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ORIGINAL RESEARCH

Two-Year Mortality and Prognostic Factors in Sepsis: A Prospective Cohort Study of 714 Danish Emergency Department Patients

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Objective: Given the lack of data on long-term outcomes among patients with sepsis, this study aimed to examine all-cause 2-year mortality and factors associated with mortality in adults admitted to an emergency department with sepsis.

Study Design: Prospective cohort study.

Methods: This study included all emergency department patients admitted with sepsis to Slagelse Hospital, Denmark, between October 1, 2017, and March 31, 2018. Data on patients with infectious diseases was prospectively extracted from electronic health records during the study period. Sepsis was defined as a Sequential Organ Failure Assessment (SOFA) score ≥ 2 from baseline. The outcome was 2-year all-cause mortality. The Kaplan-Meier method was used to estimate the mortality. Cox regression analyses were used to compute adjusted hazard ratios (aHR) with 95% confidence intervals for prognostic factors associated with mortality.

Results: A total of 714 patients (58.4% men) with a median age of 75 years were diagnosed with sepsis. After two years, 354 (49.6%; 45.9–53.3) patients had died. Factors associated with elevated mortality risk included age (< 65 years as reference) 65–85 years (aHR 1.89; 1.35–2.64) or age > 85 years (aHR 2.99; 2.07–4.31); SOFA score > 4 (aHR 2.45; 1.82–3.30) (score of 2 as reference); and history of malignancy (aHR 1.91; 1.44–2.53), ischemic heart disease (aHR 1.38; 1.03–1.84), dementia (aHR 1.84; 1.34–2.53), previous sepsis admission (aHR 1.45; 1.15–1.82), new-onset atrial fibrillation (aHR 1.56; 1.05–2.34), and mildly decreased (6.9–7.9 mmmol/L) hemoglobin values (aHR 1.68; 1.29–2.19) and significantly decreased (<6.9 mmol/L) hemoglobin values (aHR 2.30; 1.74–3.02) with normal range (≥ 8mmol/L) as reference. Skin infection was associated with diminished mortality risk (aHR 0.50; 0.29–0.85) compared to patients with other sources of infection.

Conclusion: Sepsis is associated with a poor prognosis. Our findings underscore the prognostic effects of age, SOFA score, and specific comorbidities on 2-year mortality among patients with sepsis.

Keywords: sepsis, prospective cohort study, 2-year mortality, prognostic factors

Introduction

Sepsis is characterized by a dysregulated immune response to infection leading to life-threatening organ failure and assessed by an increase in the Sequential Organ Failure Assessment (SOFA) score.[1–4] A parsimonious method for determining SOFA, quick SOFA (qSOFA), has been suggested in the Sepsis-3 definitions of sepsis as a prompt to identify possible sepsis.[1,4] However, the international guidelines from 2021 for the management of sepsis and septic shock recommend against using qSOFA instead of the National Early Warning Score (NEWS),[5] systemic inflammatory response syndrome (SIRS) criteria[6,7] or Modified Early Warning Score (MEWS).[8]

Several studies have examined the epidemiology of sepsis and found considerable variation in its incidence and prognosis.[9–15] This variability has been attributed to the heterogeneity in study designs, data sources, and sepsis definitions.

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These limitations have challenged the research in sepsis epidemiology.[13,16] The World Health Organization (WHO) has emphasized the lack of long-term outcome data for patients with sepsis and advocates for prospective studies using chart or electronic health records (EHRs) as the preferred method for evaluating sepsis epidemiology.[13] With the present study, we have followed up on this call to carry out sepsis prognosis studies based upon prospectively collected EHR data.

We have previously published in-hospital and 28-day mortality data from a prospective study of patients admitted to the emergency department (ED) with sepsis.[15] There is a need for data on the long-term prognosis and prognostic factors for sepsis. Therefore, this study was aimed at examining 2-year mortality and factors associated with mortality in adult ED patients with sepsis.

Materials and Methods

Study Design and Settings

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[17] We included patients from a prospective observational cohort study at Slagelse Hospital, Denmark.[18] That study was aimed at determining sepsis incidence and prognosis and validating new Sepsis-3 criteria for identifying adult patients with sepsis admitted to the hospitals' ED between October 1, 2017, and March 31, 2018.[15,18]

Slagelse Hospital, a tertiary care center, serves a catchment area of 198,000 adults and handled approximately 26,500 annual ED visits at the time of the study. In Denmark, the healthcare system ensures free treatment access for all citizens.[19]

Patient Selection

The method for identifying the overall cohort of patients with suspected or documented infections, the sepsis treatment protocol, inclusion and exclusion criteria, and the data collection process have been thoroughly documented in prior reports.[15,18,20]

