

### medicina intensiva





#### ORIGINAL ARTICLE

# Sepsis death risk factor score based on systemic inflammatory response syndrome, quick sequential organ failure assessment, and comorbidities



Vinicius Nakad Orsatti, Victoria Stadler Tasca Ribeiro, Carolina de Oliveira Montenegro, Clarice Juski Costa, Eduardo Albanske Raboni, Eduardo Ramos Sampaio, Fernando Michielin, Juliano Gasparetto, João Paulo Telles, Felipe Francisco Tuon\*

Laboratory of Emerging Infectious Diseases, School of Medicine, Pontifícia Universidade Católica do Paraná, Curitiba, PR, 80215-901, Brazil

Available online 4 April 2024

#### **KEYWORDS** Abstract Objective: In this study, we aimed to evaluate the death risk factors of patients included in Sepsis; the sepsis protocol bundle, using clinical data from qSOFA, SIRS, and comorbidities, as well as Antibiotic; development of a mortality risk score. Organ failure; Design: This retrospective cohort study was conducted between 2016 and 2021. Systemic Setting: Two university hospitals in Brazil. inflammatory Participants: Patients with sepsis. response syndrome; Interventions: Several clinical and laboratory data were collected focused on SIRS, qSOFA, and Shock comorbidities. Main variable of interest: In-hospital mortality was the primary outcome variable. A mortality risk score was developed after logistic regression analysis. Results: A total of 1,808 patients were included with a death rate of 36%. Ten variables remained independent factors related to death in multivariate analysis: temperature $\geq$ 38 °C (odds ratio [OR] = 0.65), previous sepsis (OR = 1.42), qSOFA $\geq$ 2 (OR = 1.43), leukocytes >12,000 or <4,000 cells/mm<sup>3</sup> (OR = 1.61), encephalic vascular accident (OR = 1.88), age >60 years (OR = 1.93), cancer (OR = 2.2), length of hospital stay before sepsis >7 days (OR = 2.22,), dialysis (OR = 2.51), and cirrhosis (OR = 3.97). Considering the equation of the binary regression logistic analysis, the score presented an area under curve of 0.668, is not a potential model for death prediction. Conclusions: Several risk factors are independently associated with mortality, allowing the development of a prediction score based on qSOFA, SIRS, and comorbidities data, however, the performance of this score is low. © 2024 Elsevier España, S.L.U. and SEMICYUC. All rights reserved.

DOI of original article: https://doi.org/10.1016/j.medin.2024.02.010

\* Corresponding author. E-mail address: felipe.tuon@pucpr.br (F.F. Tuon).

https://doi.org/10.1016/j.medine.2024.03.005

2173-5727/© 2024 Elsevier España, S.L.U. and SEMICYUC. All rights reserved.

#### PALABRAS CLAVE

Sepsis; Antibiótico; Fallo orgánico; Síndrome de respuesta inflamatoria sistémica; Shock

## Puntuación de factores de riesgo de mortalidad por sepsis basada en el síndrome de respuesta inflamatoria sistémica, el índice rápido secuencial de fallo orgánico y comorbilidades

#### Resumen

*Objetivo*: En este estudio, nuestro objetivo fue evaluar los factores de riesgo de muerte de los pacientes incluidos en el protocolo de sepsis, utilizando datos clínicos de qSOFA, SIRS y comorbilidades, así como el desarrollo de un puntaje de riesgo de mortalidad.

Diseño: Este estudio de cohorte retrospectivo se llevó a cabo entre 2016 y 2021.

Ámbito: Dos hospitales universitarios en Brasil.

Participantes: Pacientes con sepsis.

*Intervenciones:* Se recopilaron varios datos clínicos y de laboratorio centrados en SIRS, qSOFA y comorbilidades.

*Variable de interésprincipales:* La mortalidad intrahospitalaria fue la variable de resultado primaria. Se desarrolló un puntaje de riesgo de mortalidad después del análisis de regresión logística.

*Resultados:* Se incluyeron un total de 1,808 pacientes con una tasa de mortalidad del 36%. Diez variables permanecieron como factores independientes relacionados con la muerte en el análisis multivariado: temperatura  $\geq$ 38 °C (odds ratio [OR] = 0.65), sepsis previa (OR = 1.42), qSOFA $\geq$ 2 (OR = 1.43), leucocitos >12,000 o <4,000 células/mm3 (OR = 1.61), accidente cerebrovascular encefálico (OR = 1.88), edad >60 años (OR = 1.93), cáncer (OR = 2.2), duración de la estancia hospitalaria antes de la sepsis >7 días (OR = 2.22), diálisis (OR = 2.51) y cirrosis (OR = 3.97). Considerando la ecuación del análisis de regresión logística binaria, el puntaje presentó un área bajo la curva de 0.668, un modelo débil para la predicción de la muerte.

*Conclusiones*: Varios factores de riesgo se asocian de forma independiente con la mortalidad, lo que permite el desarrollo de una puntuación de predicción basada en datos de qSOFA, SIRS y comorbilidades; sin embargo, el rendimiento de esta puntuación es bajo.

© 2024 Elsevier España, S.L.U. y SEMICYUC. Todos los derechos reservados.

