

BMJ Open Use of healthcare before and after sepsis in Sweden: a case-control study

Jacob Dahlberg , Adam Linder, Lisa Mellhammar 

To cite: Dahlberg J, Linder A, Mellhammar L. Use of healthcare before and after sepsis in Sweden: a case-control study. *BMJ Open* 2023;13:e065967. doi:10.1136/bmjopen-2022-065967

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-065967>).

Received 22 June 2022

Accepted 05 February 2023

ABSTRACT

Objectives The aim of this study was to compare readmissions and death between sepsis and non-sepsis hospitalisations the first year after discharge, and to investigate what diagnoses patients with sepsis present with at readmission. The aim was also to evaluate to what degree patients hospitalised for sepsis seek medical attention prior to hospitalisation.

Design Retrospective case-control study with data validated through clinical chart review. A disproportionate stratified sampling model was used to include a relatively larger number of sepsis hospitalisations.

Setting All eight public hospitals in region Scania, Sweden (1 January to 3 December 2019).

Participants There were 447 patients hospitalised for sepsis (cases), and 541 hospitalised for other causes (control) identified through clinical chart review.

Outcome measures Cox regression was used to analyse readmission and death the year after discharge, and logistic regression was used to analyse healthcare the week prior to hospitalisation. Both analyses were made unadjusted, and adjusted for age, sex and comorbidities.

Results Out of patients who survived a sepsis hospitalisation, 48% were readmitted the year after discharge, compared with 39% for patients without sepsis (HR 1.50, 95% CI 1.03 to 2.19), $p=0.04$. The majority (52%) of readmissions occurred within 90 days and 75% within 180 days. The readmissions were most often caused by infection (32%), and 18% by cardiovascular disease. Finally, 34% of patients with sepsis had sought prehospital contact with a physician the week before hospitalisation, compared with 22% for patients without sepsis (OR 1.80, 95% CI 1.06 to 3.04), $p=0.03$.

Conclusion Patients hospitalised for sepsis had a higher risk of readmission the year after discharge compared with patients without sepsis. The most common diagnoses at readmission were infection followed by cardiovascular disease. With better follow-up, some of these readmissions could potentially be prevented. Patients hospitalised for sepsis had sought prehospital contact the week prior to hospitalisation to a greater extent than patients without sepsis.

BACKGROUND

Sepsis is a severe condition that causes large mortality and morbidity, both acutely and in long term. The yearly worldwide incidence is estimated to 49 million cases and 11 million sepsis-associated deaths.¹ This represents approximately 20% of all deaths worldwide.¹

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Clinical chart review was used for distinguishing sepsis cases, and a uniform definition of infection was used.
- ⇒ Data on comorbidities, sex and age were collected and adjusted for in statistical analysis.
- ⇒ The use of chart review to define sepsis and infection was limited to the index hospitalisation. International Classification of Diseases coding was used otherwise.
- ⇒ The definition of healthcare 7 days prior to hospitalisation was limited to contact with a physician. Other common means of contact, such as phone calls to nurses at primary care healthcare centres, or to the national healthcare guide were not included.

Mortality is also increased long term and has been reported to 30% the first year after discharge.^{2,3} An increased mortality has been shown to persist for a minimum of 5 years.⁴ Furthermore, sepsis survivors are at increased risk for developing new diagnoses and functional impairments. In a large German study, 74% of patients had gained a new diagnosis the year after sepsis, 71% had a new medical diagnosis, 18% a new psychiatric diagnosis and 18% a new cognitive diagnosis.² Readmissions after sepsis are also common, with about 40% of sepsis survivors being readmitted within 90 days.⁵ Common causes of readmissions are infection and congestive heart failure. In addition to being common, readmissions after sepsis also compose a large cost to the healthcare system.⁶

Compared with long-term effects, there are fewer studies investigating patients with sepsis prior to hospitalisation. It is well established that early recognition and treatment of sepsis is of great importance in sepsis care.⁷ Therefore, it would be beneficial to identify patients at risk of developing sepsis earlier. In a Swedish study on patients with community-acquired bloodstream infection 61% of patients had sought prehospital contact.⁸ Among these patients, a delay in time to hospitalisation was associated with an increased 30-day mortality. A recent systematic review found on average



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

Division of Infection Medicine, Department of Clinical Sciences, Lund University, Lund, Sweden

Correspondence to

Dr Lisa Mellhammar;
lisa.mellhammar@med.lu.se

33% of patients with sepsis had a healthcare encounter the week prior to sepsis, but the range between studies was big, and the definition of healthcare the week prior varied.⁹

Previous studies on sepsis epidemiology and long-term effects have mostly been based on administrative data and International Classification of Diseases (ICD) codes. However, only a minority of patients with sepsis receive an ICD code for sepsis. As an example, only a fifth of patients with sepsis in Sweden and a third in the USA were correctly given a diagnosis.^{10 11} In a recent report, WHO acknowledged this problem and emphasised clinical chart review as the gold standard for obtaining reliable data on sepsis epidemiology.¹² Therefore, this study on healthcare use before and after sepsis is based on data validated through clinical chart review. The aims of this study were to compare readmissions and death between sepsis and non-sepsis hospitalisations the year after discharge, and to investigate what diagnoses patients with sepsis present with at readmission. Lastly, the aim was also to evaluate to what degree patients hospitalised for sepsis seek medical attention prior to hospitalisation.

