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Risk Factors for Mortality, Intensive Care Unit Admission, and Bacteremia in Patients Suspected of Sepsis at the Emergency Department: A Prospective Cohort Study

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Background. There is a clear need for a better assessment of independent risk factors for in-hospital mortality, intensive care unit admission, and bacteremia in patients presenting with suspected sepsis at the emergency department.

Methods. A prospective observational cohort study including 1690 patients was performed. Two multivariable logistic regression models were used to identify independent risk factors.

Results. Sequential organ failure assessment (SOFA) score of ≥ 2 and serum lactate of ≥ 2 mmol/L were associated with all outcomes. Other independent risk factors were individual SOFA variables and systemic inflammatory response syndrome variables but varied per outcome. Mean arterial pressure < 70 mmHg negatively impacted all outcomes.

Conclusions. These readily available measurements can help with early risk stratification and prediction of prognosis.

Keywords. bacteremia; emergency department; ICU admission; risk factors; sepsis.

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Despite international efforts, mortality remains high [1]. A rapid identification of severely ill patients is necessary, and several risk-scoring systems have been proposed. The Third International Consensus Conference introduced sequential organ failure assessment (SOFA) as a risk-assessment tool for mortality. Sepsis, defined as SOFA ≥ 2 , is associated with 10% mortality risk [2]. Sequential organ failure assessment has been evaluated in the emergency department (ED) [3]. In addition, the quick SOFA (qSOFA) has been proposed for risk stratification in the ED but showed a low sensitivity for predicting unfavorable outcomes [4]. Furthermore, the previous sepsis guidelines-based systemic inflammatory response syndrome (SIRS) criteria were shown to have better performances than qSOFA [4]. Other scoring models include the modified early warning score, which performed better than qSOFA for risk stratification [5]. On the

other hand, prediction models for bacteremia have not been well implemented in clinical practice [6]. Fast and easily measurable risk factors in the ED could help in early triage and close monitoring of severely ill patients. The objective of this study was to identify potential risk factors associated with in-hospital mortality, intensive care unit (ICU) admission, and bacteremia at the start of a new episode of suspected sepsis.

METHODS

A prospective observational cohort study was performed at the ED of a 981-bed teaching hospital in Hasselt, Belgium between February 2019 and March 2020 as part of the Fast Assay for Pathogen Identification and Characterization (FAPIC) project (ClinicalTrials.gov Identifier NCT03841162). All adult patients presenting with suspected sepsis (all patients for whom blood cultures were drawn) were asked to participate. The study was approved by the medical ethics committees of Jessa hospital and Hasselt University, and written informed consent was obtained from all participants. Patients were included after collection of the first set of blood cultures at each new suspected sepsis episode (minimal interval of 7 days between positive blood cultures with the same pathogen and at least 24 hours between positive cultures with different organisms). Blood cultures were performed using the BACTEC FX (Becton Dickinson) system, bacterial identification by MALDI-TOF Biotyper (Bruker), and susceptibility testing by the Phoenix system TM 100 (Becton Dickinson). Other microbiological tests (including cultures of urine,

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lower respiratory tract, and samples of specific foci, urinary antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila* and nasopharyngeal swabs for virologic polymerase chain reaction) were performed if deemed relevant by the treating physician.

Clinical and laboratory parameters were collected at the start of each new episode. Emergency department physicians ordered clinical, biochemical, and microbiological tests guided by a suspected sepsis protocol in place at the ED. Clinical parameters included body temperature, heart rate, mean arterial pressure (MAP), oxygen saturation (SaO₂) and partial oxygen pressure (PaO₂), Glasgow Coma scale (GCS), the presence of central lines at admission, vasopressor use, and oxygen requirements. Laboratory testing included white blood cell count (WBC), platelet count, hemoglobin, red blood cell distribution width (RDW), C-reactive protein (CRP), creatinine, urea, lactate dehydrogenase (LDH), bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Additional biochemical tests ordered as part of the FAPIC study were serum lactate and ferritin, based on recent insights regarding their association with sepsis mortality [2, 7]. Recorded patient outcomes were in-hospital mortality, ICU admission (at any time during hospital admission), and the presence of bacteremia. All final infection diagnoses recorded by the treating physicians were validated by an experienced infectious diseases physician (I.C.G.) not involved in the care of study patients, according to infectious diseases definitions [8–10]. Definitions are provided in [Supplementary Table 1](#). Descriptive statistics were used to present patient's characteristics. Continuous data are shown as median (interquartile range) and categorical data are shown as frequency (percentages). Two multivariable logistic regression models were built for each outcome. Model 1 included SOFA score ≥ 2 , and model 2 included individual SOFA score variables to evaluate the association of these variables separately. All parameters were inserted in the starting model. A backwards selection based on significance level $P < .05$ was used. Odds ratios (ORs) were calculated to define independent risk factors. Sensitivity, specificity, and positive and negative predictive values were calculated for all models. All analyses were done using SPSS version 25 (IBM, Chicago, IL).