Sepsis was diagnosed according to the fulfillment of at least two SOFA criteria involving changes from the baseline SOFA scores.[1]

Inclusion and Exclusion Criteria

Patients with sepsis were included among all patients admitted during the study period with either suspected or documented infection and treated with intravenous or peroral antibiotics within 24 hours after ED admission and continued the treatment for at least 48 hours thereafter. Patients who were discharged within 48 hours of receiving antibiotics in the ED and continued treatment after discharge were also included. Foreign status, prophylactic antibiotic treatment in relation to surgery, discontinuation of antibiotic treatment within 48 hours after admission, missing data and registration error, and transfer to or from other hospitals caused exclusion from the overall infection cohort.[21] Patients were only included once; subsequent admissions during the study period did not result in re-inclusion.

Data Collection

After ED admission, all patients were triaged by a nurse; the process included documentation of vital signs and a brief acute medical history on separate registration forms. Daily reviews of these forms and EHRs were conducted by the authors (OBA and RHS), and a database with information on patients with suspected or documented infection was constructed.[20] The extracted data from this database used in the present analyses included arrival data on age, sex, sepsis admission within the last year before the index admission, ED arrival time, mental status (Glasgow Coma Scale (GCS) or Alert Voice Pain Unresponsive (AVPU) score), systolic blood pressure, respiratory rate, heart rate, temperature, white blood cell counts, peripheral oxygen saturation, C-reactive protein (CRP), creatinine, bilirubin, platelet count, lactate and heart rhythm on the electrocardiogram. Information on comorbidities was extracted from the database based on diagnoses categorized according to the Charlson Comorbidity Index (CCI). For the primary analyses, diabetes was treated as a single category, regardless of the presence of organ complications. However, the underlying data included CCI details reflecting organ involvement, which allowed us to perform a post hoc sensitivity analysis stratifying diabetes into uncomplicated and complicated forms. Additionally, we obtained information on the results of other examinations (eg

x-ray, ultrasound, computed tomography), infection source, and the discharge time. Infection source information was obtained through a thorough review of treating physicians' documentation in the EHRs.

Outcome

Mortality data, time of death, and emigration until March 15, 2020, were collected from the Danish Civil Registration System.[22]

SOFA Score

All patients without any preexisting chronic organ dysfunction defined by the CCI before the onset of infection that might influence the SOFA score calculation after arrival to the ED were assigned a baseline SOFA score of 0 according to The Third International Consensus Definitions for Sepsis and Septic Shock.[1] Patients with varying baseline degrees of organ failure (respiratory, kidney, liver, or neurological (dementia) conditions) that might potentially affect the SOFA score at ED admission had their baseline SOFA scores adjusted according to a method that we have previously described and reproduced from Bin Abdullah in Supplementary Methods.[20] Because we lacked valid data on thrombocytopenia before admission, the SOFA score at baseline was not adjusted for this condition.

Definitions

Patients with chronic diseases were classified with the CCI score,[23] according to information available in the EHRs. Disease severity was categorized into three levels: low (CCI score 0), moderate (CCI score 1–2), or high (CCI score $\geq$ 3).

New onset atrial fibrillation (NOAF) was defined as episodes of atrial fibrillation, as documented on a 12-lead electrocardiogram at admission, and an absence of prior history of atrial fibrillation.

Statistical Analysis

The primary outcome was all-cause mortality within a 2-year follow-up period from the arrival time of the index admission. Patients were followed from the date of index admission until the end of the follow-up period, emigration or death, whichever came first.

Continuous data are presented as medians with interquartile ranges (IQRs), and proportions are presented with 95% confidence intervals (CIs). Exact differences in proportions with 95% CIs were used to compare groups.

We conducted a Kaplan-Meier survival analysis to compute the survival probabilities over a two year period for patients with sepsis, stratified by baseline SOFA scores to reflect varying severity. The differences in survival probabilities across groups were assessed with the log-rank test.

Unadjusted and adjusted hazard ratios (HRs and aHRs) with 95% CIs were calculated with bivariate and multivariate Cox proportional hazard models, respectively.

The specific chronic diseases were included individually in the regression models. A post hoc sensitivity analysis of diabetes was performed by stratifying diabetes into uncomplicated diabetes with no organ damage and complicated diabetes with organ damage. Creatinine, bilirubin, platelets, chronic kidney and liver diseases were not included in the models since the SOFA score integrates information on these parameters into its calculation. Heart failure was assumed to be a potential mediator between ischemic heart disease and mortality and was, therefore, not included in the full model. Devices, central nervous system, endocarditis, facial and teeth as the origin of infections were not included in the regression models due to fewer than five observations in each group.