METHOD

Study design and setting

This study was a retrospective case–control study with data validated through clinical chart review. The study population consisted of all patients (214 707) hospitalised in the

eight public hospitals in the region of Scania, a county in Sweden, between 1 January and 31 December 2019. Exclusion criteria were: duplicate entries, inaccessible patient charts, age under 18 and living outside the region of Scania. The study population was stratified into five groups based on ICD coding strategies to identify sepsis. The patients were randomly sampled from each stratum, with disproportionately large samples from the strata more likely to contain patients with sepsis (figure 1). This was performed to gain a larger volume of patients with sepsis, since they compose a relatively small proportion of all hospitalisations. The stratified random sample aimed for 1000 patients in total with the following distribution: 32.5% direct sepsis, 22.5% implicit sepsis, 22.5% infection without organ dysfunction and 22.5% without infection (the last group was extracted from both patients with and without organ dysfunction). Details on definitions for different strata are included in online supplemental appendix I. There was no formal sample size calculation as the OR levels were unpredictable. Even though there are previous studies on readmissions after sepsis, the study designs and definitions vary too much. The sample size was instead based on feasibility. Patients with sepsis (cases) and patients hospitalised for other causes (control) were identified through clinical chart review. The main outcomes were readmissions and deaths the year after discharge, and use of healthcare the 7 days prior to sepsis hospitalisation.

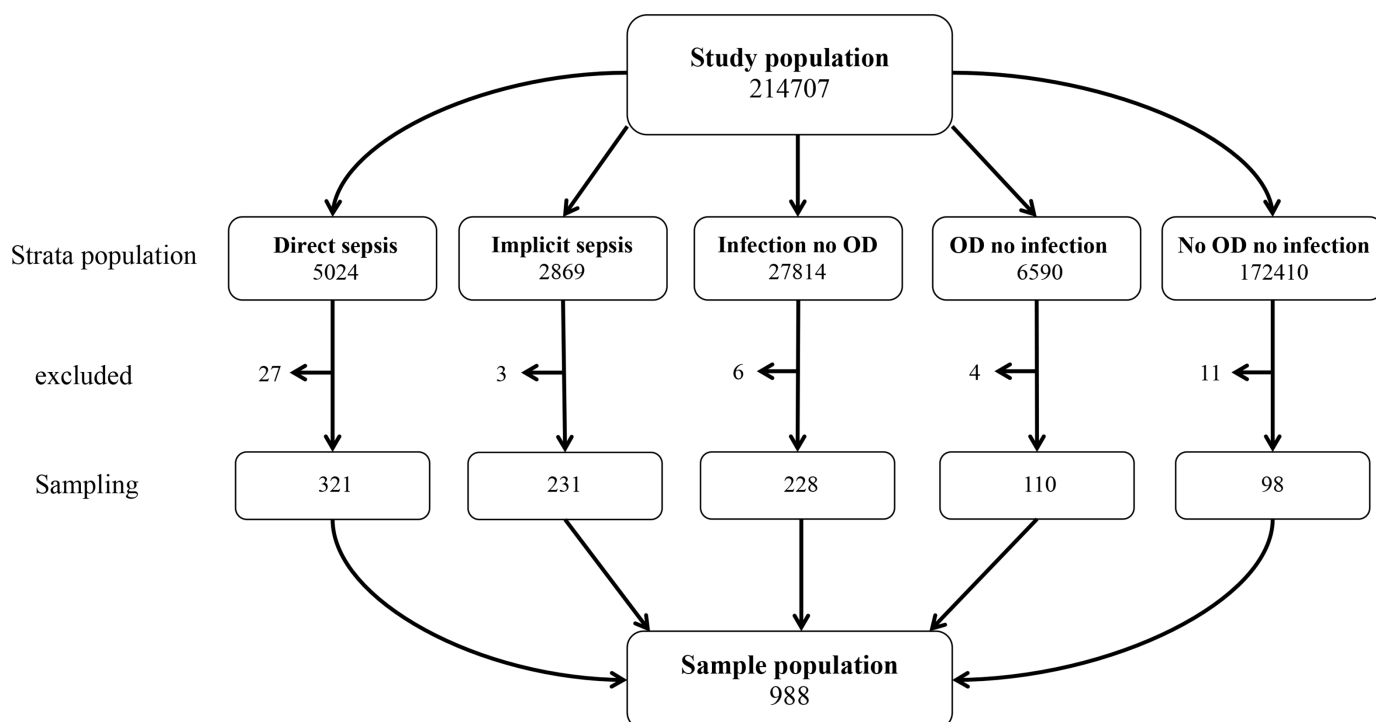


Figure 1 An illustration of the stratified random sampling of study participants. Patients were selected from five different International Classification of Diseases (ICD) coding strategies. Patients with direct and indirect ICD codings for sepsis constituted a relatively larger proportion of the sampled population as compared with the study population. n=55 patients were excluded either due to duplicate entries, inaccessible patient charts or being registered outside of region Scania. OD, organ dysfunction.

Medical researchers, who priorly had received proper training to perform the task, manually reviewed the patient charts using a structured protocol (online supplemental appendix II). The collected data were also validated by a specialist practising physician in infectious medicine. The patients' charts were accessed from the electronic medical record system. From the patient administrative system, the dates of healthcare use the 7 days prior to hospitalisation and dates of readmissions and death the year after discharge were collected. From the patient charts, detailed data to define sepsis and infection were registered for the index hospitalisation. Also, information on sex, age and comorbidities was collected. The anonymised data were entered into an online research database using Research Electronic Data Capture V.12.01.9 (REDCap, Vanderbilt University, Nashville, Tennessee).