Patient Consent Statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Documented approval for this study was obtained from the Ethics committees of Hasselt University and Jessa Hospital (18.106/infect18.03 and 19.51/infect.19.02). Written informed consent was obtained from all participants.

RESULTS

In total, 1690 admissions to the ED of 1545 unique patients were included. Patient characteristics, patient outcomes, and infection diagnoses are shown in [Table 1](#). Median age was 70 years (55–80), and 976 patients (57.8%) were male. Median Charlson Comorbidity Index (CCI) was 1 (0–3). Cardiac comorbidities, renal insufficiency, and chronic pulmonary diseases were most prevalent. Median SOFA score was 2 (0–3), 193 (11.4) patients had central lines, 316 patients (18.9%) required oxygen therapy, and 17 patients (1.0%) required the use of vasopressors. All clinical and laboratory measurements are shown in [Supplementary Table 2](#). Overall, 90 patients (5.3%) died in hospital, and 131 patients (7.8%) were admitted to the ICU. There were 253 (15.0%) admissions with true bacteremia and 82 (4.9%) with contaminated blood cultures. Isolated pathogens and major resistances are shown in [Supplementary Table 3](#).

Independent risk factors for in-hospital mortality, ICU admission, and bacteremia are shown in [Figures 1](#) and [2](#). In model 1 ([Figure 1](#)), SOFA score and serum lactate ≥ 2 mmol/L were independent risk factors for all outcomes. Independent risk factors for in-hospital mortality were older age, male sex, increased heart rate (>90 bpm), increased LDH (>250 U/L), and increased ferritin. High temperature ($>38.5^{\circ}\text{C}$) at the start of the episode was a negative independent risk factor. For ICU admission, the presence of central lines at admission, leukocytosis ($>11 \times 10^9$ WBC/L), increased urea (>49 mg/dL), and increased LDH (>250 U/L) were independent risk factors. Bacteremia was associated with older age, temperature $>38.5^{\circ}\text{C}$, the presence of central lines at admission, leukocytosis ($>11 \times 10^9$ WBC/L), decreased hemoglobin levels, increased CRP (>5 mg/L), and increased ALT levels. Lower CCI was an independent risk factor for ICU admission and for bacteremia.

In model 2 ([Figure 2](#)), patients with MAP <70 mmHg had a 2-fold risk for all outcomes. Temperature $>38.5^{\circ}\text{C}$ was negatively related to in-hospital mortality, but older age, decreased GCS (13–14 and <9), increased RDW, increased LDH (>250 U/L), serum lactate ≥ 2 mmol/L, and increased ferritin were independent risk factors. For ICU admission, serum lactate (≥ 2 mmol/L) and LDH (>250 U/L) were eliminated in model 2. The SOFA variables associated with ICU admission were decreased PaO₂/FiO₂ ratio (<300 and <100) and abnormal platelet counts ($<150 \times 10^9/\text{L}$ and $>400 \times 10^9/\text{L}$). Regarding bacteremia, increased CRP (>5 mg/L) was not an independent risk factor in model 2. Sequential organ failure assessment variables decreased platelet count ($<150 \times 10^9/\text{L}$), decreased creatinine levels, and increased bilirubin levels (>1.2 mg/dL) were independent risk factors for bacteremia.

