Intermediate-term and long-term mortality among acute medical patients hospitalized with community-acquired sepsis: a population-based study

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Objective **Admission with severe sepsis is associated with an increased short-term mortality, but it is unestablished whether sepsis severity has an impact on intermediate-term and long-term mortality following admission to an acute medical admission unit.**

Patients and methods **This was a population-based study of all adults admitted to an acute medical admission unit, Odense University Hospital, Denmark, from September 2010 to August 2011, identified by symptoms and clinical findings. We categorized the mortality periods into intermediate-term (31–180 days) and long-term (181–365, 366–730, and 731–1096 days). Mortality hazard ratios (HRs), comparing patients admitted with sepsis with those of a well-defined background population, were estimated using multivariable Cox regression. HRs were presented with 95% confidence intervals.**

Results **In total, 621 (36.3%) presented with sepsis, 1071 (62.5%) presented with severe sepsis, and 21 (1.2%) presented with septic shock. Thirty-day all-cause mortality for patients with sepsis, severe sepsis, and septic shock was 6.1, 18.8, and 38.1%, respectively. The adjusted HR among patients with sepsis of any severity within the time periods 31–180, 181–365, 366–720, and 721–1096 days was 7.1 (6.0–8.5), 2.8 (2.3–3.5), 2.1 (1.8–2.6), and 2.2 (1.7–2.9), respectively. Long-term mortality was unrelated to sepsis severity [721–1096 days: sepsis HR: 2.2 (1.5–3.2), severe sepsis HR: 2.1 (1.5–3.0)].**

Conclusion **Patients admitted with community-acquired sepsis showed high intermediate-term mortality, increasing with sepsis severity. Long-term mortality was increased two-fold compared with sepsis-free individuals, but might be explained by unmeasured confounding. Further, long-term mortality was unrelated to sepsis severity.** ***European Journal of Emergency Medicine*** **00:000–000**

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Introduction

Severe sepsis is associated with a poor prognosis and a high morbidity [1]. Short-term mortality of patients admitted to the hospital with severe sepsis has been well documented previously in different settings. Although different interventions have proven effective in reducing mortality [2,3], the short-term mortality is estimated to be 30% [1]. Newer large-scale randomized clinical trials have, however, challenged some of the interventions reducing mortality [4–6], but in general, a decrease in mortality rates has been observed the past 10 years [7]. Only a few studies have evaluated the long-term impact of severe sepsis in population-based settings, and they indicate that patients surviving a hospitalization with severe sepsis have 2-year mortality as high as 55% [8,9]. Two studies have previously found a two-fold increased mortality compared with disease-free references up to 5 years after the sepsis admission [9,10]. However, these studies did not distinguish between patients hospitalized with sepsis or severe sepsis, thus making it difficult to attribute the excess risk to the organ dysfunction or the sepsis event itself.

Our aim was to examine the association between sepsis of different severity and long-term mortality in a cohort of patients hospitalized in an acute medical admission unit (AMAU).

Patients and methods

We carried out a population-based cohort study of all patients admitted to an AMAU to describe the long-term mortality up to 3 years after admission with community-acquired sepsis.

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Ethics committee approval

In compliance with Danish law, the study was notified to and approved by the Danish Data Protection Agency (J no. 2008-58-0035) and patient record access was approved by the Danish National Board of Health (J no. 3-3013-35). No ethical approval is required for register-based studies in Denmark [11]. Patient information was anonymized and deidentified before analysis.

Setting

The study was carried out at the AMAU at Odense University Hospital, Denmark, from 1 September 2010 to 31 August 2011. The AMAU served a population of 235 598 adults and served as a medical admission unit for the following medical specialities: general internal medicine, infectious diseases, gastroenterology, geriatric medicine, rheumatology, endocrinology, and respiratory medicine. The AMAU received all acutely admitted medical patients referred either from a primary care physician or from the open general emergency department (ED), where an emergency care physician identified the patients in need of admission. Upon arrival, all patients had their vital signs measured and recorded by the nurses and blood drawn for laboratory analysis as a part of the clinical routine.