#### Introduction

Sepsis is associated with high in-hospital mortality, hospital cost, and morbidity.<sup>1</sup> According to the consensus published in 1991, sepsis is defined as the presence of suspected infection in addition to systemic inflammatory response syndrome (SIRS).<sup>2</sup> The definitions of sepsis, septic shock, and organic dysfunction have remained unchanged for more than 2 decades. Thus, the last definition of sepsis was changed to life-threatening organ dysfunction caused by a dysregulated host response to infection.<sup>3</sup>

The sequential organ failure assessment (SOFA) score has high predictive validity.<sup>4</sup> However, the SOFA score is not a practical tool in the emergency room or ward because it requires laboratory tests. Considering the high mortality associated with sepsis and that prompt intervention is necessary, a new practical measure is needed to help healthcare professionals recognize sepsis. The quick SOFA (gSOFA) comprised the following criteria: altered mental status, systolic blood pressure of 100 mmHg or less, and respiratory rate of 22/min or greater,<sup>5</sup> and the presence of two of these criteria were correlated with mortality. Although SIRS criteria are positive in almost 90% of patients with infection and organ dysfunction, neither qSOFA nor SIRS scores have been used as unique screening options, while medical evaluation and criticism should also be considered.6,7

Both scores have been used for screening of sepsis, but the evaluation of these scores in the prediction of mortality can be useful because approach to patients with higher mortality risk can be differentiated. Even though several scores have been well established, an individualized prognostic model on the basis of the nomogram could accurately predict mortality and optimize management or tailored therapy.<sup>8</sup> The SIRS, qSOFA, and pSOFA (pediatric) have been used in previous studies as a predictive model of mortality in pediatric population, pregnant and adult hematological patients.<sup>9-12</sup> These predictive models can be used for alert systems, improving the approach of patient care.<sup>13</sup>

We hypothesized that these scores and comorbidities can be used to predict mortality. In this study, we aimed to develop of a mortality risk score based on qSOFA, SIRS, and comorbidities.

#### Methods

#### Study design

This was a retrospective cohort study of patients included in the sepsis protocol in two Brazilian university hospitals. This study was approved with a waiver of informed consent by the institutional review board of the Pontificia Universidade Católica do Paraná (CAAE number: 79976517.4.0000.0020).



Figure 1 Schematic model of sepsis bundle protocol used in the hospital for screening and data analysis.

#### Settings

This study was conducted on adult patients with suspected sepsis. The cohort included patients admitted at two academic public hospitals between January 2016 and December 2021. The first hospital was composed of an emergency room, a 207-bed hospital ward, and a 29-bed mixed intensive care unit (ICU), but reference for trauma, neurosurgery, and general surgery. The second hospital wards, and a 38-bed ICU, reference for general surgery and cardiovascular surgery.

Both hospitals present the same antimicrobial stewardship team.

#### Sepsis protocol

The antibiotic therapy decisions were based on local microbial resistance profiles.<sup>14</sup> The antibiotic stewardship program (ASP) implemented a restrictive policy for dispensing carbapenems and polymyxin using a hand-filled form.<sup>15</sup> In addition, a prospective auditing and feedback process was adopted for all antimicrobial prescriptions. Dose, length of treatment adjustment, de-escalation, route of administration, and side effects were determined under the guidance of a clinical pharmacist and infectious diseases specialist.<sup>16</sup>

Once sepsis was suspected and judged that antimicrobial therapy was needed in the first hour, the physician fulfilled the protocol. However, only those with Sepsis-3 criteria were included,<sup>3</sup> which was defined within 24 hours by the antimicrobial stewardship. The patients were followed up until death or discharge. The hour-1 bundle includes: i) measuring lactate level and remeasuring lactate if initial lactate is elevated (> 2 mmol/L); ii) obtaining blood cultures before administering antibiotics; iii) administration of broad-spectrum antibiotics; iv) rapid administration of 30 mL/kg crystalloid for hypotension or lactate  $\geq$  4 mmol/L; v) application of vasopressors if the patient was hypotensive during or after fluid resuscitation to maintain a mean arterial pressure  $\geq$ 65 mmHg.<sup>7</sup> The sepsis bundle is shown in Supplementary Figure 1 (Fig. 1).

#### Participants

Inclusion criteria were (i) a hospital admission, (ii)  $\geq 18$  years of age, and (iii) a starting sepsis protocol, (iv) sepsis diagnosis according to Sepsis-3 criteria.<sup>3</sup> The only exclusion criterion was a lack of information in the patient's sepsis protocol file to avoid selection bias. Follow-up was performed using electronic medical records. Patients with more than one episode of sepsis were included as a "new" event. The population of the study included ICU, ward, and emergency room.

#### Variables

The SIRS (2 points) and qSOFA (2 points), as well as other clinical data were considered at the moment of protocol. The SIRS criteria (i.e., temperature >  $38 \degree C$ , heart rate >90/min, respiratory rate >20/min, and leukocytes >12,000 or <4,000 cell/mm<sup>3</sup>)<sup>17</sup> and qSOFA score (i.e., systolic blood pressure <100 mmHg, respiratory rate >22 rpm, and Glasgow coma scale <15) were used.<sup>18</sup> Comorbidities were analyzed according to the Charlson comorbidity index.<sup>19</sup> Hospital-acquired infection were defined according with the Centers for Disease Control and Prevention were included.<sup>20</sup> Community-acquired infection, using the International Classification of Diseases, Tenth Revision (ICD-10), and diagnosis codes.  $^{\rm 21}$ 

The primary outcome was global mortality. The timing of antibiotic treatment relative to clinical diagnosis was evaluated. The cultures were evaluated, and appropriate antimicrobial therapy was provided to patients with sepsis. The length of hospital stay was also assessed. Outcomes were compared according to SIRS criteria and qSOFA scores, hospital unit (ICU, ward, or emergency room [ER]), and positive cultures.

