188 (0.038–0.923)

APACHE: Acute Physiological and Chronic Health Evaluation; SOFA D1: Sequential Organ Failure Assessment at Day 1; OR: odds ratio; CI: confidence interval. Multinomial analysis.

■ DISCUSSION

This study showed that both illness severity and early recognition were associated with early death. In the multinomial analysis, we demonstrated that the APACHE II score, presence of chronic renal failure, sepsis-induced hepatic dysfunction, duration of organ dysfunction, and SOFA score in the first day after initial organ dysfunction were able to distinguish early non-survivors from late non-survivors. We also demonstrated that compared with the survivors, early death was associated with age, illness severity at admission (APACHE II), illness severity on the first day (SOFA D1), and hospital-acquired infection. All of these issues are well-known risk factors for sepsis mortality. However, our study identified 2 other risk factors that have not been frequently described in previous studies: the presence of hepatic dysfunction and the duration of organ dysfunction. Both issues were not only risk factors for early mortality but also identified the patients who would die early among the non-survivors.

Only 3 studies have focused on early mortality risk factors in sepsis patients (8–10). A multicenter French study showed that 27% of all fatalities occurred in the first 2 days of severe sepsis, and the illness severity, as assessed by the SAPS II score, number of organ failures and the presence of shock or acidosis were associated with death (8). In their study, later mortality was associated with the underlying disease and chronic liver and heart failure. Blanco et al. analyzed risk factors related to death within the first 48 hours, during which 14.8% of all deaths occurred (9). Neither of these studies included variables related to the adequacy of treatment or the duration of organ dysfunction in their analysis. These studies included patients observed in 1993 and 2002, when the relevance of early detection and intervention was not as widely recognized. This early approach could have impacted early deaths, as we showed a lower proportion of early death compared to the previous authors.

The association between hepatic dysfunction and early death that was found in our study and by Blanco et al. is interesting. We assessed acute hepatic dysfunction related to sepsis and not chronic hepatic failure, which has already been described to be associated with late death (8). There are multiple possible explanations for this finding. First, liver dysfunction has been associated with the inability of the immune system to adequately react to host invasion by pathogenic organisms (16–18). Indeed, infected patients with chronic or acute liver dysfunction present with worse prognoses (19). Second, the liver is also responsible for coagulation factor synthesis, and its impairment is clearly related to prognosis (20,21). Activated prothrombin time and fibrinogen level can be predictors of early death (12). Finally, liver impairment is a neglected dysfunction in sepsis; thus, other studies might not have found this association simply because they did not evaluate it.

Non-compliance with the SSC bundles was not related to early or late death. This finding contrasts with other studies, which have shown a clear association between SSC bundle adherence and survival (22–27). A possible explanation is that patients who will die earlier could appear sicker at inclusion and are thus more prone to receive early and adequate care, which is not enough to permit survival in the face of severe disease. Another explanation is that we evaluated compliance at the time of sepsis diagnosis. In Brazil, the time between the onset of organ dysfunction and a proper sepsis diagnosis can be long (28). In this context, the compliance measure after diagnosis would not reflect the appropriateness of the treatment.

One of the most important contributions of this study was to clearly demonstrate that the delay in diagnosis and, consequently, treatment was related to not only death but also early death among non-survivors. Although previous studies have already addressed this issue (28–30), they did not associate these delays with early death. Moreover, in our study, the best cut-off value for predicting death was 1 hour. The impact of small delays has already been demonstrated. Kumar et al. showed that the mortality of septic shock patients increased after delaying adequate antibiotic administration (31) by only 1 hour. Thus, it is unsurprising that even small delays in sepsis recognition could have substantial impacts on both global mortality and early mortality.

Another interesting finding was the association between lactate level and the risk of early death. Although this association could not be tested in an appropriate multinomial analysis because of excessive missing values, high lactate and its non-clearance are clearly associated with mortality (27,32–34). However, this is the first study to show that high lactate is associated with early mortality, even when only non-survivors are considered.

There are strengths and limitations to our study. One of its strengths is its multicentric nature, which comprised both private and public hospitals. Second, we used a strict definition of ''early death'' that considered the initiation of organ dysfunction in addition to diagnosing sepsis or ICU admissions. Third, we obtained robust data that was related to the specific therapeutic actions of the clinical team based on the SSC bundles. Although they were not related to mortality, most likely because of the long time between the initiation of organ dysfunction and adequate treatment, we provided an unprecedented analysis of the early mortality risk factors. Fourth, our multinomial analysis allowed us to clearly identify the risk factors for early or late death as well as the risk factors for early death among non-survivors.

One of our study limitations was the absence of information on withholding or withdrawal of life support, primarily in the early death group. However, as palliative care patients were not included, any initiative to stop life support would most likely reflect the severity of sepsis and not the severity of the underlying disease, for which palliative care would be advisable. Another weakness was the lack of information on causes of death. We should also consider the potential interaction between the presence of liver dysfunction and the SOFA score as a limitation. However, our covariance analysis using the Jaccard test did not show the presence of collinearity.

In summary, in a large, multicenter severe sepsis database, both the severity of disease and late recognition of sepsis were associated with early death.

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■ AUTHOR CONTRIBUTIONS

Machado FR, Salomão R, Rigato O, and Silva E designed and coordinated the study. All the authors contributed to the data collection.

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