Sepsis cohort

The methods of data collection have been described elsewhere in detail [12]. In brief, we manually reviewed electronic medical records of all adult patients (≥15 years) admitted to the AMAU or directly to the medical ICU within the study period to identify the presence of community-acquired infection ($N = 8358$). We used a structured protocol based on the National Healthcare Safety Network criteria [13] in combination with a predefined definition, requiring that the site of infection was clinically evident within the first 48 h after admission. We evaluated these first days of each patient's course of admission a month after the patients were admitted; thus, imaging descriptions and test results were available in the electronic patient files. Some patients presented with symptoms, signs, and paraclinical evidence of infection on the basis of which it was not possible to clearly determine a site of infection. We defined this as 'unknown site of infection'.

Results from the vital signs recorded in the electronic medical records at arrival to the hospital were extracted from the records to identify the presence of systemic inflammatory response syndrome and supplemented with data from the hospitals laboratory information systems to identify the presence of organ dysfunction. Patients were categorized as having sepsis, severe sepsis, or septic shock at arrival to the hospital according to the ACCP/SCCM published criteria [14]. We adapted the organ dysfunction criteria to meet the constraints of the registered vital signs in the AMAU, where the PaO_2/FiO_2 was replaced with an oxygen saturation measurement. The adapted organ dysfunction criteria were based on previously validated definitions based in ED settings [15–17] (Appendix 1, Supplemental digital content 1, *http://links.lww.com/EJEM/A107*).

As patient populations, microbial spectrum, and outcomes differ between patients admitted with community-acquired and hospital-acquired infections [18], we excluded possible hospital-acquired infections by excluding patients with hospitalization up to 7 days before the current admission.

Patients transferred from other hospitals and patients residing outside the hospital's catchment area at the time of admission were also excluded. Patients were included in the sepsis cohort the first time they presented with sepsis of any severity within the study period. The patients in the sepsis cohort were followed for a median 2.2 years [interquartile range (IQR): 0.4–2.6 years], with a total of 2910 person-years of follow-up.

Sepsis-free cohort

To establish a sepsis-free reference cohort, we sampled all adults (≥15 years) with residence in the hospital catchment area ($N = 235\,598$). Each individual was assigned a random cohort entry date during the study period and was included in the cohort if the individual was a resident in the catchment area that day and had not been discharged from a hospital less than 7 days before the random cohort entry date. The 225 341 individuals included in the sepsis-free reference cohort were followed for a median 2.6 years (IQR: 2.4–2.8 years), with a total of 569 977 person-years of follow-up. We chose a density-based sampling method to define the reference cohort as we wanted the reference cohort to resemble the background population as closely as possible. Further, this enabled us to ascertain age and sex as prognostic factors of intermediate-term and long-term mortality, which would not be possible in a matched cohort design.

Data sources

Data were supplemented by information from the Danish National Patient Register [19], Odense Pharmacoepidemiological Database [20], and the Danish National Cancer Register, as well as the Danish National Alcohol Treatment Register, with the aim of identifying patients with comorbidity, adapted from definitions proposed by Charlson *et al.* [21], immunosuppression and alcoholism-related conditions. A more detailed description of the adapted comorbidity score has been published elsewhere previously [22]. Data on birth, deaths, and migration status were obtained from the Civil Registration System in Denmark [23]. Definitions of comorbidity, immunosuppression, and alcoholism-related conditions are presented in Appendix 1 (Supplemental digital content 1, *http://links.lww.com/EJEM/A107*).

Analysis

Data were presented as medians with IQR or proportions with 95% confidence intervals (CIs) calculated under the assumption of a binomial distribution. For incidence rates, 95% CIs were calculated under the assumption of a Poisson distribution of the outcome. Both cohorts were followed until death, emigration, or 1 September 2013 (end of study period), whichever came first. Individuals in the sepsis-free cohort were also censored upon hospitalization with sepsis of any severity. Long-term mortality among patients hospitalized with sepsis, severe sepsis, and septic shock was presented in a Kaplan–Meier plot and comparisons between groups were performed using a log-rank test.

Follow-up was divided into short term (0–30 days), intermediate term (31–180 days), and long term (181–365, 366–730, and 731–1096 days). Cumulative all-cause mortality proportions were calculated for patients with sepsis, severe sepsis, septic shock, and sepsis of any severity for each segment of follow-up.