#### Statistical analysis

The continuous variables were expressed was mean or median according with normality test (Kolmogorov–Smirnov test). The descriptive variables were expressed as percentages. The dispersion of variables were standard deviation or 95% confidence interval.

In the bivariate analysis, P-values were calculated using the  $\chi^2$  or Fisher's exact test for categorical variables and the Student's t-test or Mann-Whitney test for continuous variables. The covariates were compared based on the criteria for sepsis and outcomes. Covariates were compared between survivors versus non-survivors. In the forward stepwise regression, variables with *P*-values  $\leq$  0.2 were included in the model, while those with *P*-values  $\leq$  0.10 were maintained in the model. Multicollinearity was calculated with the variance inflation factor for each independent variable. Variables which included other variables (e.g., SIRS and gSOFA) were not included in the model. All tests were two-tailed. A P significance was set at P < 0.05. A receiver operating characteristic (ROC) curve was constructed based on independent variables associated with mortality and the logistic binary regression model. The score was based on coefficient (beta) of each variable in the multivariable analvsis. The area under the curve (AUC) was calculated to determine the internal performance of the score based on multivariable analysis.

#### Results

#### General data

A total of 2,232 were screened and 205 were excluded due to lack of data, and 219 patients do not fulfill sepsis-3 criteria. Thus, 1,808 were included in the study. The mean age was 60 years (interquartile range [IQR]: 42-72), and 38% of the patients were men. The SIRS criteria ( $\geq$ 2) and  $qSOFA (\geq 2)$  accounted for 63% (n = 1,278) and 29% (n = 593), respectively. The main sites of infection were the lungs (42% [n = 657]) and abdomen (15% [n = 236]). The median length of hospital stay after sepsis was 10 days (IQR: 4-22), while death occurred in 36.8% of patients (n = 666). The mortality in patients admitted at ICU was 47.7%, at emergency room 26.2%, and those with diagnosis of sepsis in the ward was 26.8%. The main comorbidities were systemic arterial hypertension (SAH) (42% [n = 782]), diabetes mellitus (DM) (16% [n = 303]), previous stroke (14.7% [n = 274]), and cancer (8.3% [n = 155]). Among the patients with microbiological data, 45% (n = 626) presented with positive culture results.

Blood cultures were obtained from all patients and other cultures, according to the medical decision.

#### Variables associated with mortality

The data from patients who died or survived are described in the Table 1. The mortality, the outcome variable, was higher in ICU admitted patients (p < 0.001), but similar between emergency room and ward. Twenty variables were found to be related to death after univariate analysis. Major variables were age (64 vs. 52 years, P < 0.001), length of hospital stay before sepsis (10 vs. 5.4 days, P<0.001), temperature >38°C (26% vs. 39%, P<0.001), leukocytes >12,000 or <4,000 cells/mm<sup>3</sup> (49% vs. 38%, P=0.001), gSOFA criteria >2 (35% vs. 25%, P<0.001), altered level of consciousness (30% vs. 21%, P<0.001), low blood pressure (i.e., systolic blood pressure [SBP] <90 mmHg) (31% vs. 21%, P<0.001), minutes to antimicrobial infusion (45 min vs. 35 min, P < 0.001), heart failure (9.5% vs. 4.8%, P<0.0001), previous stroke (20% vs. 11%, P<0.0001), SAH (47% vs. 38%, P<0.001), cancer (13% vs. 5.5%, P < 0.001), previous sepsis (35% vs. 18%, P < 0.0001), and positive culture (50% vs. 39%, P<0.0001).

#### Multivariable analysis

Despite these 20 variables, after multivariate analysis, half of them remained independent variables related to death (Table 2). Characteristics such as (i) cirrhosis, (ii) dialysis, and (iii) cancer at least doubled the risk of death: (i) (odds ratio [OR]=3.97, 95% confidence interval [CI] 1.41–11.16, P=0.009), (ii) (OR=2.51, 95% CI 1.54–4.10, P < 0.0001), and (iii) (OR=2.2, 95% CI 1.49–3.24, P < 0.0001). Other variables were also related to poor prognosis increasing between 42–93% the odds of death: previous sepsis (OR=1.42, 95% CI 1.08–1.87, P=0.012), qSOFA criteria  $\geq 2$  (OR=1.43, 95% CI 1.12–1.84, P=0.04), leukocytes >12,000 or <4,000 cells/mm<sup>3</sup> (OR=1.61, 95% CI 1.27–2.03, P < 0.0001), and previous stroke (OR=1.88, 95% CI 1.39–2.55, P < 0.0001). A temperature >38 °C was related to survival (OR=0.65, 95% CI 0.51–0.83, P=0.0001].

#### Score definition

Considering the equation of the binary regreslogistic analysis, the weight of each sion significant variable was calculated using the following equation: mortality score =  $2.186 \times (chronic)$ renal failure) + 2.51  $\times$  (cerebrovascular disease) + 2.629  $\times$  (cancer) + 2.992  $\times$  (cirrhosis) + 1.842  $\times$  (presepsis) + 2.040  $\times$  (fever) + 1.387  $\times$  (leukocytosis vious or leukopenia). The mortality risk according to the scores is presented in Table 3.