The main ICD codes were used to categorise diagnosis at readmission and admission the year prior to hospitalisation. These were divided into the following categories: infection, cardiovascular, pulmonary, neurological, abdominal, endocrine, cancer, orthopaedics, urinary tract and other. The infection category was further subdivided into sepsis, abdomen and gastrointestinal, skin and soft tissue, respiratory tract, urinary tract, foreign material and other.

Definitions

Infection

Infection was defined according to the Linder-Mellhammar Criteria of Infection (LMCI) system.¹³ LMCI is a modified version of the International Sepsis Forum definition of infection. The original definitions were developed for the intensive care unit (ICU), but the LMCI has been adapted to identify infection outside the ICU.¹⁴ Suspected infection was defined as having 2–3 points, while 4 points or more were considered as infection. The focus of infection was considered the site with the highest score. If two foci had the same score, both were considered (online supplemental appendix III).

Sepsis

Sepsis was defined according to the Sepsis-3 criteria as a change in Sequential Organ Failure Assessment (SOFA) score of 2 or more from the patient's baseline. A time window of 30 hours was used, and the time window with the highest change in SOFA score was chosen. The 30-hour window was used to maximise the chances of obtaining a complete SOFA score, including both vital parameters and morning blood samples. For the respiratory score, partial pressure of oxygen from arterial blood draw was recorded. If unavailable, saturation from a pulse oximeter was used. For patients on oxygen therapy, the Severinghaus conversion equation was used to convert the patient's saturation with oxygen to a corresponding value without oxygen therapy.¹⁵ For the cardiovascular score, mean arterial pressure was estimated based on systolic and diastolic blood pressure. Glasgow Coma Scale (GCS) was used to quantify the central nervous system

score. If unavailable, Reaction Level Scale (RLS), which has been validated to correlate with GCS, was used.¹⁶ The patient's RLS was converted into a corresponding GCS based on a study by Walther *et al.*¹⁷ We regarded missing values in the SOFA score as within the range of the values from adjacent days, since this is most in accordance with clinical management and a common approach in retrospective sepsis studies.¹⁸

Comorbidity

The following comorbidities were recorded: myocardial infarction, congestive heart failure, cerebrovascular accident, peripheral vascular disease, malignancies, chronic obstructive pulmonary disease (COPD), dementia, diabetes mellitus and chronic kidney disease (CKD). For statistical analysis, myocardial infarction, congestive heart failure, cerebrovascular accident and peripheral vascular disease were grouped together as cardiovascular disease.

Healthcare 7 days prior to hospitalisation

Healthcare the week prior to hospitalisation was defined as any physical appointment with a physician.

Patient and public involvement

There was no patient and public involvement in the design, conduct or reporting.

Statistical analysis

To account for the disproportionate stratified sampling design of the study, participants from each stratum were assigned a study weight. The weight was calculated as $W=S/s$, where W represents the study weight, S the total number of patients in the stratum and s the number of included study participants from the stratum. Statistical analyses were performed in the complex sample module of SPSS (V.28.0) in which the complex study design was accounted for. Complex sample Cox regression was used for analysis on 1-year mortality and readmissions, HRs with 95% CI were calculated, comparing sepsis to non-sepsis hospitalisations. Death is a potential competing risk on analysis of readmissions, and we therefore also analysed death or readmission combined. For analysis on healthcare 7 days before sepsis admission, complex sample logistic regression was used. Both analyses were performed unadjusted, and adjusted for sex, age and presence of comorbidities (cardiovascular disease, diabetes, COPD, dementia, cancer and CKD). These variables have been associated with both readmissions and long-term mortality after sepsis.^{19 20} Patients with missing data on outcomes were excluded from statistical analysis. Adjusted ORs with 95% CI were used to compare patients with and without sepsis for having an encounter with a physician the week prior to hospitalisation. Statistical tests were considered significant at $p<0.05$.

RESULTS

A total of 1043 patients were randomly selected for analysis. Patients were excluded due to duplicate entries or

Table 1 The weighted baseline characteristics for the sample population, and for the sepsis and non-sepsis subgroups

	Sample population	Sepsis	No sepsis	P value
Population size, n	988	447	541	
Age, median	71	76	70	
Sex, female, % (95% CI)	47 (39 to 55)	52 (44 to 59)	47 (38 to 55)	0.4
Comorbidities, % (95% CI)				
Cardiovascular disease	25 (19 to 32)	46 (38 to 53)	23 (17 to 31)	<0.01
Diabetes	16 (11 to 22)	29 (23 to 37)	15 (10 to 22)	0.03
Cancer	14 (9 to 20)	18 (13 to 25)	14 (9 to 20)	0.3
COPD	7 (4 to 11)	15 (11 to 22)	6 (3 to 11)	0.08
CKD	2 (1 to 4)	5 (3 to 10)	1 (0 to 5)	0.04
Dementia	6 (3 to 11)	10 (6 to 15)	6 (3 to 12)	0.2
Number of comorbidities, % (95% CI)				
0	53 (45 to 61)	26 (20 to 34)	55 (46 to 63)	<0.01
1	29 (22 to 37)	35 (28 to 43)	29 (22 to 37)	0.2
2	15 (10 to 22)	29 (22 to 37)	14 (9 to 21)	<0.01
3	2 (1 to 5)	8 (5 to 14)	2 (1 to 5)	<0.01
4 or more	1 (0 to 5)	1 (1 to 3)	1 (0 to 6)	0.8

The statistics used was complex sample frequencies. P values were calculated using complex sample χ^2 test (SPSS V.28.0). CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

inaccessible patient charts. Also, patients registered outside region Scania were excluded, since mortality and rehospitalisation data were unavailable for these patients. After exclusion of 55 patients, 988 remained for statistical analysis (figure 1). After clinical chart review, 447 sepsis cases and 541 control cases (hospitalised for other causes) were identified.