We presented three Cox proportional hazard regression models where the outcome of interest was all-cause mortality within each segment of follow-up and exposure of interest was admission with sepsis, severe sepsis, and sepsis of any severity: (i) an unadjusted analysis, (ii) a multivariable analysis adjusted for sex and age in age categories, (iii) a multivariable analysis adjusted for age in age categories, sex, alcoholism-related conditions, immunosuppression, and the accumulated number of comorbidities.

We did not carry out multivariable Cox regression analysis in the septic shock category because of the low number of events [24]. In all instances, the Cox regression model included a category of sepsis patients and used the sepsis-free cohort as a reference. For each segment of follow-up, the hazard ratios (HRs) were calculated conditional on survival in the previous segment.

The proportional hazards assumption was checked for each sepsis category by visual inspection of log–log plots of survival and by the method described by Grambsch and Therneau [25] using the scaled Schoenfeld residuals. We found no violations of the proportional hazard assumptions.

Statistical analyses were carried out using Stata (version 13.1; Stata Corporation LP, College Station, Texas, USA).

Results

Patient characteristics

We registered 1984 first-time admissions to the AMAU within the study period with sepsis of any severity. We excluded 271 patients because of discharge less than 7 days before inclusion ($N = 143$), the nonvalid personal identification number ($N = 4$), or residence outside of the hospital catchment area ($N = 124$). A total of 1713 patients were included in the sepsis cohort. In total, 621 (36.3%) presented with sepsis, 1071 (62.5%) presented with severe sepsis, and 21 (1.2%) presented with septic shock. The median age of the patients included was 72 years (IQR: 57–81 years) and 793 (46.3%) were men. A detailed presentation of the sepsis cohort is presented in Table 1.

Transfer to the intensive care unit

Within the same day and up to a day after admission, 79/1713 (4.6%) of patients with sepsis of any severity presenting to the AMAU were transferred to the ICU (including patients admitted directly to the ICU after a short stay in the open general emergency room): 2/621 (0.3%) of patients presenting with sepsis; 68/1071 (6.4%) of patients with severe sepsis; and 9/21 (42.9%) of patients with septic shock.

A comparison of demographic characteristics among patients admitted to the AMAU with sepsis of any severity (sepsis cohort) and the sepsis-free cohort is presented in Table 2.

Short-term mortality

The mortality curves for patients in the sepsis cohort during the 3 years following hospitalization with sepsis, severe sepsis, septic shock, and sepsis of any severity are presented in Fig. 1. Cumulative all-cause mortality the first 30 days for patients hospitalized with sepsis of any severity was 14.4% (95% CI: 12.8–16.2). We found a significantly higher 30-day mortality for patients hospitalized with severe sepsis and septic shock compared with sepsis [sepsis: 6.1% (95% CI: 4.4–8.3) vs. severe sepsis: 18.8% (95% CI: 16.5–21.2), septic shock: 38.1% (95% CI: 18.1–61.6)].

Intermediate-term mortality

Among patients hospitalized with sepsis of any severity surviving the first 30 days after admission, the adjusted HR was 7.1 (95% CI: 6.0–8.5) within the time period 31–180 days. The adjusted HR was significantly higher for patients admitted with severe sepsis compared with patients admitted with sepsis [sepsis HR: 3.6 (95% CI: 2.6–4.8), severe sepsis HR: 7.8 (95% CI: 6.5–9.3)].

Long-term mortality

Cumulative all-cause mortality 3 years after hospitalization with sepsis, severe sepsis, and septic shock was 31.4% (95% CI: 27.8–35.2), 50.0% (95% CI: 46.9–53.0), and 71.4% (95% CI: 47.8–88.7), respectively.