When applying the score, a ROC curve was constructed, as shown in Fig. 2, considering the sensitivity and specificity of the mortality prediction score. The AUC was 0.668 (95% CI 0.623–0.702), suggesting that the mortality score based on the multivariable analysis was weak. We also performed a ROC curve for SIRS and qSOFA, with AUC = 0.522 (95% CI 0.481–0.563) and 0.583 (95% CI 0.535–0.631), respectively (Supplementary material).

|--|

	(n = 666)		
	(11 000)	(n = 1142)	
Male sex, n (%)	276 (41)	410 (36)	0.017
Age, mean (SD)	64 (16)	52 (19)	<0.001
Length of hospital stay before sepsis,	10 (14)	5.4 (10)	<0.001
SIPS criteria $>2$ n (%)	177 (63)	711 (62)	0.640
Tomporature >29.2°C $n(\%)$	177 (26)	454 (20)	<0.01
Cardiac frequency $>90$ hpm $n$ (%)	352 (52)	502 (52)	0.001
Pospiratory frequency >22 rpm $(n^{\circ})$	314 (47)	455 (40)	0.005
Loukocytos >12,000 or	314 (47)	433 (40)	0.09
<4,000 cell/mm <sup>3</sup> , n (%)	309 (49)	442 (36)	0.001
qSOFA criteria $\geq$ 1, n (%)	319 (47)	461 (40)	0.002
qSOFA criteria $\geq$ 2, n (%)	239 (35)	286 (25)	<0.001
Glasgow Coma Scale <15, n (%)	201 (30)	242 (21)	<0.001
Low mean blood pressure (<60 mmHg), n (%)	207 (31)	247 (21)	<0.001
	45 (20-90)	35 (15-79)	<0.001
Time to antimicrobial infusion,			
Previous ICU admission, n (%)	116 (17)	138 (12)	0.002
Previous hospital admission n (%)	176 (26)	267 (23)	0.154
HIV n (%)	13 (1.9)	20 (1 7)	0 764
DM. n (%)	114 (17)	170 (15)	0.216
Dialvsis, n (%)	50 (7.6)	50 (4.4)	0.006
Heart stroke, n (%)	36 (5.4)	46 (4)	0.178
Heart failure, n (%)	62 (9.5)	54 (4.8)	<0.0001
Peripheral arterial disease. n (%)	69 (10)	73 (6.5)	0.003
EVA. n (%)	137 (20)	128 (11)	<0.0001
Hemiplegia, n (%)	17 (2.5)	24 (2.1)	0.540
Dementia. n (%)	20 (3)	29 (2.5)	0.564
COPD. n (%)	61 (9,1)	87 (7.7)	0.996
SAH, n (%)	314 (47)	437 (38)	<0.001
Cancer. n (%)	85 (13)	62 (5.5)	< 0.001
Cirrhosis. n (%)	12 (1.8)	8 (0.7)	0.037
Steroids chronic use, n (%)	45 (6.8)	58 (5.1)	0.142
Trauma, n (%)	182 (27)	313 (27)	-
Elective surgery, n (%)	107 (16)	203 (18)	0.365
Emergency surgery, n (%)	227 (34)	343 (30)	0.082
Previous sepsis, n (%)	203 (35)	210 (18)	< 0.0001
Palliative care patient, n (%)	20 (3.2)	5 (0.4)	<0.0001
Positive culture, n (%)	277 (50)	312 (39)	<0.0001
Antimicrobial adequacy	174/278 (62)	202/312(65)	0.324
Setting	352 (52.8)	385 (33.7)	<0.0001
Ward	40 (6)	109 (9 5)	*
Emergency room	210 (31.5)	591 (51.7)	*

SD: standard deviation; IQR: interquartile range; SIRS: systemic inflammatory response syndrome; qSOFA: quick Sequential Organ Failure Assessment; ICU: intensive care unit; HIV: human immunodeficiency virus; DM: diabetes mellitus; EVA: encephalic vascular accident; COPD: chronic obstructive pulmonary disease; SAH: systemic arterial hypertension. \* comparison with ICU setting.

#### Discussion

Since the introduction of the qSOFA, several publications have validated this score in different institutions and used it to assess specific infection sites. The qSOFA has been used to assess patients with pyelonephritis,<sup>22</sup> community-acquired pneumonia,<sup>23</sup> healthcare-associated pneumonia,<sup>24</sup>

and burn.<sup>25</sup> Additionally, a subgroup analysis revealed that qSOFA is superior to CURB-65 in predicting the prognosis of ICU admission.<sup>23</sup> Nevertheless, the last surviving sepsis campaign stated that qSOFA criteria should not be used alone for sepsis screening, while medical judgment must be considered.<sup>7</sup> Indeed, according to our cohort results, the positivity of the qSOFA and SIRS criteria was lower than

hospitals and mortality score based of						
	Coefficient (beta)	Error	Wald	OR	95% CI	Р
Chronic renal failure under dialysis	2.186	0.24	10.616	2.51	1.54-4.10	<0.0001
Cerebrovascular disease	2.51	0.155	35.245	1.88	1.39-2.55	<0.0001
Cancer	2.629	0.195	24.546	2.20	1.49-3.24	<0.0001
Cirrhosis	2.992	0.507	4.676	3.97	1.41-11.16	0.009
Previous sepsis	1.842	0.13	22.225	1.42	1.08-1.87	0.012
Fever (temperature >38.3 °C)	2.04	0.123	33.396	0.65	0.51-0.83	<0.001
Leukocytosis or leukopenia	1.387	0.114	8.202	1.61	1.27-2.03	<0.0001
Constant	-1.587	0.14	128.952			

 Table 2
 Multivariable analysis of risk factors of mortality in 1,808 patients included in a sepsis protocol bundle in two Brazilian hospitals and mortality score based on beta coefficient.