The weighted baseline characteristics of the study population are presented in table 1. The median age for patients with a sepsis hospitalisation was 76 years and this group comprised 52% female patients. In the non-sepsis subgroup, the median age was slightly lower at 71 years, and the percentage of female patients in this group was 47%. Regarding comorbidities, a generally higher level was seen in the sepsis subgroup compared with patients without sepsis.

Within 1 year after discharge, 48% (95% CI 40 to 57) of patients with sepsis who survived the initial hospitalisation were readmitted, compared with 39% (95% CI 31

to 47) of patients without sepsis. The risk of readmission was significantly higher among sepsis survivors compared with patients without sepsis (HR 1.50, 95% CI 1.03 to 2.19), $p=0.04$. The higher risk remained significant when adjusting for age, sex and comorbidities (HR 1.55, 95% CI 1.05 to 2.27) (table 2 and figure 2). The 1-year mortality among sepsis survivors was 24% (95% CI 18 to 32), and 9% (95% CI 5 to 14) for patients without sepsis. Patients (108 with sepsis and 26 without) who died during the initial hospitalisation were excluded from analysis on death and readmission the year after hospitalisation. The in-hospital mortality in the sepsis subgroup was 13% (95% CI 10 to 18) and 2% (95% CI 1 to 7) in the non-sepsis subgroup. Data on sepsis and mortality for different strata are found in online supplemental appendix IV, table 1.

Patients who survived the initial hospitalisation were followed a year after discharge. Readmissions and main diagnoses at readmission were recorded. The results are reported unweighted. A total of 184 (54%) of sepsis

Table 2 Complex sample Cox regression model of readmissions, deaths and both combined the year following hospitalisation

Outcome	Unadjusted			Adjusted (age, sex and comorbidities)		
	Patients, n	HR (95% CI)	P value	Patients, n	HR (95% CI)	P value
Death	850	3.13 (1.62 to 6.04)	<0.01	846	2.00 (0.98 to 4.09)	0.06
Readmissions	830	1.50 (1.03 to 2.19)	0.04	826	1.55 (1.05 to 2.27)	0.03
Death or readmission	830	1.62 (1.13 to 2.33)	0.008	826	1.55 (1.07 to 2.27)	0.02

134 (108 with sepsis and 26 without) patients who died during hospitalisation were excluded from analysis. HRs are presented, comparing sepsis hospitalisations to non-sepsis hospitalisations. The comorbidities adjusted for were cardiovascular disease, diabetes, chronic obstructive pulmonary disease (COPD), dementia, cancer and chronic kidney disease (CKD).

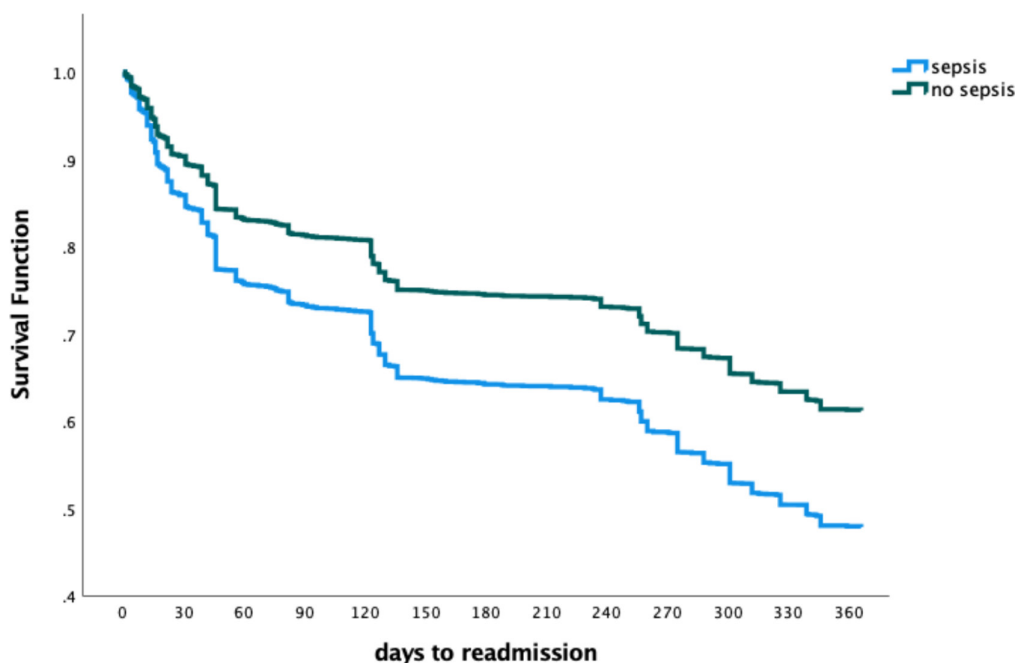


Figure 2 Unadjusted survival function for readmissions the year after discharge, with separate lines for sepsis and non-sepsis hospitalisations. Patients with incomplete data, and those who died during the index hospitalisation were excluded from analysis.