The adjusted HRs were unrelated to the degree of sepsis severity among patients surviving the first 2 years after the sepsis event when adjusting for age and sex [sepsis HR: 3.9 (95% CI: 2.6–5.8) vs. severe sepsis HR: 3.8 [95% CI: 2.7–5.3)] as well as when adjusting for age, sex, immunosuppression, comorbidity, and alcoholism-related

Table 1 Characteristics of patients hospitalized with community-acquired sepsis of any severity who survived up to 3 years after admission and those who died

		N (%)		
	Total (*N*)	Survived 3 years	Died within 30 days	Survived 30 days, but died within 3 years
Total	1713	978 (57.1)	247 (14.4)	488 (28.5)
Admission at entry				
Directly to the AMAU[a]	1098	648 (59.0)	141 (12.8)	309 (28.1)
Open general emergency room[b]	590	315 (53.4)	101 (17.1)	174 (29.5)
Directly to the ICU[c]	25	15 (60.0)	5 (20.0)	5 (20.0)
Bacteremia				
No	1541	884 (57.4)	211 (13.7)	446 (28.9)
Yes	172	94 (54.7)	36 (20.9)	42 (24.4)
Sites of infection per patient (*N*)				
1	1453	854 (58.8)	199 (13.7)	400 (27.5)
2	242	112 (46.3)	45 (18.6)	85 (35.1)
3	18	12 (66.7)	3 (16.7)	3 (16.7)
Sites of infection[d]				
Central nervous system	18	13 (72.2)	2 (11.1)	3 (16.7)
Lower respiratory tract	1077	549 (51.0)	174 (16.2)	354 (32.9)
Urinary tract	415	225 (54.2)	61 (14.7)	129 (31.1)
Abdominal	184	119 (64.7)	27 (14.7)	38 (20.7)
Cardiovascular	11	7 (63.6)	2 (18.2)	2 (18.2)
Skin, muscles, bones	98	67 (68.4)	10 (10.2)	21 (21.4)
Viral/systemic	42	37 (88.1)	1 (2.4)	4 (9.5)
Unknown with bacteremia	23	9 (39.1)	8 (34.8)	6 (26.1)
Unknown without bacteremia	75	50 (66.7)	10 (13.3)	15 (20.0)
Other	39	32 (82.1)	2 (5.1)	5 (12.8)
SIRS				
Pulse rate	1314	758 (57.7)	181 (13.8)	375 (28.5)
Temperature	968	631 (65.2)	104 (10.7)	233 (24.1)
Respiratory rate	1071	576 (53.8)	173 (16.2)	322 (30.1)
Leukocyte count	1228	665 (54.2)	203 (16.5)	360 (29.3)
SIRS positive criteria				
2	815	457 (56.1)	112 (13.7)	246 (30.2)
3	641	368 (57.4)	103 (16.1)	170 (26.5)
4	257	153 (59.5)	32 (12.5)	72 (28.0)
Number of organ failures[d]				
0	621	430 (69.2)	38 (6.1)	153 (24.6)
1	651	367 (56.4)	81 (12.4)	203 (31.2)
2	300	141 (47.0)	73 (24.3)	86 (28.7)
3+	141	40 (28.4)	55 (39.0)	46 (32.6)
Site of organ failure				
CNS	333	122 (36.6)	98 (29.4)	113 (33.9)
Metabolic	226	86 (38.1)	71 (31.4)	69 (30.5)
Cardiovascular	100	40 (40.0)	29 (29.0)	31 (31.0)
Respiratory	709	363 (51.2)	124 (17.5)	222 (31.3)
Renal	106	39 (36.8)	35 (33.0)	32 (30.2)
Hepatic	55	30 (54.5)	14 (25.5)	11 (20.0)
Coagulation	209	106 (50.7)	50 (23.9)	53 (25.4)

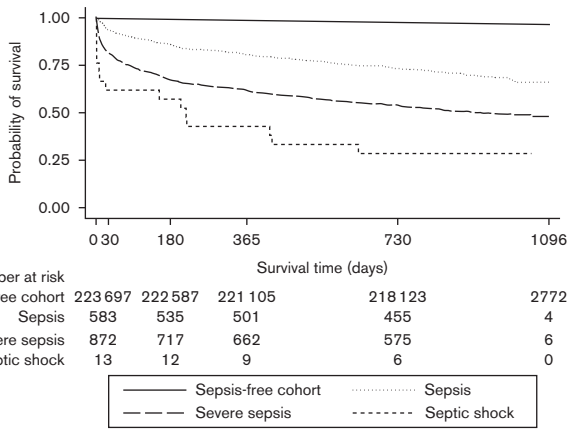
AMAU, acute medical admission unit; CNS, central nervous system; SIRS, systemic inflammatory response syndrome.
[a]Patients admitted directly to the AMAU by their general practitioner.
[b]From the emergency room, where they called the ambulance themselves, and transferred to the AMAU after a short stay in the emergency room.
[c]Transferred to the ICU directly from the emergency room.
[d]The added number of individual sites of infection exceeds the number of patients because one patient could have more than one site of infection or organ failure associated with the admission.

conditions. For a more detailed presentation of the mortality rates, unadjusted, and adjusted HR, see Table 3.

