Causes of late mortality among ICU-treated patients with sepsis

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Abstract
Background: Patients with sepsis may have an increased risk of late mortality, but the causes of late death are unclear. This retrospective matched cohort study aimed to determine the causes of late death (≥1 year) among patients with sepsis compared to patients without sepsis.

Methods: 8760 patients with severe sepsis or septic shock (2001 consensus criteria) registered in the Swedish Intensive Care Registry (2008-2013) were compared with a 1:1 matched (gender, age, SAPS3 probability for death, ICU length of stay) control group consisting of non-septic ICU patients. Causes of death (International Classification of Diseases codes) were obtained from the Swedish Cause of Death Register (2008-2014).

Results: During 2008-2014, 903 patients with sepsis died at ≥365 days after their initial septic event, compared to 884 patients in the control group. Median time of follow-up was 313 days (sepsis group, interquartile range 11-838 days) vs 288 days (control group, 9-836 days). The most common causes of death were heart diseases (sepsis: 50.2%, non-septic: 48.6%) and cancer (sepsis: 33.7%, non-septic: 31.7%). Infectious diseases were significantly more common cause of death in the sepsis group (24.3% vs 19.6%, respectively; P < .05). Pneumonia was a common infectious cause of death in both groups, whereas sepsis was more common in the sepsis group.

Conclusions: The most common causes of late death after ICU admission among patients with and without sepsis were heart diseases and cancer. However, patients with sepsis more frequently had infectious diseases as a cause of late death, compared to non-septic patients.

1 | BACKGROUND

Severe sepsis involves an infection that causes the host's immune response to damage its own tissues and organs, which can lead to organ dysfunction and death in some cases.1-3 Despite improved awareness in recent years, the acute mortality rates remain high for sepsis (15% based on the Sepsis-3 definition)3 and septic shock (50%).4,5 There is on-going debate regarding whether the sepsis episode itself contributes to long-term mortality, or if late mortality is primarily influenced by comorbidities that existed before the septic event.6 The actual causes of late death in patients with a previous sepsis episode are to a large extent unknown.

In a systematic review from 2010, Winters et al concluded that patients with sepsis have increased mortality, even years
after their admission for sepsis, although the 1-year mortality rate after discharge varied substantially (7%-43%). In addition, Winters et al noted that many of the studies regarding late mortality after sepsis were of poor quality, with small cohorts and occasionally no control group. A more recent meta-analysis by Shankar-Hari et al revealed that the post-acute mortality rate (difference between cumulative 1-year mortality and acute mortality) was 16.1%. In studies with non-septic control groups, sepsis was not consistently associated with a higher risk of post-acute mortality, and the risk of late mortality among patients with sepsis was greatest when they were compared to the general population. Shankar-Hari et al also noted that many studies regarding long-term mortality after sepsis were of insufficient quality, which raises questions regarding the relationship between sepsis and additional post-acute mortality. Prescott et al attempted to address whether late mortality (31 days to 2 years) after sepsis was driven by pre-existing disease or was the result of sepsis itself. They used matched control groups (non-hospitalized adults, patients admitted with non-septic infections and patients admitted with sterile inflammatory conditions), and found that sepsis was associated with a 22% absolute increase in late mortality relative to non-hospitalized adults. This increase in late mortality was also observed, albeit at lower magnitudes, when the other control groups were used. In contrast, a recent study focused on ICU-treated critically ill could not confirm an increase in late deaths after sepsis.

Many of the studies regarding late mortality in sepsis are regist-based. This implies some general limitations, for example potential lack of validation for registration of diagnoses, and lack of data. On the other hand, register-based studies may often present results that is necessary for the design of prospective studies.

More information about actual causes of late death in patients with previous episodes of sepsis may in the long-run result in better post-ICU care for this group of patients. It may also generate new hypotheses regarding longstanding physiological or immunological alterations in patients with sepsis.