survivors were readmitted the year after discharge. The number of readmissions recorded ranged from 1 to 5 and 52% (n=95) of the patients had at least 2 readmissions, 27% (n=50) had at least 3, 13% (n=23) had at least 4 and 4% (n=8) had 5. The total amount of readmissions among these 184 patients was 361. As shown in [figure 3A](#), the most common type of diagnosis among these 361 readmissions was infection, representing about a third of all readmissions (n=116). Looking at the type of infection diagnosis, respiratory tract at 40 (34%), urinary tract at 30 (26%) and sepsis at 14 (12%) were the most common. The majority (83, 72%) of the infection readmissions occurred within 180 days, and 50 (43%) in the first 90 days ([figure 3B](#)). Cardiovascular disease also stood for a large portion of readmissions at 65 (18%). Of these, 49 (77%) occurred in the first 180 days, and 34 (53%) in the first 90 days ([figure 3B](#)). All readmissions considered, 266 (75%) occurred within 180 days, and 185 (52%) within 90 days.

Looking at individual patients, 83 out of 184 (45%) readmitted patients with sepsis had an infection as the cause of readmission at least once the first year after discharge. Out of these 83 patients, 38 (46%) had the same focus of infection as in the initial sepsis hospitalisation in one or more of their rehospitalisations. Further, hospitalisation the year prior to sepsis hospitalisation was investigated among these 184 patients and 105 (57%) were hospitalised the previous year, and 35 of these (33%) suffered one or more hospitalisations for infection. Of the patients hospitalised for infection the previous year, 11 (31%) had the same focus of infection as in the main sepsis hospitalisation at least once.

Of the patients hospitalised for sepsis, data on health-care contact prior to hospitalisation were available for 975 patients of whom 34% (95% CI 27 to 42) had sought medical contact with a physician the 7 days prior to hospitalisation, compared with 22% (95% CI 16 to 30) of patients hospitalised for other causes. This was a statistically significant difference with an OR of 1.80 (95% CI 1.06 to 3.04), $p=0.03$, that remained significant when corrected for age, sex and comorbidities (OR 1.91, 95% CI 1.09 to 3.34), $p=0.02$ ([table 3](#)).

DISCUSSION

The main finding of this report is that patients who survive a sepsis hospitalisation are more susceptible to readmission the year after hospitalisation than patients without sepsis. A large proportion of sepsis survivors were readmitted, and about half of all readmissions consisted of either infection or cardiovascular disease. In addition, the study also shows that patients hospitalised for sepsis to a larger extent have contact with a physician the week prior to hospitalisation than patients hospitalised for other causes.

Sepsis survivors had a higher risk of readmission after hospitalisation than patients without sepsis, indicating that this is a group in large need of healthcare recourses. In this study, infection and cardiovascular disease were the most important contributors to readmission. Previous studies have also noted infection, followed by cardiovascular disease, as the most common cause of readmission after sepsis.^{5 21–24} It is also known that patients hospitalised with cardiovascular diseases, in particular myocardial