Table 2 Comparison of demographic characteristics among patients admitted to an acute medical admission unit with sepsis of any severity (sepsis cohort) and a sepsis-free reference cohort

	Sepsis of any severity [*N* (%)]	Sepsis-free cohort [*N* (%)]
Total	*n* = 1713	*n* = 225 341
Sex		
Female	920 (53.7)	114 853 (51.0)
Male	793 (46.3)	110 488 (49.0)
Age groups (years)		
15–64	633 (37.0)	178 269 (79.1)
65–84	815 (47.6)	41 481 (18.4)
85+	265 (15.5)	5591 (2.5)
Immunosuppression	355 (20.7)	3556 (1.6)
Alcoholism-related conditions	174 (10.2)	6523 (2.9)
Comorbidities		
Psychotic disorder	163 (9.5)	5914 (2.6)
Neurological	389 (22.7)	9196 (4.1)
Respiratory	507 (29.6)	9346 (4.1)
Cardiovascular	376 (21.9)	8468 (3.8)
Diabetes	255 (14.9)	7744 (3.4)
Cancer	203 (11.9)	8186 (3.6)
Gastrointestinal	180 (10.5)	4330 (1.9)
Renal	82 (4.8)	1713 (0.8)

Fig. 1



Stratified Kaplan–Meier curves for patients hospitalized to the acute medical admission unit over a 1-year period with sepsis, severe sepsis, and septic shock, as well as in survival curves for included sepsis-free individuals.

Discussion

In this large population-based study of intermediate-term and long-term mortality among patients admitted with sepsis of any severity identified by symptoms and clinical findings, we found an increased risk of mortality up to 3 years after the sepsis event. We found that the intermediate-term mortality (31–180 days) was highly influenced by the sepsis severity. However, the severity of the disease had no impact on long-term mortality among patients surviving the 6 months after admission.

As expected, we found that the proportion of patients who were admitted with sepsis of any severity who died within the first 30 days was influenced by the sepsis severity. Previous studies have shown a large variation in

Table 3 Intermediate-term and long-term mortality in patients hospitalized with community-acquired sepsis of any severity compared with a sepsis-free cohort