Variables showing increased HR >1.2 in the crude analysis were included in a full regression model. This model examined the effect of each potential prognostic factor on the 2-year mortality while adjusting for all other variables included in the model.

The validity of the proportional hazards assumption was verified with plots of the log(-log) survival curves and the Global test based on Schoenfeld residuals. Including age as a continuous variable in the Cox models violated the proportional hazards assumption. Therefore, age was stratified into three groups (< 65, 65–85, or > 85 years). SOFA was stratified into three severity score levels (2, 3–4, or > 4) in all models. CRP, white blood cell counts, and hemoglobin were also stratified in three groups based on clinical relevance.

The number of missing lactate values was assumed to be non-random and too high (42%) for inclusion in multiple imputation models; therefore, lactate values were excluded from the analyses. Other missing laboratory variables constituted less than 5% of the data and were ignored in the analyses.

Stata 17.1 SE was used for all analyses (StataCorp, College Station, Texas, USA).

Results

The Sepsis Cohort

The total number of patients (N=12,092) admitted to the ED, the number of patients (N=3176) with suspected infections, the number of excluded patients (N=1066), and the reasons for exclusion among the overall infection cohort patients have previously been reported.[21] Among the remaining 2110 patients, a total of 714 patients (58.4% men) with a median age of 75.2 (IQR 66.2–84.1) years met the SOFA criteria for sepsis and were included in the present study.

Baseline Characteristics

Baseline characteristics are shown in Table 1. The patient population consisted of relatively older individuals, predominantly men. A total of 22.6% of patients were older than 85 years. One-fourth had at least three comorbidities. Heart

Table 1 Baseline Characteristics Among 714 Patients Admitted to the Emergency Department with Sepsis

Female sex, n (%)	297 (41.6)
Age; years, median (IQR)	75.2 (66.2–84.1)
< 65 years, n (%)	168 (23.5)
65–85 years, n (%)	385 (53.9)
>85 years, n (%)	161 (22.6)
Comorbidities, n (%)	
Charlson Comorbidity Index	
0	175 (24.5)
1–2	350 (49.0)
3+	189 (26.5)
Heart failure	110 (15.4)
Ischemic heart disease[a]	95 (13.3)
Cerebrovascular disease[b]	128 (17.9)
Chronic pulmonary disease	174 (24.4)
Diabetes[c]	152 (21.3)
Malignancy[d]	100 (14.0)
Chronic kidney disease[e]	61 (8.5)
Chronic mild or severe liver disease	14 (2.0)
Dementia	66 (9.2)
Hypertension	260 (36.4)
Pacemaker/Implantable cardioverter defibrillator	31 (4.3)
Previous admission with sepsis, n (%)	214 (30.0)
Severity of disease upon admission	
Systolic blood pressure; mmHg, median (IQR)	124 (106–145)
Systolic blood pressure ≤90 mmHg, n (%)	49 (6.9)
Respiratory rate; min^{-1}, median (IQR)	20 (17–24)
Heart rate; min^{-1}, median (IQR)	92 (72–108)
O_2-Saturation; %, median (IQR)	95 (93–97)
Core temperature; ° Celcius, n (%)	
Normothermia (36.1–38.0 °C)	454 (63.6)
Hyperthermia (>38.0 °C)	216 (30.3)
Hypothermia (<36.1 °C)	44 (6.1)
Altered mental state; n (%)	196 (27.5)

(*Continued*)

Table 1 (Continued).

Total SOFA score upon admission, median (IQR; range)	3 (2–4; 2–10)
Score 2, n (%)	337 (47.2)
Score 3–4, n (%)	282 (39.6)
Score >4, n (%)	94 (13.2)
Atrial fibrillation, n (%)	
None	536 (75.1)
A history of atrial fibrillation	140 (19.6)
New onset atrial fibrillation	38 (5.3)
Length of stay, days, median (IQR)	6 (4–10)
Laboratory results	
Hemoglobin; mmol/L, median (IQR)	8 (8.6–16.4)
Normal range (≥8.0 mmol/L)[f], n (%)	359 (50.3)
Mildly decreased (6.9–7.9 mmol/L)[g], n (%)	198 (27.7)
Significantly decreased (< 6.9 mmol/L)[h], n (%)	157 (22.0)
CRP; median mg/L (IQR)[i]	78 (23–148)
Normal range (<10 mg/L), n (%)	78 (10.9)
Moderately elevated (10–100 mg/L), n (%)	352 (49.4)
Highly elevated (> 100 mg/L), n (%)	283 (39.7)
White blood cell counts $x10^9$/L; median (IQR)	11.8 (8.6–16.4)
Normal range (4.0–10.0 x 10^9 cells/L), n (%)	239 (33.5)
Decreased (< 4.0×10^9 cells/L), n (%)	20 (2.8)
Elevated (> 10.0×10^9 cells/L), n (%)	455 (63.7)
Creatinine; µmol/L, median (IQR)	114 (76–175)
Bilirubin; mmol/L, median (IQR)[j]	10 (7–17)
Platelets; $x10^9$/L, median (IQR)[k]	213 (148–290)
Lactate; mmol/L, median (IQR)[l]	1.3 (0.9–2.1)
Source of infection, n (%)[m]	
Lungs	423 (59.2)
Urine	157 (22.0)
Abdomen	71 (9.9)
Wounds/skin	48 (6.7)
Endocarditis	3 (0.4)
Central nervous system	5 (0.7)
Devices	1 (0.1)
Facial, teeth, others	2 (0.3)
Other	3 (0.4)
Unknown	60 (8.4)