For all models, performance characteristics to predict the respective outcome at admission are shown in [Supplementary Table 4](#), and receiver operating curves are shown in [Supplementary Figure 1](#). Model 1 was able to predict mortality,

Table 1. Patient Characteristics, Disease Severity, Clinical Outcomes, Final Infection Diagnoses, and Proportion of Patients With Bacteremia

Variable	Total n = 1690		
Demographics			
Age (years; median IQR)	70 (55–80)		
Sex			
Male	976 (57.8)		
Female	714 (42.2)		
Charlson Comorbidity Index			
Cardiac comorbidities	301 (17.8)		
Hypertension	373 (22.1)		
Chronic pulmonary disease	263 (15.6)		
Cerebrovascular disease ^a	139 (8.2)		
Renal insufficiency	255 (15.1)		
Liver disease	53 (3.1)		
Diabetes	255 (15.1)		
Solid malignancies	176 (10.4)		
Solid metastatic malignancies	177 (10.5)		
Hematological malignancies	53 (3.2)		
SOFA score at admission (median IQR)	2 (0–3)		
Central line ^b at admission	193 (11.4)		
Oxygen Therapy			
Noninvasive	307 (18.2)		
Invasive	11 (0.7)		
Vasopressor use	17 (1.0)		
Outcomes			
In-hospital mortality	90 (5.3)		
ICU admission	131 (7.8)		
Bacteremia	253 (15.0)		
LOS (days; median IQR)	5 (3–10)		
ICU LOS (days; median IQR)	3 (2–8)		
Clinical Infection Diagnosis			
		Bacteremia (n = 253)	No Bacteremia (n = 1437)
Pneumonia	291 (17.2)	24 (9.5)	267 (18.6)
ABSSSI	164 (9.7)	14 (5.5)	150 (10.4)
Intra-abdominal infection	158 (9.3)	43 (17.0)	115 (8.0)
Urosepsis	97 (5.7)	97 (38.3)	0 (0.0)
Influenza	97 (5.7)	0 (0.0)	97 (6.8)
IRTI	93 (5.5)	0 (0.0)	93 (6.5)
BSI, CLABSI, and endocarditis	73 (4.3)	73 (28.9)	0 (0.0)
uUTI	60 (3.6)	0 (0.0)	60 (4.2)
Other Infection			
Fever	127 (7.5)	0 (0.0)	127 (8.8)
IUTI	90 (5.3)	0 (0.0)	90 (6.3)
uRTI	66 (3.9)	0 (0.0)	66 (4.6)
Neutropenic fever	33 (2.0)	0 (0.0)	32 (2.3)
Bone and joint infection	13 (0.8)	1 (0.4)	12 (0.8)
Viral infection ^c	12 (0.7)	0 (0.0)	12 (0.8)
CNS infection	9 (0.5)	1 (0.4)	8 (0.6)
Other	9 (0.5)	0 (0.0)	9 (0.6)
Other bacterial/parasitic infection	4 (0.2)	0 (0.0)	4 (0.3)
No Infection Diagnosis			
Suspected infection	230 (13.6)	0 (0.0)	230 (16.0)
Suspected viral infection	44 (2.6)	0 (0.0)	44 (3.1)
Inflammatory diseases	20 (1.2)	0 (0.0)	20 (1.4)

Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; BSI, bloodstream infection; CLABSI, central line-associated BSI; CNS, central nervous system; ICU, intensive care unit; IQR, interquartile range; IRTI, lower respiratory tract infection; IUTI, lower urinary tract infection; LOS, length of stay; SOFA, sequential organ failure assessment; uRTI, upper respiratory tract infection; uUTI, upper urinary tract infection.

NOTE: Numbers are presented as N (%) unless specified.

^aCerebrovascular disease included strokes and *transient ischemic attack*.

^bThese were 188 portal catheters and 5 Hickman catheters.

^cViral infections were herpes zoster (n = 3), cytomegalovirus (n = 2), Epstein-Barr virus, herpes simplex, enterovirus, measles, rhinovirus, parainfluenza virus, and human immunodeficiency virus (all n = 1).