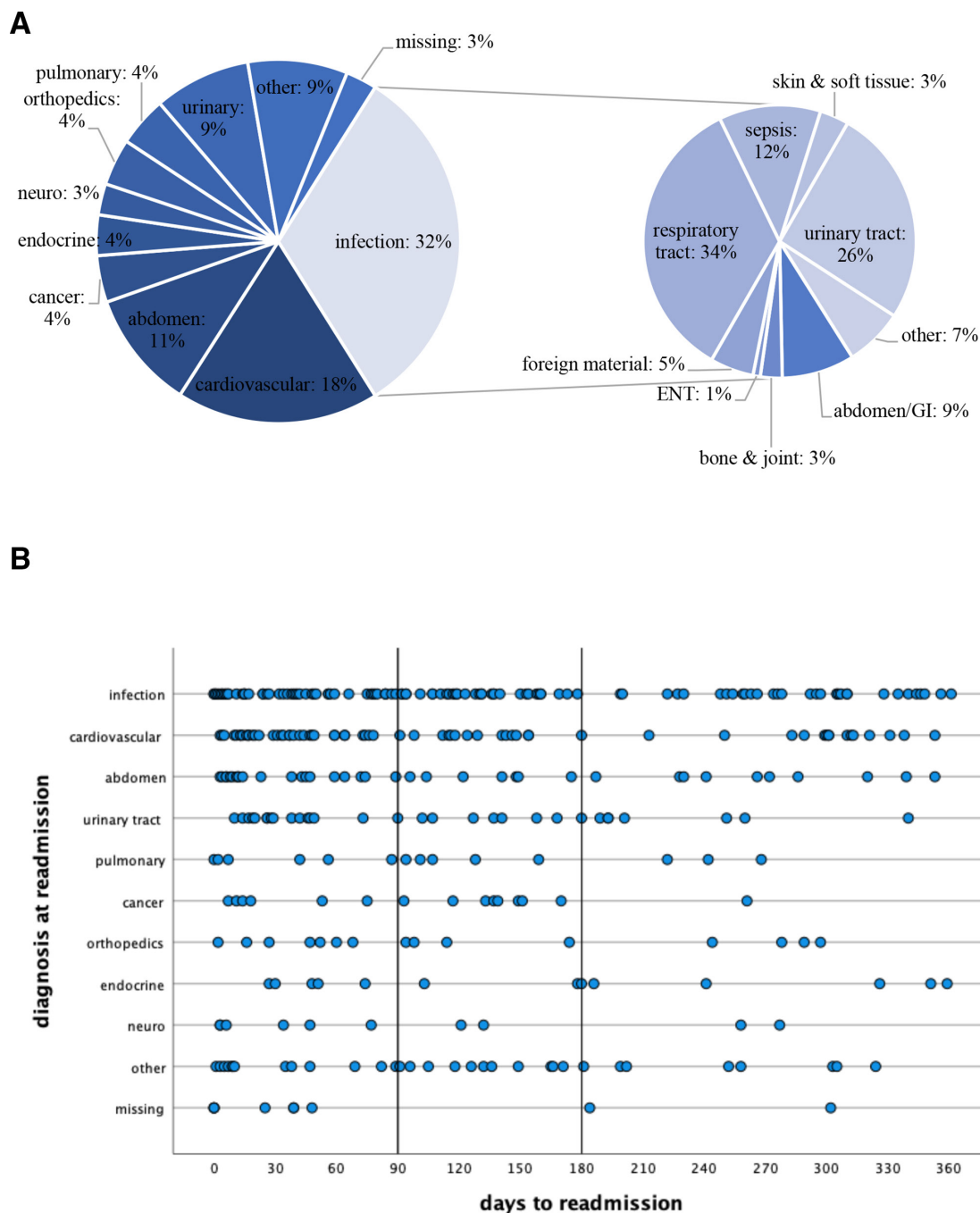


Figure 3 Representation of readmissions among sepsis survivors. (A) One hundred and eighty-four patients hospitalised for sepsis were readmitted the year after discharge, with a total of 361 readmissions. The pie chart to the left shows a categorisation of all the main International Classification of Diseases (ICD) codes the patients received at readmission. The infection category was further subdivided into focus of infection, represented in the right-hand pie chart. Any single patient can be represented up to five times. The most common ICD categories at readmission were infection and cardiovascular disease, together representing half of all readmissions. (B) Scatter plot comparing days to readmission for the different readmission diagnoses. Each dot represents a readmission, and a patient can be represented up to five times. Vertical lines are placed at 90 and 180 days. ENT, ear, nose and throat; GI, gastrointestinal.

infarction and congestive heart failure, are prone to rehospitalisation in a similar level to sepsis survivors.²⁵ Interestingly, both infection and congestive heart failure are diagnoses where hospital admissions are believed to sometimes be preventable in an outpatient setting, meaning structured follow-up could be beneficial for many sepsis survivors.⁵ The increased risk of cardiovascular events

after sepsis compared with in matched controls suggests sepsis contributes to the development or progression of these diseases.^{23 26} Moreover, a majority of readmissions occurred during the first 180 days after discharge, with a large proportion taking place in the first 90 days. Follow-up after sepsis is recommended in the latest iteration of the surviving sepsis campaign, and the data on

Table 3 Correlation between being hospitalised for sepsis and having an encounter with a physician the week prior to hospitalisation

Model	Variables adjusted for	Participants, n	OR (95% CI)	P value
Unadjusted	None	975	1.80 (1.06 to 3.04)	0.03
Adjusted	Age, sex, comorbidities	971	1.91 (1.09 to 3.34)	0.02
	Age	971	0.99 (0.96 to 1.01)	0.27
	Sex (female)	971	1.02 (0.47 to 2.25)	0.94
	Diabetes	971	2.49 (0.99 to 6.24)	0.05
	Cardiovascular disease	971	0.696 (0.27 to 1.80)	0.45
	Dementia	971	0.21 (0.064 to 0.71)	0.01
	CKD	971	0.76 (0.19 to 3.11)	0.70
	COPD	971	1.33 (0.44 to 4.01)	0.62
	Cancer	971	2.12 (0.74 to 6.12)	0.16

ORs presented are for sepsis compared with non-sepsis hospitalisations and were calculated using complex sample logistic regression. The comorbidities adjusted for were cardiovascular disease, diabetes, chronic obstructive pulmonary disease (COPD), dementia, cancer and chronic kidney disease (CKD).

diagnosis and time to readmission presented in this study are of importance in the structure of such follow-up programmes.²⁷ Other studies have demonstrated a 3.5-fold increase in moderate to severe cognitive impairment and on average 1.5 new limitations of activities of daily living, these long-term effects are not directly evaluated in this study.²⁸ Several studies have shown high prevalence of mental illness such as depression (28%–34%), anxiety (30%–40%) and post-traumatic stress disorder (36%–42%).^{29–31} The prevalence is higher than population norms, but these studies do not present a baseline. A longitudinal cohort found the same prevalence before and after sepsis, suggesting that mental illness is more common among people vulnerable to sepsis.³² These disorders are mainly cared for in outpatient settings and not included in the present study. Still, mental illness is common after sepsis and needs to be addressed following sepsis.

Many of the patients who were readmitted after sepsis were also hospitalised the year prior to the index hospitalisation. Previous studies have identified hospitalisation the year prior to sepsis as an independent risk factor for subsequent rehospitalisation.^{21 33} Notably, infection and cardiovascular disease were the most common diagnoses both the year after and prior to hospitalisation, although it is difficult to draw any conclusions regarding this since these are also common diagnoses overall. For example, in US hospitals in the year 2018 the two most common diagnoses for hospitalised patients were sepsis and heart failure.³⁴

The 1-year mortality among sepsis survivors was higher than for patients without sepsis, although the difference was not significant when adjusted for age, sex and comorbidities. Patients had an increased risk of mortality up to 5 years after sepsis in a large propensity matched study and the association between sepsis and mortality was stronger for younger patients and for patients with greater acute

illness severity.⁴ The older age and a less proportion treated in intensive care in our cohort may be causes why the mortality did not differ between patients with and without sepsis in this study, but the sample size is also a likely explanation.