Notes: [a]Myocardial infarction or other ischemic heart disease prior to admission. [b]History of cerebrovascular disease, including transient ischemic attacks. [c]Uncomplicated or end-organ damage. [d]Tumor without metastasis, leukemia, lymphoma, or metastatic tumors. [e]Mild or severe kidney disease. [f]12.9 g/dl. [g]11–12.8 g/dl. [h]< 11 g/dl. [i]1 missing. [j]11 missing. [k]2 missing. [l]301 missing. [m]Some patients had more than one focus of infection.
Abbreviations: CI, confidence interval; CRP, C-reactive protein; ICD, Implantable Cardioverter Defibrillator; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment.

failure, ischemic heart disease, cerebrovascular diseases, hypertension, chronic lung disease, dementia, and malignant diseases were relatively common chronic conditions, and almost one-third had been hospitalized with sepsis within the last year before the index admission (Table 1).

A total of 49 (6.9%) patients had a systolic blood pressure below 90 mmHg at admission to the ED, and 44 (6.1%) experienced hypothermia (< 36.1 °C). More than half the patients had a SOFA score above two, and 13.2% had a SOFA score of above four at ED arrival (Table 1). A total of 38 (5.3%) patients had NOAF. The median duration of hospitalization was 6 days (IQR 4–10). Most patients' infection foci were in the lungs (59.2%), genitourinary system (22.0%), or gastrointestinal system (9.9%) (Table 1).

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Outcomes

A total of 354 (49.6%, 95% CI 45.9–53.3) patients died within the 2-year follow-up period (Table 2). The 3-month and 1-year mortality were 23.2% (95% CI 20.2–26.5) and 38.4% (95% CI 35.0–42.1), respectively (Table 2). The 2-year mortality was 38.7% (33.7–44.0) and 60.9% (55.3–65.8) (difference 22.2; 15.0–29.4) among patients with baseline SOFA scores of 0 (n=361) and SOFA scores > 0 (n=353), respectively. The Kaplan-Meier survival curves clearly indicated that the presence of any degree of organ dysfunction (as indicated by a SOFA score > 0) at baseline was associated with poorer survival than the absence of baseline organ dysfunction (p<0.001) (Figure 1).

Prognostic Factors for 2-Year Mortality

The 2-year mortality according to baseline characteristics, and HRs for mortality in the long-term follow-up period are shown in Table 3. Cox regression analysis revealed that the following variables were associated with 2-year mortality: age 65–85 years (aHR 1.89; 1.35–2.64), age > 85 years (aHR 2.99; 2.07–4.31), SOFA score > 4 at admission (aHR 2.45; 1.82–3.30), dementia (aHR 1.84; 1.34–2.53), malignancy (aHR 1.91; 1.44–2.53), prior sepsis admission (aHR 1.45; 1.15–1.82), ischemic heart disease (aHR 1.38; 1.03–1.84), NOAF (aHR 1.56; 1.05-2.34), and mildly decreased (6.9–7.9 mmmol/L) hemoglobin values (aHR 1.68; 1.29–2.19) and significantly decreased (<6.9 mmol/L) hemoglobin values (aHR 2.30; 1.74–3.02). Additionally, a SOFA score > 4 was associated with 2-year mortality (aHR 1.86; 1.27–2.74) in a model limited to patients who survived for the first 28 days after admission. There was a trend toward lower 2-year mortality in female patients compared to males, but the estimate was imprecise (aHR 0.82; 95% CI: 0.66–1.03). The hazard of 2-year mortality was 50% lower among the patients with skin infection as the source of sepsis compared to those with other sources of infection after adjusting for other variables in the model (Table 3).