In summary, the results of studies regarding late mortality in sepsis are disparate. With that in mind, information about the actual causes of death after the initial sepsis event could provide additional insight in this field. Therefore, the present study was undertaken to determine the causes of late deaths in sepsis patients treated in the ICU compared to a matched cohort of non-sepsis ICU patients with similar disease severity.

2 METHODS

The present cohort study identified patients in the Swedish Intensive care Registry (SIR) database who were treated in an ICU during 2008-2013 for severe sepsis or septic shock, based on the 2001 consensus criteria. All diagnoses in the SIR database are registered by the treating ICU physician, and sepsis is one of a handful of key diagnoses in SIR. For key diagnoses, SIR provides specific guidelines. For sepsis, these guidelines include definitions according to the 2001 consensus criteria for sepsis to assert that sepsis is reproducibly identified and diagnosed when present in the ICU. Patients were considered eligible if they were ≥16 years old and had a diagnosis of severe sepsis, although only the first admission was considered in cases with multiple admissions. Patients with incorrect personal identification numbers and patients who could not be followed-up were excluded (eg foreign citizens without Swedish personal identification numbers). The SIR database was also used to create a control group of ICU-treated patients who did not have severe sepsis. The patients in the control group were individually matched 1:1 to patients with severe sepsis according to age, gender, length of ICU stay and severity of illness according to the Simplified Acute Physiology Score version 3 (SAPS3) probability for death. SAPS3 probabilities for death were grouped in 0.1 intervals and ICU stay in 24 hours intervals before matching. The matching procedure were undertaken at ICU admission, and this was also the time for start of follow-up (ICU admission day = day 0).

All Swedish residents have a personal identification number, and this number was used to link the SIR data to the Swedish Cause of Death Register, which is administered by the Swedish National Board of Health and Welfare. The data linking process was performed by the Swedish National Board of Health and Welfare, which generated lists of anonymous individual serial numbers before we received the data for analysis. The Swedish Cause of Death Register was used to obtain data regarding date of death, as well as primary and secondary causes of death (based on the Swedish modification of the International Classification of Diseases, version 10 [ICD-10]). The causes of death in the Swedish Cause of Death Register are reported by the treating physician (hospital physician or general practitioner). The most common and clinically significant causes of death were grouped using ICD-10 code clusters, such as codes that involved cancer or infection (Supplemental Digital Content; Appendix 1). All included patients were followed until their death or December 31, 2014.

The primary outcomes of interest were the primary and secondary causes of death at ≥365 days after the initial ICU admission (day 0). The secondary outcomes were mortality rates (in the ICU and at 30 days, 90 days, 180 days and 365 days), as well as causes of death at ≤365 days after the initial ICU admission. The study’s protocol was approved by the Regional Ethics Review Board in Linköping, Sweden (2014/31-31 and 2017/238-32), and the requirement for informed consent was waived.
2.1 | Statistical analysis

Demographic data were reported as mean (standard deviation) or median (95% confidence intervals). All statistical analyses were performed using STATA SE software (version 14; StataCorp).

3 | RESULTS

During 2008-2013, the SIR database included 15,141 patients with severe sepsis or septic shock at their first admission. These patients were matched 1:1 to non-septic cases according to age, gender, length of ICU stay and SAPS3 probability for death. This produced 9,144 matched pairs of patients with and without sepsis, as well as 5,997 patients with sepsis but no appropriate matching control patient in the SIR database. Compared to the matched patients with sepsis, the unmatched patients generally had higher SAPS3 probabilities for death (55% vs 45%) and longer ICU stays (6 days vs 1 day) (Table 1). We excluded 384 matched pairs because of missing follow-up mortality data, and 8,760 matched pairs were ultimately included in the analyses (Figure 1). Most included patients were male (58.3%) and the mean age was 68.8 years (14.4 years) (Table 1). The total follow-up time for the patients with sepsis was 12,255 person-years (median 313 days, interquartile range 11-838 days) and for the matched patients without sepsis 12,054 years (median 288 days, interquartile range 9-836 days).