About a third of patients hospitalised for sepsis had contact with a physician the week prior to hospitalisation. The proportion was comparable to earlier reported numbers, although only a handful of studies have been made, and all differ slightly in the way healthcare the 7 days prior is defined.⁹ Still, a considerable amount of patients with sepsis seek prehospital medical attention. The high rate could reflect a higher comorbidity burden across this patient group, although this was something we tried to adjust for. There is also a possibility that these encounters could present an opportunity to prevent sepsis development in some patients. Future studies with focus on diagnosis and eventual treatment within these healthcare encounters could help fill these gaps in knowledge.

This study was based on chart review to produce a reliable representation of sepsis. Sepsis recognition using claims data is often unreliable since patients are not always given an ICD code for sepsis despite meeting the Sepsis-3 criteria.^{10 11} Using chart reviews, also more mild cases of sepsis might be recognised and included. Moreover, both community-acquired and hospital-acquired sepsis cases were represented in this study. Thus, the chart review approach aims to more accurately represent the whole spectrum of patients with sepsis as defined by Sepsis-3. The drawback of chart review is that the study is limited to a smaller group of patients. The disproportionate sampling of study participants was designed to compensate for this, but a large register-based approach will still yield greater statistical power. Another strength of the chart review approach is that a uniform definition of infection was used. Part of the definition of sepsis is that the patient has an infection, yet the way infection is



defined in sepsis research varies. The LMCI system brings a clear and uniform definition of infection, allowing for more comparable results between studies.

A weakness of the study is that the extensive chart review, which is very time consuming, was performed only for the index hospitalisation. Therefore, the ways sepsis and infection were defined differed between the index hospitalisation, and the rehospitalisations and hospitalisations prior to sepsis. While sepsis was defined according to Sepsis-3 and infection according to LMCI at the index hospitalisation, ICD coding was used otherwise. Also, because only the main diagnosis was considered in these cases, infections may have been missed if they were not recorded as the main reason for hospitalisation. Another limitation with the collected data was that some parameters were missing or not clearly documented in the patients' charts. This applies to the SOFA score parameters, there were frequently either blood samples or vital parameters missing, since these were not all completed and available in any given 30-hour time window. This risks that some sepsis cases could have been missed.

Sepsis is sometimes a complex syndrome not easily identifiable by criteria and there might be patients with a sepsis syndrome not fulfilling the Sepsis-3 definitions in the control group, this could have smoothed out differences in long-term effects or prehospital contact between patients with and without sepsis. One way to handle that would be to have a control group without infections, but it would then be even more difficult to differ between long-term effects and prehospital contact for infection or sepsis. A control group without hospitalisation would perhaps be even better to detect long-term effects or prehospital contacts in sepsis, but our hypothesis was that patients with sepsis lack proper follow-up compared with other patients.

Also, the result could be affected by including community-acquired and hospital-acquired sepsis. The hospital-acquired sepsis has probably to a lesser extent had contact with healthcare prior to the hospitalisation. As hospital-acquired sepsis is about one-third of all sepsis cases it is important to include these patients as well in epidemiological research.

CONCLUSION

In conclusion, patients who survive a sepsis hospitalisation have a higher risk of readmission the year following hospitalisation than patients without sepsis. The most common causes of readmission for patients with sepsis were infection and cardiovascular disease, and a large proportion of these readmissions occurred in the first 90 and 180 days after discharge. With better knowledge and more structured follow-up, some of these readmissions could potentially be prevented. Lastly, about a third of patients hospitalised for sepsis seek medical attention from a physician the week prior to hospitalisation. This might present an opportunity for early intervention in the development of sepsis.

Acknowledgements Kliniska Studier Sverige–Forum Söder for extraction of patient charts.

Contributors All authors (JD, AL and LM) conceived and designed the study. JD analysed the data and wrote the manuscript, with guidance from AL and LM. All authors reviewed and approved the final version of the manuscript. LM is responsible for the overall content as the guarantor.

Funding This study was financed by Lions Forskningsfond Skåne, the Swedish government research funds (ALF Project) and the Alfred Österlund Foundation.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Swedish Ethical Review Agency (ethics approval number: 2020-03316).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. All data relevant to the study are included in the article.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Jacob Dahlberg <http://orcid.org/0000-0003-3987-3127>

Lisa Mellhammar <http://orcid.org/0000-0002-7623-0342>

REFERENCES

- Rudd KE, Johnson SC, Agesa KM, *et al.* Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the global burden of disease study. *Lancet* 2020;395:200–11.
- Fleischmann-Struzek C, Rose N, Freytag A, *et al.* Epidemiology and costs of postsepsis morbidity, nursing care dependency, and mortality in Germany, 2013 to 2017. *JAMA Netw Open* 2021;4:e2134290.
- Prescott HC, Angus DC. Enhancing recovery from sepsis: a review. *JAMA* 2018;319:62–75.
- Farrah K, McIntyre L, Doig CJ, *et al.* Sepsis-associated mortality, resource use, and healthcare costs: a propensity-matched cohort study. *Crit Care Med* 2021;49:215–27.
- Prescott HC, Langa KM, Iwashyna TJ. Readmission diagnoses after hospitalization for severe sepsis and other acute medical conditions. *JAMA* 2015;313:1055–7.
- Mayr FB, Talisa VB, Balakumar V, *et al.* Proportion and cost of unplanned 30-day readmissions after sepsis compared with other medical conditions. *JAMA* 2017;317:530–1.
- Seymour CW, Gesten F, Prescott HC, *et al.* Time to treatment and mortality during mandated emergency care for sepsis. *N Engl J Med* 2017;376:2235–44.
- Holmbom M, Andersson M, Berg S, *et al.* Prehospital delay is an important risk factor for mortality in community-acquired bloodstream infection (CA-BSI): a matched case-control study. *BMJ Open* 2021;11:e02582.
- Flannery AH, Venn CM, Gusovsky A, *et al.* Frequency and types of healthcare encounters in the week preceding a sepsis hospitalization: a systematic review. *Crit Care Explor* 2022;4:e0635.