We conducted a sensitivity analysis to stratify diabetes into uncomplicated (no organ damage) and complicated (with organ damage) diabetes. Uncomplicated diabetes was not associated with mortality (aHR 0.98; 0.74–1.31), while diabetes with complications (with organ damage) showed an increased risk (aHR 1.47; 0.94–2.31) of 2-year mortality, however, with an imprecise estimate.

Discussion

Around half the patients admitted to the ED with sepsis had died within two years. The most important prognostic factors were high age; SOFA score > 4; new onset atrial fibrillation, a history of malignant disease, ischemic heart disease, dementia, anemia, and previous sepsis admission. Skin infections were associated with a reduced risk of mortality.

Our findings expanded on existing literature. Most long-term mortality studies extending beyond one year have relied on retrospective data, including ICU records, insurance claims, registry-based data sources, and International Classification of Diseases (ICD) discharge codes to identify patients with sepsis.[13,24–31] Those studies have reported 5-year mortality rates of 37%–74%. However, using hospital administrative data and ICD discharge codes for sepsis identification, as well as retrospective data collection, has disadvantages with respect to real-time, prospective data collection based on EHRs.[13,16] ICD codes and administrative data might not precisely capture the clinical picture of sepsis and might be biased. Sepsis-specific codes underestimate sepsis prevalence, whereas combining infection and organ dysfunction codes might lead to overestimation.[13] Therefore, more studies on long-term mortality after sepsis must be conducted with prospectively collected clinical information and investigation of prognostic factors. By focusing on

Table 2 Outcomes Among 714 Patients Admitted to the Emergency Department with Sepsis

Outcomes	
Primary, n (%, 95% CI)	
2-year mortality	354 (49.6; 45.9–53.3)
Secondary, n (%, 95% CI)	
3-month mortality	166 (23.2; 20.2–26.5)
1-year mortality	274 (38.4; 35.0–42.1)

Abbreviation: CI, confidence interval.

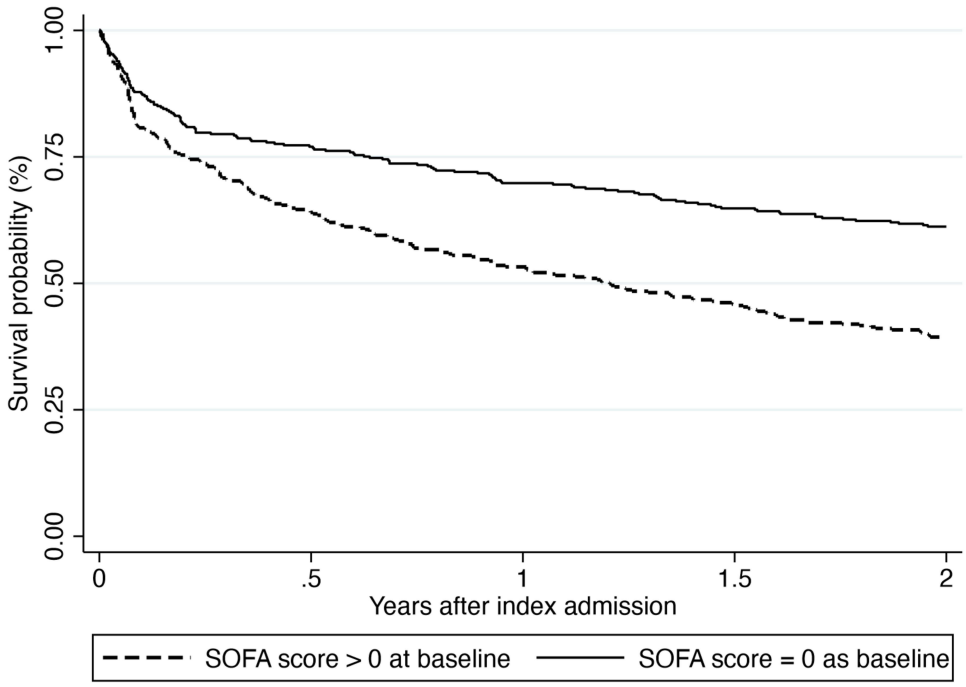

Figure 1 Kaplan–Meier estimates of 2-year survival probability among patients admitted with sepsis, stratified by baseline SOFA score status (p<0.001, Log rank test).

long-term all-cause mortality and providing long-term mortality prognostic data based on a prospective study with controlled real-time data collection from EHRs, our study addresses a gap in understanding of sepsis epidemiology.[13]