	Number at start	Died [*N* (%)]	Person-years	Crude n/1000 person-years (95% CI)	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)	Adjusted[b] HR (95% CI)
Intermediate-term mortality							
31–180 days							
Sepsis-free cohort	223 688	901 (0.4)	91 631	10 (9–10)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Sepsis	583	49 (8.4)	228	215 (163–285)	18.8 (14.1–25.0)	7.2 (5.4–9.6)	3.6 (2.6–4.8)
Severe sepsis	870	151 (17.4)	321	470 (401–552)	45.2 (38.1–53.7)	14.5 (12.2–17.3)	7.8 (6.5–9.3)
Septic shock	13	1 (7.7)	5	190 (27–1349)	15.9 (2.2–113.0)	–	–
Sepsis of any severity	1466	201 (13.7)	554	363 (316–417)	36.8 (31.6–42.9)	13.0 (11.1–15.2)	7.1 (6.0–8.5)
Long-term mortality							
181–365 days							
Sepsis-free cohort	222 577	1219 (0.5)	112 367	11 (10–11)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Sepsis	534	34 (6.4)	261	130 (93–182)	11.5 (8.2–16.1)	4.4 (3.2–6.3)	2.5 (1.7–3.5)
Severe sepsis	717	57 (7.9)	347	164 (127–213)	14.7 (11.3–19.2)	4.8 (3.7–6.3)	2.7 (2.1–3.6)
Septic shock	12	3 (25.0)	5	621 (200–1925)	53.7 (17.3–166.8)	–	–
Sepsis of any severity	1263	94 (7.4)	613	153 (125–188)	14.1 (11.5–17.4)	5.0 (4.0–6.2)	2.8 (2.3–3.5)
366–730 days (1–2 years)							
Sepsis-free cohort	221 089	2440 (1.1)	219 475	11 (11–12)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Sepsis	500	45 (9.0)	477	94 (70–126)	8.2 (6.1–11.0)	3.4 (2.5–4.5)	1.7 (1.3–2.3)
Severe sepsis	660	85 (12.9)	611	139 (112–172)	12.3 (9.9–15.3)	4.2 (3.4–5.2)	2.2 (1.8–2.8)
Septic shock	9	3 (33.3)	7	426 (137–1320)	36.6 (11.8–113.5)	–	–
Sepsis of any severity	1169	133 (11.4)	1095	122 (103–144)	10.9 (9.2–13.0)	4.0 (3.4–4.8)	2.1 (1.8–2.6)
731–1096 days (2–3 years)							
Sepsis-free cohort	218 110	1521 (0.7)	127 505	12 (11–13)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Sepsis	454	25 (5.5)	239	104 (71–155)	8.6 (5.8–12.7)	3.9 (2.6–5.8)	2.2 (1.5–3.2)
Severe sepsis	574	35 (6.1)	274	128 (92–178)	10.5 (7.5–14.7)	3.8 (2.7–5.3)	2.1 (1.5–3.0)
Septic shock	6	0 (0.0)	4	–	–	–	–
Sepsis of any severity	1034	60 (5.8)	517	116 (90–149)	9.7 (7.5–12.6)	3.9 (3.0–5.1)	2.2 (1.7–2.9)

Adjusted HRs were not determined in the septic shock category because of the small number of patients.
CI, confidence interval; HR, hazard ratio.
[a]Multivariable Cox regression analysis including sex and age in age categories.
[b]Multivariable Cox regression analysis including sex, age in age categories, alcoholism-related conditions, immunosuppression, and comorbidity.

short-term mortality, and is likely because of differences in settings and case identification methods [10,15,26–30].

Half of the patients hospitalized with severe sepsis died within 3 years after the sepsis event and almost half of the nonsurviving patients hospitalized with severe sepsis died within the first 30 days. This is in agreement with results from a recent review on long-term mortality in septic patients [8].

We confirmed what previous population-based studies have found in terms of the increased risk of mortality among septic patients initially surviving the acute phase of the disease [9,10,31]. The three studies, as well as the present, found a two-fold increased risk of mortality among patients surviving the first year after the sepsis incident compared with a reference population.

It is notable that all three studies showed an increased risk of mortality, even among the sepsis patients surviving up to 2 years after admission. This could be explained by several theories. It could be because of a causal relation where the sepsis event was the primary reason for the long-term effect on mortality. Studies on the pathophysiology of sepsis describe a stage of anti-inflammatory response leading to an immunosuppressive phase [32]. This might lead to readmission with infections and a subsequently increased risk of mortality, but the time frame of this immunosuppressive phase is not well described. A study by Wang *et al.* [33] found that patients admitted to an ICU with severe sepsis were at greater risk of a readmission with an infectious cause within the following year compared with patients admitted to the ICU with noninfectious conditions despite controlling for potential confounders [29]. The sepsis event could also possibly induce sequelae (kidney injury, cognitive impairment, atrial fibrillation) leading to excess mortality among the survivors of sepsis [9, 34–36] or lead to increased healthcare utilization after discharge with sepsis [37,38].

We found that patients surviving 6 months after the sepsis event had the same increased risk of mortality irrespective of the severity of sepsis they presented to the hospital with. Therefore, we believe that in the present study, the severity of sepsis measured at arrival to the hospital had no long-term measureable influence on the organs following the event. A biological explanation could be the

so-called 'hibernation theory', where the cells enter a hibernation-like state, and although the organs fail biochemically or physiologically, almost no cell death occurs [32,39]. Another and perhaps more plausible explanation could be selection, where the patients with severe sepsis surviving the first 6 months only had less severe organ dysfunction at the time of admission.