The 1-year mortality rates were 52.9% (n = 4,634) in the matched sepsis group and 53.8% (n = 4,713) in the control group. During the study period (2008-2014), 903 patients in the sepsis group died at ≥365 days after their initial ICU admission, compared to 884 patients in the control group (Table 2). The most frequent primary and secondary causes of death in both groups were heart disease (sepsis: 453/903, 50.2% vs control: 430/884, 48.6%). Chronic obstructive pulmonary disease was a significantly more common cause of death in the control group (sepsis: 116/903, 12.9% vs control: 169/884, 19.1%), whereas infectious diseases were more common causes of death in the sepsis group (sepsis: 219/903, 24.3% vs control: 173/884, 19.6%). When only the primary causes of death were included, a significant difference was observed for COPD, although the difference for infectious diseases was not statistically significant.

Analysing more recent deaths after the initial admission revealed several significant differences between the groups. When we considered mortality within 30 days, we found that cancer was significantly more common in the sepsis group, while heart diseases were more common in the control group (Table 3). In addition, the 30-day and 180-day mortality rates were slightly higher in the control group (Table 4), with 180-day mortality rates of 44.4% (3889/8760) in the control group and 42.4% (3714/8760) in the sepsis group. No significant difference was observed for the 1-year mortality rates in the sepsis group (52.9%, 4634/8760) and control group (53.8%, 4713/8760) (Table 5). In patients with infectious diseases as a cause of late death, pneumonia was the most common diagnose (Table 5).

4 | DISCUSSION

The present study of critically ill ICU patients revealed that infectious disease as a cause of death were more common in initial survivors of sepsis than in a non-sepsis control group. To the best of our

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**TABLE 1** Factors used in the matching procedure

| Factor          | Sepsis (n = 8,760) | Control (n = 8,760) | Unmatched sepsis (n = 5,997) | Matched sepsis surviving ≥365d (n = 4125) | Matched control surviving ≥365d (n = 4048) |
|-----------------|--------------------|--------------------|------------------------------|-------------------------------------------|---------------------------------------------|
| Male gender     | 58.3%              | 58.3%              | 52.7%                        | 58.6%                                     | 56.8%                                      |
| Age (y)         | 68.8 (14.4)        | 68.8 (14.4)        | 64.5 (16.1)                  | 64.9 (15.8)                               | 64.5 (16.0)                                |
| SAPS3 probability | 45%               | 45%                | 55%                          | 36%                                       | 35%                                        |
| SAPS3 score     | 64 (14)            | 64 (14)            | 71 (15)                     | 60 (12)                                   | 58 (12)                                    |
| Median LOS (d)  | 1                  | 1                  | 6                            | 24                                        | 24                                         |

Note: Data are shown as percentage, mean (standard deviation) or number unless otherwise specified. Abbreviations: LOS, length of stay; SAPS3, Simplified Acute Physiology Score version 3.

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knowledge, this is the first report to describe the causes of death among ICU patients who survived their initial septic event.

The most common causes of death in the general Swedish population involve circulatory diseases (including heart diseases) and cancer.\textsuperscript{13} We observed similar results in this patient population, with heart diseases and cancer being the most common causes of death in both study groups. However, we also found that infectious diseases were more common causes of death in the sepsis group, compared to the control group. As expected, this difference was most apparent when analysing the most immediate deaths after the ICU event (0-30 days after their initial event). However, the difference between the groups persisted and remained when we examined deaths at ≥1 year after the patient’s initial admission.