Our findings revealed that, with respect to the reference group, patients 65–85 years of age had an 89% higher risk of 2-year mortality, and patients older than 85 years had almost three times the risk. This finding highlights a strong age-associated gradient in long-term mortality risk, which agrees with clinical expectations and previous studies.[27–29]

Table 3 2-year Mortality, Crude and Full Cox Regression Model for Mortality Among 714 Patients Admitted to an Emergency Department with Sepsis

	Mortality (%; 95% CI)	**Crude HR (95% CI)**	**Adjusted[a] HR (Full Model) (95% CI)**
Sex			
Male	52.0 (47.1–56.9)	Reference	Reference
Female	46.1 (40.4–52.0)	0.85 (0.68–1.05)	0.82 (0.66–1.03)
Age			
< 65 years	26.8 (20.3–34.2)	Reference	Reference
65–85 years	50.7 (45.5–55.8)	2.28 (1.65–3.15)	1.89 (1.35–2.64)
>85 years	70.8 (63.1–77.7)	3.63 (2.57–5.14)	2.99 (2.07–4.31)
Comorbidities			
Ischemic heart disease	63.2 (52.6–72.8)	1.59 (1.20–2.10)	1.38 (1.03–1.84)
Cerebrovascular disease	56.3 (47.2–65.0)	1.25 (0.97–1.68)	1.06 (0.80–1.39)
Chronic pulmonary disease	54.0 (46.3–61.6)	1.15 (0.91–1.45)	–
Diabetes	53.3 (45.0–61.4)	1.14 (0.89–1.46)	–
Malignancy	75.0 (65.3–83.1)	2.16 (1.67–2.78)	1.91 (1.44–2.53)
Dementia	79.8 (67.0–87.9)	2.18 (1.62–2.93)	1.84 (1.34–2.53)
Hypertension	49.8 (42.6–55.1)	0.97 (0.78–1.20)	–
Pacemaker/Implantable cardioverter defibrillator	54.8 (36.0–72.7)	1.17 (0.72–1.90)	–
Previous admission with sepsis	61.2 (54.3–67.8)	1.65 (1.33–2.04)	1.45 (1.15–1.82)

(*Continued*)

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Table 3 (Continued).

	Mortality (%; 95% CI)	Crude HR (95% CI)	Adjusted[a] HR (Full Model) (95% CI)
Severity of disease upon admission			
SOFA score 2	43.6 (38.3–49.1)	Reference	Reference
SOFA score 3–4	49.1 (43.2–55.1)	1.20 (0.95–1.51)	1.15 (0.91–1.46)
SOFA score >4	72.3 (62.2–81.1)	2.43 (1.83–3.25)	2.45 (1.82–3.30)
Atrial fibrillation			
None	46.5 (42.2–50.8)	Reference	Reference
A history of atrial fibrillation	55.7 (47.1–64.1)	1.21 (0.94–1.57)	1.00 (0.77–1.31)
New onset atrial fibrillation	71.1 (54.1–84.6)	2.01 (1.35–3.00)	1.56 (1.05–2.34)
Laboratory results			
CRP			
Normal range (<10 mg/L)	47.1 (35.1–59.4)	Reference	Reference
Moderately elevated (10–100 mg/L)	55.8 (50.5–61.0)	1.32 (0.91–1.90)	1.11 (0.75–1.63)
Highly elevated (> 100 mg/L)	42.3 (36.4–48.2)	0.92 (0.63–1.35)	0.75 (0.50–1.12)
White blood cell counts			
Normal range (4.0–10.0 x 10^9 cells/L)	52.7 (46.2–59.2)	Reference	–
Decreased (< 4.0×10^9 cells/L)	45.0 (23.0–68.5)	0.87 (0.44–1.71)	–
Elevated (> 10.0×10^9 cells/L)	48.1 (43.5–52.8)	0.88 (0.70–1.09)	–
Hemoglobin			
Normal range (≥8.0 mmol/L)[b]	35.7 (30.7–40.9)	Reference	Reference
Mildly decreased (6.9–7.9 mmol/L)[c]	59.1 (51.9–66.0)	1.97 (1.53–2.53)	1.68 (1.29–2.19)
Significantly decreased (<6.9 mmol/L)[d]	69.4 (61.6–76.5)	2.62 (2.03–3.39)	2.30 (1.74–3.02)
Source of infection[e]			
Lungs	49.2 (44.3–54.0)	0.99 (0.80–1.22)	–
Urine	56.1 (47.9–64.0)	1.25 (0.99–1.60)	1.10 (0.86–1.40)
Abdomen	42.3 (30.6–54.6)	0.78 (0.54–1.14)	–
Wounds/skin	31.3 (18.7–46.3)	0.51 (0.31–0.87)	0.50 (0.29–0.85)
Unknown	53.3 (40.0–66.3)	1.10 (0.77–1.59)	–

Notes: [a]The model examined the effect of each potential prognostic factor on the 2-year mortality while controlling for all other variables included. [b]12.9 g/dl. [c]11–12.9g/dl. [d]< 11 g/dl. [e]Devices, Central Nervous System, Endocarditis, Facial-Teeth-Others not included due to less than five observations in each group.