OR: odds ratio; CI: confidence interval; qSOFA: quick Sequential Organ Failure Assessment; EVA: encephalic vascular accident. Mortality score =  $2.186 \times$  (Chronic renal failure) +  $2.51 \times$  (Cerebrovascular disease) +  $2.629 \times$  (neoplasm) +  $2.992 \times$  (cirrhosis) +  $1.842 \times$  (2nd sepsis) +  $2.040 \times$  (fever) +  $1.387 \times$  (leukocytosis).

Table 3	Mortality according to risk score in 1,808 patients
included i	n a sepsis protocol bundle in two Brazilian hospital.

Score (points)	Risk of mortality
0-2	20%
2.1-3	29%
3.1-4	40%
4.1-5	43%
5.1-6	56%
6.1-7	53%
7.1-8	<b>67</b> %
>8	76%

expected (29% and 63%, respectively). Therefore, medical judgment started our sepsis protocol in 71% and 37% of patients without the qSOFA or SIRS criteria, respectively. Despite the use of medical judgment as a possible starting point for the overdiagnosis of sepsis, the global mortality rate was 37%. This is in accordance with the World Health Organization's global estimation of sepsis-treated death rates. For instance, 27% of in-hospital mortality is related to all treated sepsis, and 42% of in-hospital mortality is specifically related to sepsis diagnosed in the ICU.<sup>26</sup> As expected, differences according to world regions may exist, and convergent with our results, the general treated-sepsis death rates vary from 25–36%. Even though SIRS and qSOFA are screening tool for sepsis, these scores can also be used for prediction of death in patients with diagnosis of sepsis.<sup>27</sup>

In our multivariate analysis, the SIRS criteria were not related to poor prognosis, whereas qSOFA  $\geq$  2 was an independent variable related to death. This reinforces the qSOFA criteria as a prognostic tool rather than a screening pathway. Therefore, the use of these criteria must be well allocated on a daily basis to decrease the causality of sepsis-related death, considering a lower diagnosis if only qSOFA is used. In six studies, the sensitivity and specificity of qSOFA for mortality varied from 68% to 90% and from 27.4% to 79.5%, respectively.<sup>28</sup> In the same studies, the sensitivity of the SIRS criteria was higher (93.0–97.4%), but the specificity was very low (2–27.5%). Although these scores lacked sensitivity or specificity (according to the number of points), combining other markers, such as lactate<sup>29,30</sup> and red blood cell distribution,<sup>31</sup> can be a good strategy.<sup>23,32–39</sup> However,



**Figure 2** Receiver operating characteristic (ROC) curve from equation model obtained after multivariable analysis of risk factors associated with death in patients included in a sepsis protocol bundle. The AUC of the ROC curve was 0.66.

a tool that fits it will probably not become real, given the difference between screening and prognosis steps.  $^{40}\,$ 

In our cohort, the absence of fever was an independent factor associated with poor prognosis. This can be explained by the following two points: immunosuppression at the onset of sepsis,<sup>41</sup> and the absence of fever may falsely give a ''not so bad'' impression to the medical team regarding the patient's status, leading to a softened re-evaluation pathway. Additionally, previous studies have converged with these hypotheses and found that 30-day mortality is higher in patients with afebrile bacteremia.<sup>42</sup>

Sepsis can be present without qSOFA criteria owing to the different forms of organ dysfunction and qSOFA criteria without infection, such as heart failure. Some studies have suggested that SIRS criteria should not be used.<sup>43</sup> However, the approach to patients is not based on specific clinical or laboratory criteria. These criteria are important for didactic reasoning and diagnostic classification in clinical studies. However, some studies still confuse definitions with action strategies.<sup>40,44,45</sup>

Interestingly, SIRS and qSOFA have been studied in many publications as a score risk of mortality, but generally limited to specific populations, such as *S. aureus* infections, pre-hospital care, emphysematous pyelonephritis, among others.<sup>27,46-49</sup> Liu et al. evaluated qSOFA as a risk of mortality with a AUC ROC of 0.54, similar with our results.<sup>50</sup> Another large retrospective cohort showed that SOFA was better than qSOFA and SIRS, with AUC ROC of 0.58 and 0.60 respectively.<sup>51</sup> These data confirm the results of our study.

Other studies evaluated in different hospitals, but not in Brazilian hospitals, and also without the description of analysis with implementation of bundles, where intervention measures tend to be standardized and lower mortality.<sup>52,53</sup> Despite this, our score reached values very close to studies in the literature. We even performed a ROC curve analysis for qSOFA and SIRS with our patients (supplementary material), but the AUC was extremely unfavorable.