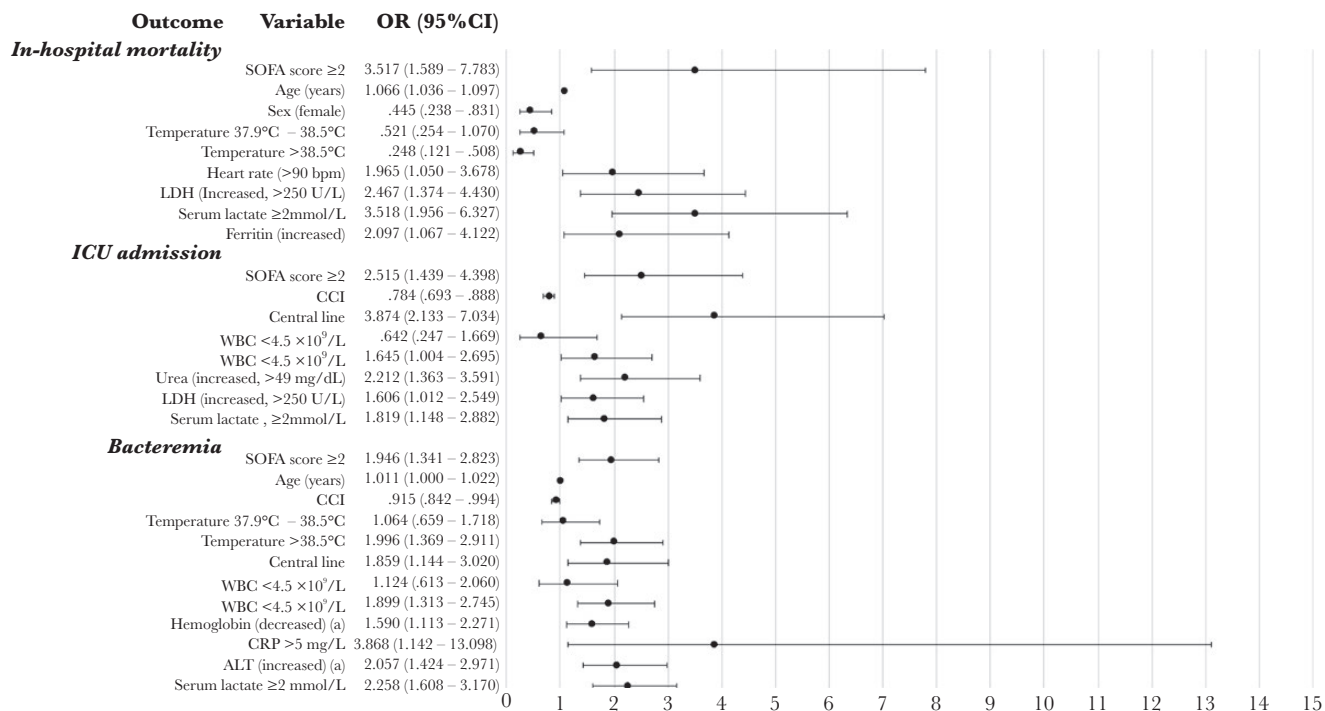


Figure 1. Forest plot of multivariable logistic regression analysis (model 1) of the association of clinical and laboratory parameters with mortality, intensive care unit (ICU) admission, and presence of bacteremia at admission. Model 1: Sequential organ failure assessment (SOFA) score ≥ 2 and other parameters. ^aReference levels for abnormal values (decreased or increased) are age and sex dependent. *Odds ratio (OR) and *P* value for increased hemoglobin were not calculated for this model because of low numbers of patients for that group (data not shown). Two patients with body temperature $<35^\circ\text{C}$ were excluded for multivariable analysis because of the low number in that group. ALT, alanine aminotransferase; CCI, Charlson Comorbidity Index; CI, confidence interval; CRP, C-reactive protein; GCS, Glasgow coma scale; LDH, lactate dehydrogenase; MAP, mean arterial pressure; WBC, white blood cell count.

ICU admission, and bacteremia with a sensitivity and specificity of 7.9% and 99.5%, 5.4% and 99.9%, and 4.2% and 99.1%, respectively. Model 2 was able to predict mortality, ICU admission, and bacteremia with a sensitivity and specificity of 18.0% and 99.7%, 10.0% and 99.9%, and 16.2% and 98.1%, respectively.

DISCUSSION

This study shows several independent risk factors for in-hospital mortality, ICU admission, and bacteremia in a population presenting at the ED with suspected sepsis. Most importantly, SOFA score of ≥ 2 and serum lactate of ≥ 2 mmol/L were associated with all outcomes. Mean arterial pressure <70 mmHg was associated with an increased risk for all outcomes in one model. Age and CCI were important confounders. This is in accordance with previous research, in which CCI was higher in patients with *Staphylococcus aureus* bacteremia for more than 1 day [11] and was found to be an independent predictor for mortality in bloodstream infection due to Enterobacterales [12]. Independent risk factors for mortality were clinical (temperature $\leq 38.5^\circ\text{C}$, decreased GCS) and laboratory parameters (leukocytosis, increased RDW, LDH, and ferritin). It is interesting to note that, consistent with other studies in the ED [13], higher temperature at admission was negatively associated with