Abbreviations: CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; SOFA, sequential organ failure assessment.

We observed a trend toward lower 2-year mortality in female patients compared to males, which aligns with prior studies suggesting modest sex-related differences in outcomes among patients with infectious diseases and sepsis.[21,28]

In general, baseline health status, particularly organ function, as measured by the baseline SOFA score, affected patient outcomes in terms of survival over the two years, and a SOFA score > 4 points above baseline was associated with a risk of death more than twice that of the reference group. This elevated risk of mortality was also observed in a model including only patients who survived for the first 28 days. Therefore, assessment of the degree of organ dysfunction in patients with sepsis should be considered in future long-term mortality studies. Furthermore, investigating the effects of sepsis-associated organ failure and the degree of severity on mortality, as well as worsening organ failure after discharge and consequent effects on prognosis, may be relevant.

Patients with a history of dementia had an aHR of 1.84, thus indicating a significantly elevated likelihood of dying during the follow-up. Similar findings have been reported in a Veterans Affairs Administrative study.[25] Our data did not allow for a thorough investigation of the mechanisms underlying the elevated risk in patients with dementia. Therefore, further research is required to clarify these mechanisms. Several prognostic factors in dementia have been identified,[32–35] and examining their roles in sepsis outcomes in patients with dementia, as well as the risk of dementia development after sepsis, would be valuable, as suggested in some studies.[36,37] Outcome prediction models such as the Advanced Dementia

Prognostic Tool model incorporate different clinical and patient characteristics in advanced dementia,[38] although not developed among patients with infectious diseases and sepsis, might also be helpful to consider in future research.

Patients with malignant diseases are a diverse group with various types of cancer. We lacked detailed information on the duration of the disease, stage, and treatment. However, in agreement with other long-term sepsis research findings, these patients expected a significantly elevated risk of long-term mortality.[27] Along with other comorbidities,[27,28] particularly ischemic heart disease, anemia and diabetes with complications, as shown in the present study, as well as heart failure,[39] patients with malignant diseases should be included in the development of mortality prediction models. The sensitivity analysis of diabetic patients underscores that not all patients with diabetes have the same risk profile, and future studies may benefit from incorporating more detailed disease severity categories.

Patients hospitalized with sepsis have an elevated risk of rehospitalization with infection and sepsis.[40] An immunosuppressive phase is typical after hospital discharge and is a component of post-sepsis syndrome (PSS), a combination of physical, medical, cognitive, and psychological conditions following sepsis.[40] The high rate of fatal infections and recurrent sepsis might be associated with PSS and enhanced susceptibility to new infections.[40] We have previously demonstrated that prior hospitalization for sepsis within one year before the index hospitalization is an independent risk factor for long-term death among patients with suspected bacterial infection.[21] The current findings confirmed the association between previous hospitalization for sepsis and the risk of long-term mortality.

NOAF, but not a history of AF, was associated with an elevated risk of 2-year mortality in the present study. We have previously shown that NOAF at ED admission is associated with an elevated risk of achieving a composite endpoint of in-hospital mortality or ICU transfer.[41] NOAF has also been associated with elevated long-term mortality risk.[42] However, whether NOAF independently affects prognosis or is a marker of disease severity remains unclear.[41] NOAF has been suggested to be an additional sign of organ dysfunction in sepsis.[43] However, the pathophysiological mechanisms of NOAF and the risk of death are complex and not well-defined.[41] The uncertainty regarding the direct effects of NOAF on prognosis and the lack of evidence of specific interventions, such as anticoagulation, underscores the need for further research in this area.