Despite the inclusion of >2,000 patients in this study, there were several limitations. First, this was a retrospective study, which could have led to misinterpretation after the extraction of data from medical records. This novel score should be validated in another cohort of patients to determine an external validation. In the model, patients from different settings were included, and if we categorize this groups, the strength of the model would decrease.

#### Conclusion

In conclusion, the SIRS and qSOFA scores are not independent scores for death. The the association of clinical and laboratorial data from these scores together with comorbidities resulted in a better score but not a robust predictor of death. Fever was related to a better prognosis, while cirrhosis, dialysis, prolonged length of stay, and cancer had at least double the odds of death. Therefore, medical teams must be aware of these variables as prognosis in patients with sepsis.

#### Author's contribution

Vinicius Nakad Orsatti – idealization, draft text

Victoria Stadler Tasca Ribeiro - text review

Carolina de Oliveira Montenegro - data manager

Clarice Juski Costa - data manager

Eduardo Albanske Raboni – draft text, data manager Eduardo Ramos Sampaio – draft text, data manager

Fernando Michielin – final review

Juliano Gasparetto – idealization, statistical analysis João Paulo Telles – statistical analysis, final text

Felipe Francisco Tuon – idealization, statistical analysis, final text

Financial disclosures: None.

#### **Conflicts of interest**

None.

#### Acknowledgment

None.

#### Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10. 1016/j.medine.2024.03.005.

#### References

- 1. Liu V, Escobar GJ, Greene JD, Soule J, Whippy A, Angus DC, et al. Hospital deaths in patients with sepsis from 2 independent cohorts. JAMA. 2014;312(1):90-2, http://dx.doi.org/10.1001/jama.2014.5804.
- Sprung CL. Definitions of sepsis-have we reached a consensus? Crit Care Med. 1991;19(7):849–51 https://www.ncbi.nlm .nih.gov/pubmed/2055068
- Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801–10, http://dx.doi.org/10 .1001/jama.2016.0287.
- 4. Vincent JL, de Mendonca A, Cantraine F, Moreno R, Takala J, Suter PM, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med. 1998;26(11):1793-800 https://www.ncbi.nlm.nih.gov/pubmed/9824069
- Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):762–74, http://dx.doi.org/10.1001/jama.2016.0288.
- Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic inflammatory response syndrome criteria in defining severe sepsis. N Engl J Med. 2015;372(17):1629–38, http://dx.doi.org/10.1056/NEJMoa1415236.
- Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47(11):1181–247, http://dx.doi.org/10.1007/s00134-021-06506-y.
- He Y, Xu J, Shang X, Fang X, Gao C, Sun D, et al. Clinical characteristics and risk factors associated with ICU-acquired infections in sepsis: a retrospective cohort study. Front Cell Infect Microbiol. 2022;12:962470, http://dx.doi.org/10.3389/fcimb.2022.962470.
- 9. Zhao C, Xin MY, Li J, Zhao JF, Wang YJ, Wang W, et al. Comparing the precision of the pSOFA and SIRS scores in predicting sepsis-related deaths among hospitalized children: a multi-center retrospective cohort study. World J Emerg Med. 2022;13(4):259–65, http://dx.doi.org/10 .5847/wjem.j.1920-8642.2022.060.
- Lind ML, Mooney SJ, Carone M, Althouse BM, Liu C, Evans LE, et al. Development and validation of a machine learning model to estimate bacterial sepsis among immunocompromised recipients of stem cell transplant. JAMA Netw Open. 2021;4(4):e214514, http://dx.doi.org/10. 1001/jamanetworkopen.2021.4514.
- 11. Wang L, Zou Z, Ding K, Hou C. Predictive risk score model for severe fever with thrombocytopenia syndrome mortality based on qSOFA and SIRS scoring system.

BMC Infect Dis. 2020;20(1):595, http://dx.doi.org/10 .1186/s12879-020-05299-7.