mortality. Reasons can be late recognition of infection, and consequently a later start of antibiotics in the absence of fever, or a poor immune and fever response [13]. Hypothermia is associated with an increased mortality risk [13], which could not be confirmed due to the small number of patients with hypothermia in our cohort. Intensive care unit admission was associated with decreased $\text{PaO}_2/\text{FiO}_2$, the presence of central lines at admission, leukocytosis, and increased levels of urea and LDH. In addition, lower CCI was an independent risk factor for ICU admission, although this can reflect patient management in our hospital. Risk factors for bacteremia were temperature $>38.5^\circ\text{C}$, the presence of central lines at admission, and laboratory parameters (leukocytosis, increased levels of CRP and ALT, and decreased levels of platelets, hemoglobin, and creatinine). All measurements can be easily and rapidly determined at admission.

According to the sepsis-3 guidelines, SOFA score is useful for defining sepsis, and a score of ≥ 2 is associated with a 10% mortality risk. Furthermore, hyperlactatemia is associated with a 25.7% mortality risk [2], and significant increases in OR of in-hospital mortality were reported with each increase in serum lactate values [14]. In our population, the association of mortality with SOFA score and serum lactate was confirmed. In addition, both factors were associated with ICU admission and

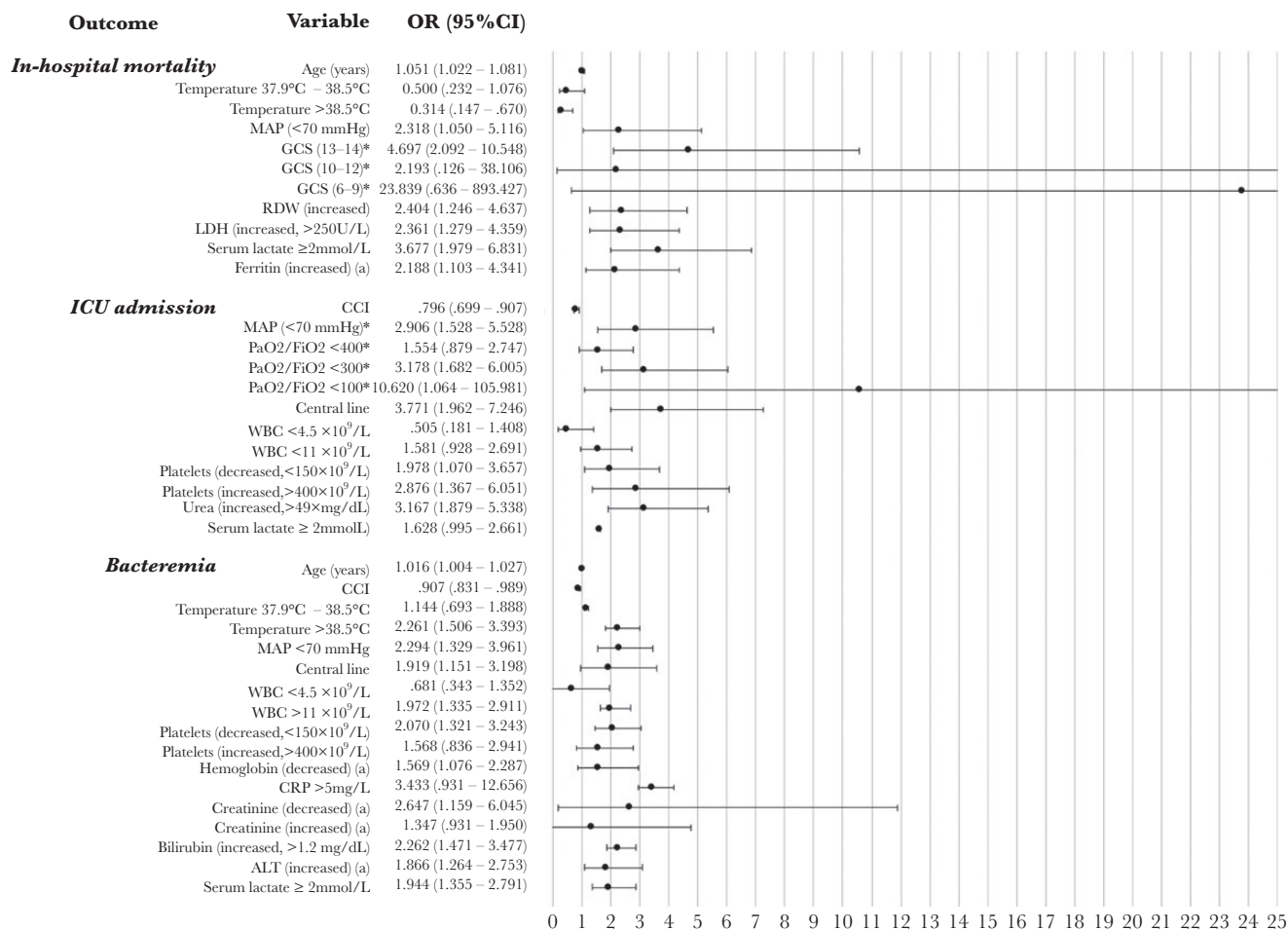


Figure 2. Forest plot of multivariable logistic regression analysis (model 2) of the association of clinical and laboratory parameters with mortality, intensive care unit (ICU) admission, and presence of bacteremia at admission. Model 2: Separate variables of sequential organ failure assessment (SOFA) score and other parameters. ^aReference levels for abnormal values (decreased or increased) are age and sex dependent. *Odds ratio (OR) and *P* value for decreased red blood cell distribution width (RDW), increased hemoglobin, a Glasgow coma scale (GCS) <6, and a PaO₂/FiO₂ <200 were not calculated for this model because of low numbers of patients for that group (data not shown). Two patients with body temperature <35°C were excluded for multivariable analysis because of the low number in that group. ALT, alanine aminotransferase; CCI, Charlson Comorbidity Index; CI, confidence interval; LDH, lactate dehydrogenase; MAP, mean arterial pressure; WBC, white blood cell count.

bacteremia. Furthermore, when SOFA score was replaced by its individual variables, most independent risk factors that were identified in model 1 remained similar. Mean arterial pressure <70 mmHg was an independent risk factor at admission for all outcomes, confirming the earlier findings of one retrospective study [15]. Moreover, fever, hypotension, and leukocytosis were identified as independent risk factors for bacteremia. These parameters are part of the SIRS criteria in the sepsis-1 and -2 guidelines [16]. Although studies show better performance of SOFA score in describing prognosis [17], these factors could still be useful in risk stratification, and our findings suggest the use of a combination of both assessment scores.