Skin infections were associated with a diminished risk of death. We have previously shown that the proportion of patients with skin infection and signs of organ failure (SOFA ≥ 2) was lower than the proportion of patients with all other infections with organ failure.[21] The better outcomes observed in patients with rather than without skin infections might have been due to the visibility of skin infections, thus enabling early identification and treatment of the infection foci.[21]

Implications

Knowledge of factors associated with mortality shown in the present study may help clinicians stratify patients based on their risk of death. However, it is recommended that new prospective studies be conducted aimed at validating our findings. Furthermore, the increased mortality among patients with ischemic heart disease and dementia should be examined in new studies to investigate the underlying mechanisms behind the poorer survival among these patients. Including other important physical, medical, cognitive, and psychological factors involved in PSS after discharge might improve the regression model and address several knowledge gaps regarding sepsis epidemiology.[13,40]

Notably, we used all-cause mortality as the primary outcome. Patients with sepsis are often frail older individuals with several comorbidities, and some of the deaths might potentially not have been directly attributable to PSS.[44] Consequently, further research is needed to clarify the exact numbers of long-term deaths that might have been caused by sepsis and PSS and the number of preventable deaths.

Strengths and Limitations

The studys' prospective design enabled standardized data collection and minimized the risk of selection and referral bias. Complete follow-up was ensured by linkage of the patients' unique personal identification numbers in the Danish Civil Registration System to the vital status data for all Danish citizens. Using EHRs enabled us to obtain detailed and real-time data on patient demographics, clinical variables, treatment, and outcomes.

This study has several limitations. First, we cannot exclude the possibility that some ED patients with infections might have been misclassified. The diagnosis of infection, either suspected or proven, relied on the delivery of antibiotics

within a given period, as ordered by the attending physicians and supervised by a senior physician. However, disagreements and lack of consensus among physicians regarding the diagnosis and source of infection have been reported to occur, and a gold standard biomarker to confirm the diagnosis remains lacking.

Second, we used only the admission variables to calculate the SOFA score. Serial SOFA measurements might have detected more patients meeting the criteria for sepsis and resulted in an underestimation of sepsis prevalence. Third, the SOFA corrections were performed retrospectively, and the information on chronic diseases was based on diseases registered in the CCI system. We lacked precise information on chronic disease severity before admission, and in the absence of pre-admission cognitive or neurological function, we used a history of dementia as a proxy to adjust the neurological component of the SOFA score at baseline. While this approach could be clinically reasoned and aligned with our overall correction method, it has not been externally validated and may have introduced some misclassification. Furthermore, we lacked precise information on thrombocytopenia before admission. Consequently, we were unable to adjust for chronic thrombocytopenia. Therefore, we cannot exclude potential misclassification of patients according to SOFA scores.

Fourth, we might have underestimated the prevalence of NOAF. This study was not designed to capture all patients with NOAF, because only the arrival ECG findings were analyzed for arrhythmias. However, patients may develop NOAF in the first days after admission to the ED.[41] Fifth, we have only recorded CRP and white blood cell counts upon arrival at the ED. These infection parameters may have changed significantly during the hospitalization, which we have not included in our analyses. Sixth, the variables included in the regression analyses are not necessarily exhaustive. We lacked information on functional status and frailty before admission, which could be potential predictors of mortality after sepsis. Finally, the relatively small sample size might have decreased the reliability of some estimates and restrict the complexity of our models. Specifically, we did not include interaction terms between prognostic factors. Although interactions—such as between age, comorbidities, and SOFA score—might influence outcomes, exploring them in this study would risk overfitting, reduced statistical power, and interpretative complexity. Future studies with larger sample sizes should address these interactions to refine prognostic models.

Conclusion

Around half of all patients admitted to our ED with sepsis died within a maximum follow-up period of 2 years. Age $\geq$ 65 years; SOFA score > 4; and history of malignant disease, ischemic heart disease, dementia, new-onset atrial fibrillation, anemia, and previous sepsis admission were prognostic factors for 2-year mortality. Skin infections were associated with diminished mortality risk.

Abbreviations

aHR, Adjusted hazard ratio; CCI, Charlson comorbidity index; CI, Confidence interval; ED, Emergency department; EHR, Electronic health record; HR, Hazard ratio; ICD, International Classification of Diseases; IQR, Interquartile range; NOAF, New onset atrial fibrillation; ICU, Intensive Care Unit; PSS, Post sepsis syndrome; SOFA, Sequential organ failure assessment; WHO, World Health Organization.

Data Sharing Statement

The dataset used and/or analyzed during the current study is available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study was reported to the Danish Data Protection Agency (REG-105-2017). The accessed data complied with relevant data protection and privacy regulations. On May 16, 2017, the study was defined as a quality project by the Secretariat of the Committee on Health Research Ethics of Region Zealand. Therefore, it was not covered by the Committee Act and was not obligated to report to the ethics committee system. Administrative permission to access the data was accepted on September 25, 2018, from the head of the Slagelse Hospital Administration. The data were anonymized. The data are stored electronically on Slagelse Hospital's SharePoint Team Site under the responsibility of the emergency department's research leader. Only the research leader and the authors (FEN, OBA, and RHS) can access the data.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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