The multivariable regression models showed a decrease in HRs from a 10-fold increase in the unadjusted model, to a four-fold increase in the model adjusting for age and sex, to a two-fold increase in the fully adjusted model among patients surviving the first 2 years after hospitalization with sepsis of any severity. This large difference in the HR estimates with different levels of confounder adjustment indicates a likely presence of unmeasured confounders, which again might explain the increased risk after 2 years of follow-up entirely.

Hospitalization with an acute illness with the potential of full recovery other than sepsis (e.g. upper gastrointestinal bleeding [40]) has also shown a two-fold risk of mortality among patients surviving the first year after hospitalization. This also applies to an illness such as stroke [41], where the risk of permanent morbidity is higher, possibly influencing the increased long-term mortality.

The prognosis of sepsis is most likely multifactorial, with individual factors such as comorbid conditions and socioeconomic status [9,10] as well as community-based factors such as preventive health management impacting on the mortality [42].

Strengths and limitations

Because of the uniformly organized Danish public healthcare system, we could identify all patients included in the study in the different population-based registers for a full medical history. We used manual chart review with a structured protocol to collect data on the presence of infections at the time of admission to minimize ascertainment bias. Subsequent validation of the cohort identified by a manual review of 2.5% of all contacts yielded a κ value of 0.68, corresponding to a considerable strength of agreement [12,43]. Further, we could identify a population-based sepsis-free cohort where we had complete follow-up on all individuals.

We could account for well-known prognostic factors such as sex, age, comorbidity, and immunosuppression, and had complete information on this in both cohorts.

The current work was a single-center study from an AMAU at a university hospital. The results may not be generalizable to other hospitals. However, the hospital serves as the primary hospital (and the only hospital) in a well-defined catchment area.

We restricted the sample population to patients admitted to the AMAU. Patients admitted with neutropenic sepsis because of chemotherapy, patients admitted because of the need for dialysis as well as patients admitted to the department of surgery were not included in the study.

Another limitation induced by restricting the sample population to patients admitted to the AMAU was the inability to identify whether individuals in the sepsis-free cohort were admitted to other departments with sepsis. This could potentially underestimate the long-term risk of mortality presented in this study because the sepsis-free individuals inaccurately could be registered as non-exposed to sepsis.

We could not adjust for other potential confounders such as functional status or place of residence (nursing home or home) because the registers used in the study did not contain this information on the sepsis patients or the sepsis-free cohort. It was not possible to identify individuals in the sepsis-free cohort with an advanced care directive where maximal supportive care was deemed inappropriate. This could act as a potential confounder as well.

We identified a lower number of septic shock cases because of our definition of septic shock. We defined septic shock as the occurrence of sepsis plus a systolic blood pressure of 90 mmHg or less as well as a lactate value greater than 4.0 mmol/l within 4 h after arrival to the hospital, or the use of vasopressor agents within the first 24 h after arrival. We did not have information on fluid therapy, which could underestimate the septic shock cases and thus classify them as severe sepsis. Further, only 43% of all patients with septic shock were transferred to the ICU within day 0 to 1 after admission. This could be because of the organizational structure of ICUs in the Danish healthcare system, where there are on average 2.2 ICU beds per 100 acute care beds [44]. This could also be because of the fact that we included all septic patients irrespective of high age, much comorbidity, or a do not resuscitate order.

The diagnosis of infection was applied retrospectively, which is a potential source of bias, as some sites of infection were not evident at the time of admission. We addressed this by waiting a month before evaluating the first days of each patient's course of admission; thus, test results and imaging descriptions were available in the electronic patient files. Despite this, some patients had symptoms, signs, and paraclinical evidence of infection, where it was not possible to determine the specific site. We defined these as 'unknown site of infection'.

Conclusion

We found that patients admitted with community-acquired sepsis identified by symptoms and clinical findings showed a two-fold higher risk of mortality up to 3 years after the sepsis event compared with sepsis-free individuals. The severity of the disease had a high impact on intermediate-term mortality, but no impact on long-

term mortality among patients admitted with sepsis or severe sepsis surviving 6 months after the admission.

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Conflicts of interest

There are no conflicts of interest.

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