All models were able to predict all outcomes with high specificity but with low sensitivity. Therefore, these risk factors could be used in the ED as a screening tool for “ruling in” patients most at risk for a severe disease course, but they should not be used for ruling these patients out. Sensitivity increased in model

2 compared to model 1. This indicates that the use of separate independent risk factors can add value in screening patients at the ED, compared with using SOFA score as a composite score.

The prospective inclusion of patients and collection of data is a major strength of this study. This resulted in a well defined and uniform cohort and a limited amount of missing data; for all variables, more than 90% of values were available (data not shown). Furthermore, the complete study period covered 1 year, which accounted for a representation of different infectious diseases in all seasons and a large sample size of approximately 1700 episodes. The last patient included was on February 29, 2020 before the start of the coronavirus disease 2019 pandemic in Belgium. Some limitations exist. First, our population is a subset of patients that present to the ED with severe symptoms of infection. Therefore, the extrapolation of these results to all patients with suspected infection at admission is impossible. Second, this is a single-center setting with a low level of

antimicrobial resistance, and the external validity could be limited. However, patient demography, diagnoses of infection, and isolated pathogens from blood are comparable to other similar settings in a high-income country [18, 19]. Third, all parameters were assessed at the start of a new suspected sepsis episode. We did not follow patients during hospitalization, and later events could have affected mortality and ICU admission.

CONCLUSIONS

In conclusion, several independent risk factors for in-hospital mortality, ICU admission, and bacteremia were identified in a population of patients with suspected sepsis at admission. The outcomes are representative of a severe disease course, and these factors can help to identify patients most at risk and guide management and empirical antibiotic therapy. The SOFA score and hyperlactatemia, as defined in the sepsis-3 guidelines, and MAP <70 mmHg are important risk factors for all outcomes. These findings can be of high value in early risk stratification, and they could be used to direct diagnostics and close patient monitoring, leading to earlier therapies in high-risk patients.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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