- 10 Rhee C, Dantes R, Epstein L, *et al.* Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014. *JAMA* 2017;318:1241-9.
- 11 Wilhelms SB, Walther SM, Huss F, *et al.* Severe sepsis in the ICU is often missing in hospital discharge codes. *Acta Anaesthesiol Scand* 2017;61:186-93.
- 12 Angus DC, Derde L, Al-Beidh F, *et al.* Effect of hydrocortisone on mortality and organ support in patients with severe covid-19: the remap-cap covid-19 corticosteroid domain randomized clinical trial. *JAMA* 2020;324:1317-29.
- 13 Mellhammar L, Elén S, Ehrhard S, *et al.* New, useful criteria for assessing the evidence of infection in sepsis research. *Crit Care Explor* 2022;4:e0697.
- 14 Calandra T, Cohen J, International Sepsis Forum Definition of Infection in the ICU Consensus Conference. The International sepsis forum consensus conference on definitions of infection in the intensive care unit. *Crit Care Med* 2005;33:1538-48.
- 15 Severinghaus JW. Simple, accurate equations for human blood O₂ dissociation computations. *J Appl Physiol Respir Environ Exerc Physiol* 1979;46:599-602.
- 16 Starmark JE, Stålhammar D, Holmgren E, *et al.* A comparison of the Glasgow coma scale and the reaction level scale (RLS85). *J Neurosurg* 1988;69:699-706.
- 17 Walther SM, Jonasson U, Gill H. Comparison of the Glasgow coma scale and the reaction level scale for assessment of cerebral responsiveness in the critically ill. *Intensive Care Med* 2003;29:933-8.
- 18 Rhee C, Zhang Z, Kadri SS, *et al.* Sepsis surveillance using adult sepsis events simplified esofa criteria versus sepsis-3 sequential organ failure assessment criteria. *Crit Care Med* 2019;47:307-14.
- 19 Shankar-Hari M, Saha R, Wilson J, *et al.* Rate and risk factors for rehospitalisation in sepsis survivors: systematic review and meta-analysis. *Intensive Care Med* 2020;46:619-36.
- 20 Shankar-Hari M, Harrison DA, Ferrando-Vivas P, *et al.* Risk factors at index hospitalization associated with longer-term mortality in adult sepsis survivors. *JAMA Netw Open* 2019;2:e194900.
- 21 Sun A, Netzer G, Small DS, *et al.* Association between index hospitalization and hospital readmission in sepsis survivors. *Crit Care Med* 2016;44:478-87.
- 22 Bergh C, Fall K, Udumyan R, *et al.* Severe infections and subsequent delayed cardiovascular disease. *Eur J Prev Cardiol* 2017;24:1958-66.
- 23 Ou S-M, Chu H, Chao P-W, *et al.* Long-term mortality and major adverse cardiovascular events in sepsis survivors. A nationwide population-based study. *Am J Respir Crit Care Med* 2016;194:209-17.
- 24 Yende S, Linde-Zwirble W, Mayr F, *et al.* Risk of cardiovascular events in survivors of severe sepsis. *Am J Respir Crit Care Med* 2014;189:1065-74.
- 25 Chang DW, Tseng CH, Shapiro MF. Rehospitalizations following sepsis: common and costly. *Crit Care Med* 2015;43:2085-93.
- 26 Yende S, D'Angelo G, Kellum JA, *et al.* Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis. *Am J Respir Crit Care Med* 2008;177:1242-7.
- 27 Evans L, Rhodes A, Alhazzani W, *et al.* Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med* 2021;47:1181-247.
- 28 Iwashyna TJ, Ely EW, Smith DM, *et al.* Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA* 2010;304:1787-94.
- 29 Nikayin S, Rabiee A, Hashem MD, *et al.* Anxiety symptoms in survivors of critical illness: a systematic review and meta-analysis. *Gen Hosp Psychiatry* 2016;43:23-9.
- 30 Rabiee A, Nikayin S, Hashem MD, *et al.* Depressive symptoms after critical illness: a systematic review and meta-analysis. *Crit Care Med* 2016;44:1744-53.
- 31 Parker AM, Sricharoenchai T, Rappala S, *et al.* Posttraumatic stress disorder in critical illness survivors: a metaanalysis. *Crit Care Med* 2015;43:1121-9.
- 32 Davydow DS, Hough CL, Langa KM, *et al.* Symptoms of depression in survivors of severe sepsis: a prospective cohort study of older Americans. *Am J Geriatr Psychiatry* 2013;21:887-97.
- 33 Jones TK, Fuchs BD, Small DS, *et al.* Post-acute care use and hospital readmission after sepsis. *Ann Am Thorac Soc* 2015;12:904-13.
- 34 McDermott KW, Roemer M. Most frequent principal diagnoses for inpatient stays in U.S. hospitals, 2018: statistical brief #277. Rockville (MD): Agency for Healthcare Research and Quality (US), 2006.