- Bauer ME, Housey M, Bauer ST, Behrmann S, Chau A, Clancy C, et al. Risk factors, etiologies, and screening tools for sepsis in pregnant women: a multicenter case-control study. Anesth Analg. 2019;129(6):1613–20, http://dx.doi.org/10.1213/ANE.00000000003709.
- 13. Liu VX, Lu Y, Carey KA, Gilbert ER, Afshar M, Akel M, et al. Comparison of early warning scoring systems for hospitalized patients with and without infection at risk for in-hospital mortality and transfer to the intensive care unit. JAMA Netw Open. 2020;3(5):e205191, http://dx.doi.org/10.1001/jamanetworkopen.2020.5191.
- Tuon FF, Telles JP, Cieslinski J, Borghi MB, Bertoldo RZ, Ribeiro VST. Development and validation of a risk score for predicting positivity of blood cultures and mortality in patients with bacteremia and fungemia. Braz J Microbiol. 2021;52(4):1865–71, http://dx.doi.org/10.1007/s42770-021-00581-5.
- Tuon FF, Rymsza AM, Penteado-Filho SR, Pilonetto M, Arend LN, Levin AS. Should polymyxin be used empirically to treat infections in patients under high risk for carbapenemresistant Acinetobacter? J Infect. 2011;62(3):246–9, http://dx.doi.org/10.1016/j.jinf.2011.01.005.
- 16. Zequinao T, Gasparetto J, Oliveira DDS, Silva GT, Telles JP, Tuon FF. A broad-spectrum beta-lactam-sparing steward-ship program in a middle-income country public hospital: antibiotic use and expenditure outcomes and antimicrobial susceptibility profiles. Braz J Infect Dis. 2020;24(3):221–30, http://dx.doi.org/10.1016/j.bjid.2020.05.005.
- 17. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101(6):1644–55 https://www.ncbi.nlm.nih.gov/pubmed/1303622
- Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Developing a new definition and assessing new clinical criteria for septic shock: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):775–87, http://dx.doi.org/10.1001/jama.2016.0289.
- Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83 https://www.ncbi.nlm.nih.gov/pubmed/3558716
- Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008;36(5):309–32, http://dx.doi.org/10.1016/j.ajic.2008.03.002.
- World Health Organization. International statistical classification of diseases and related health problems, Vol. 3; 2010.
- Fukushima H, Kobayashi M, Kawano K, Morimoto S. Performance of qSOFA and SOFA for predicting mortality in patients with acute pyelonephritis associated with upper urinary tract calculi. J Urol. 2017, http://dx.doi.org/10.1016/j.juro.2017.12.052.
- Muller M, Guignard V, Schefold JC, Leichtle AB, Exadaktylos AK, Pfortmueller CA. Utility of quick sepsis-related organ failure assessment (qSOFA) to predict outcome in patients with pneumonia. PLoS One. 2017;12(12):e0188913, http://dx.doi.org/10.1371/journal.pone.0188913.
- 24. Asai N, Watanabe H, Shiota A, Kato H, Sakanashi D, Hagihara M, et al. Could qSOFA and SOFA score be correctly estimating the severity of healthcare-associated pneumonia? J Infect Chemother. 2017, http://dx.doi.org/10 .1016/j.jiac.2017.10.004.

- 25. Ladhani HA, Sajankila N, Zosa BM, He JC, Yowler CJ, Brandt C, et al. Utility of sequential organ failure assessment score in predicting bacteremia in critically ill burn patients. Am J Surg. 2017;215:478–81, http://dx.doi.org/10. 1016/j.amjsurg.2017.09.034.
- **26.** WHO. Global report on the epidemiology and burden of sepsis: current evidence, identifying gaps and future directions; 2020.
- Gupta S, Rudd KE, Tandhavanant S, Suntornsut P, Chetchotisakd P, Angus DC, et al. Predictive validity of the qSOFA score for sepsis in adults with community-onset Staphylococcal infection in Thailand. J Clin Med. 2019;8(11), http://dx.doi.org/10.3390/jcm8111908.
- 28. Serafim R, Gomes JA, Salluh J, Povoa P. A comparison of the quick-SOFA (qSOFA) and SIRS criteria for the diagnosis of sepsis and prediction of mortality: a systematic review and meta-analysis. Chest. 2017, http://dx.doi.org/10.1016/j.chest.2017.12.015.
- Biyikli E, Kayipmaz AE, Kavalci C. Effect of plateletlymphocyte ratio and lactate levels obtained on mortality with sepsis and septic shock. Am J Emerg Med. 2017, http://dx.doi.org/10.1016/j.ajem.2017.12.010.
- Shetty A, MacDonald SP, Williams JM, van Bockxmeer J, de Groot B, et al. Lactate &/=2 mmol/L plus qSOFA improves utility over qSOFA alone in emergency department patients presenting with suspected sepsis. Emerg Med Australas. 2017;29(6):626–34, http://dx.doi.org/10.1111/1742-6723.12894.
- Wang AY, Ma HP, Kao WF, Tsai SH, Chang CK. Red blood cell distribution width is associated with mortality in elderly patients with sepsis. Am J Emerg Med. 2017;36:949–53, http://dx.doi.org/10.1016/j.ajem.2017.10.056.
- 32. Khwannimit B, Bhurayanontachai R, Vattanavanit V. Comparison of the performance of SOFA, qSOFA and SIRS for predicting mortality and organ failure among sepsis patients admitted to the intensive care unit in a middle-income country. J Crit Care. 2017;44:156–60, http://dx.doi.org/10.1016/j.jcrc.2017.10.023.
- 33. Tusgul S, Carron PN, Yersin B, Calandra T, Dami F. Low sensitivity of qSOFA, SIRS criteria and sepsis definition to identify infected patients at risk of complication in the prehospital setting and at the emergency department triage. Scand J Trauma Resusc Emerg Med. 2017;25(1):108, http://dx.doi.org/10.1186/s13049-017-0449-y.
- 34. Guirgis FW, Puskarich MA, Smotherman C, Sterling SA, Gautam S, Moore FA, et al. Development of a simple sequential organ failure assessment score for risk assessment of emergency department patients with sepsis. J Intensive Care Med. 2017:885066617741284, http://dx.doi.org/10.1177/0885066617741284.
- 35. Jouffroy R, Saade A, Ellouze S, Carpentier A, Michaloux M, Carli P, et al. Prehospital triage of septic patients at the SAMU regulation: comparison of qSOFA, MRST, MEWS and PRESEP scores. Am J Emerg Med. 2017;36:820-4, http://dx.doi.org/10.1016/j.ajem.2017.10.030.
- 36. Caironi P. A call for research on sepsis in developing countries. Minerva Anestesiol. 2012;78(11):1196-8 https://www.ncbi.nlm.nih.gov/pubmed/23132260
- Bozza FA, Salluh JI. An urban perspective on sepsis in developing countries. Lancet Infect Dis. 2010;10(5):290-1, http://dx.doi.org/10.1016/S1473-3099(10)70074-8.
- Taniguchi LU, Bierrenbach AL, Toscano CM, Schettino GP, Azevedo LC. Sepsis-related deaths in Brazil: an analysis of the national mortality registry from 2002 to 2010. Crit Care. 2014;18(6):608, http://dx.doi.org/10. 1186/s13054-014-0608-8.
- 39. Machado FR, Cavalcanti AB, Bozza FA, Ferreira EM, Angotti Carrara FS, et al. The epidemiology of sepsis in Brazilian intensive care units (the Sepsis PREvalence Assessment Database, SPREAD): an observational study. Lancet

Infect Dis. 2017;17(11):1180-9, http://dx.doi.org/10. 1016/S1473-3099(17)30322-5.

- 40. Solligard E, Damas JK. SOFA criteria predict infection-related in-hospital mortality in ICU patients better than SIRS criteria and the qSOFA score. Evid Based Med. 2017;22(6):211, http://dx.doi.org/10.1136/ebmed-2017-110727.
- 41. Lazzaro A, De Girolamo G, Filippi V, Innocenti GP, Santinelli L, Ceccarelli G, et al. The interplay between host defense, infection, and clinical status in septic patients: a narrative review. Int J Mol Sci. 2022;23(2), http://dx.doi.org/10.3390/ijms23020803.
- 42. Chen HY, Hsu YC. Afebrile bacteremia in adult emergency department patients with liver cirrhosis: clinical characteristics and outcomes. Sci Rep. 2020;10(1):7617, http://dx.doi.org/10.1038/s41598-020-64644-7.
- 43. Wu S, Zhou X, Ye Y. Goodbye to the SIRS, the reason why we do not need you. Am J Emerg Med. 2017;36:1316-7, http://dx.doi.org/10.1016/j.ajem.2017.11.044.
- 44. Szakmany T, Pugh R, Kopczynska M, Lundin RM, Sharif B, Morgan P, et al. Defining sepsis on the wards: results of a multi-centre point-prevalence study comparing two sepsis definitions. Anaesthesia. 2017;73:195–204, http://dx.doi.org/10.1111/anae.14062.
- 45. Kushimoto S, Gando S, Ogura H. The qSOFA requires validation as a promptly applicable clinical criterion. Acute Med Surg. 2017;4(3):225–6, http://dx.doi.org/10.1002/ams2.287.
- 46. Elbaset MA, Zahran MH, Hashem A, Ghobrial FK, Elrefaie E, Badawy M, et al. Could platelet to leucocytic count ratio (PLR) predict sepsis and clinical outcomes in patients with emphysematous pyelonephritis? J Infect Chemother. 2019;25(10):791–6, http://dx.doi.org/10.1016/j.jiac.2019.04.008.
- 47. Lane DJ, Lin S, Scales DC. Classification versus prediction of mortality risk using the SIRS and qSOFA scores in patients with infection transported by paramedics. Prehosp Emerg Care. 2020;24(2):282–9, http://dx.doi.org/10. 1080/10903127.2019.1624901.

- 48. Boulos D, Shehabi Y, Moghaddas JA, Birrell M, Choy A, Giang V, et al. Predictive value of quick sepsis-related organ failure scores following sepsis-related Medical Emergency Team calls: a retrospective cohort study. Anaesth Intensive Care. 2017;45(6):688–94, http://dx.doi.org/10.1177/0310057X1704500607.
- 49. Jouffroy R, Saade A, Carpentier A, Ellouze S, Philippe P, Idialisoa R, et al. Triage of septic patients using qSOFA criteria at the SAMU regulation: a retrospective analysis. Prehosp Emerg Care. 2018;22(1):84–90, http://dx.doi.org/10. 1080/10903127.2017.1347733.
- 50. Liu Z, Meng Z, Li Y, Zhao J, Wu S, Gou S, et al. Prognostic accuracy of the serum lactate level, the SOFA score and the qSOFA score for mortality among adults with sepsis. Scand J Trauma Resusc Emerg Med. 2019;27(1):51, http://dx.doi.org/10.1186/s13049-019-0609-3.
- 51. Raith EP, Udy AA, Bailey M, McGloughlin S, MacIsaac C, Bellomo R, et al. Prognostic accuracy of the SOFA score, SIRS criteria, and qSOFA score for in-hospital mortality among adults with suspected infection admitted to the intensive care unit. JAMA. 2017;317(3):290–300, http://dx.doi.org/10.1001/jama.2016.20328.
- 52. Chen FC, Kung CT, Cheng HH, Cheng CY, Tsai TC, Hsiao SY, et al. Quick sepsis-related organ failure assessment predicts 72-h mortality in patients with suspected infection. Eur J Emerg Med. 2019;26(5):323–8, http://dx.doi.org/10.1097/MEJ.0000000000563.
- 53. Rudd KE, Seymour CW, Aluisio AR, Augustin ME, Bagenda DS, et al. Association of the quick sequential (sepsis-related) organ failure assessment (qSOFA) score with excess hospital mortality in adults with suspected infection in low-and middle-income countries. JAMA. 2018;319(21):2202–11, http://dx.doi.org/10.1001/jama.2018.6229.