Further analysis of infectious disease-related deaths revealed that pneumonia was a common cause of death in both groups. In general, pneumonia is a common cause of sepsis,\textsuperscript{14} but it is also a common complication among patients with COPD.\textsuperscript{15,16} The prevalence of COPD was higher in our control group compared to the sepsis group, which may contribute to a high incidence of pneumonia in the control group. However, codes for sepsis as a cause of death were much more common in the sepsis group, even at 1 year after their initial ICU admission, which indicates that new episodes of sepsis may contribute to late mortality. Furthermore, this finding may indicate that sepsis pre-disposes patients to subsequent septic infections, and previous studies have also indicated that patients have a high degree of readmission for severe sepsis.\textsuperscript{17}

Most Swedish ICUs report data to the SIR, with 92% of the ICUs reporting data during 2013.\textsuperscript{18} Thus, in addition to the present study’s large sample size, it is unlikely that it is biased by centre-specific characteristics (eg by only including academic centres or specific geographical areas). Moreover, deaths for all Swedish citizens must be reported to the Cause of Death Register. Therefore, linking the two databases through the Swedish personal identification numbers facilitated the high follow-up rate in the present study.

The 1-year mortality rates were similar in the control and sepsis groups, although previous studies have revealed conflicting findings, such as the study by Prescott et al\textsuperscript{8} The most apparent explanation for this discrepancy is that our control group was different from that used by Prescott et al. Our control group consisted of other ICU-treated patients with very severe illnesses, which is highlighted by the fact that the control group had higher 30-day and 180-day mortality rates, compared to the sepsis group.

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|}
\hline
\textbf{Cause of death} & \textbf{Primary cause of death} & \textbf{Primary + secondary causes of death} \\
& \textbf{Sepsis (n = 903)} (%) & \textbf{Control (n = 884)} (%) \\
\hline
Heart diseases & 201 (22.2) & 453 (50.2) \\
& 212 (24.0) & 430 (48.6) \\
Cancer & 267 (29.6) & 304 (33.7) \\
& 240 (27.1) & 280 (31.7) \\
Infection & 54 (6.0) & 219 (24.3) \\
& 44 (5.0) & 173 (19.6) \\
Renal failure & 11 (1.2) & 143 (15.8) \\
& 14 (1.6) & 144 (16.3) \\
Diabetes & 26 (2.9) & 156 (17.3) \\
& 30 (3.4) & 129 (15.0) \\
COPD & 47 (5.2) & 116 (12.8) \\
& 94 (10.6) & 169 (19.1) \\
\hline
\end{tabular}
\caption{Causes of death among patients who died within 30 days after the initial intensive care unit admission}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|}
\hline
\textbf{Cause of death} & \textbf{Primary + secondary causes of death} \\
& \textbf{Sepsis (n = 2584)} (%) & \textbf{Control (n = 2743)} (%) \\
\hline
Infection & 1693 (65.5) & 592 (21.6) \\
Heart diseases & 1100 (42.6) & 1390 (50.7) \\
Cancer & 649 (25.1) & 466 (17.0) \\
Renal failure & 314 (12.2) & 317 (11.6) \\
Diabetes & 276 (10.7) & 278 (10.1) \\
COPD & 194 (7.5) & 327 (11.9) \\
\hline
\end{tabular}
\caption{Causes of death ≥365 days after the initial intensive care unit admission}
\end{table}

Abbreviation: COPD, chronic obstructive pulmonary disease.

\begin{table}[h]
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\begin{tabular}{|l|c|c|}
\hline
\textbf{Time after admission} & \textbf{Mortality rate} & \textbf{Mortality rate} \\
& \textbf{Sepsis, %} & \textbf{Control, %} \\
\hline
30 d & 29.7 & 31.4 \\
180 d & 42.4 & 44.4 \\
365 & 52.9 & 53.8 \\
\hline
\end{tabular}
\caption{Mortality rates at 30 days, 180 days, and 365 days}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|}
\hline
\textbf{Cause of death} & \textbf{Sepsis, n} & \textbf{Control, n} \\
& & \\
\hline
Pneumonia (J18) & 100 & 98 \\
Sepsis (A41) & 86 & 46 \\
Infectious disease, not specified (B99) & 19 & 19 \\
Intestinal infection (A04) & 8 & 4 \\
Chronic hepatitis (B18) & 6 & 5 \\
\hline
\end{tabular}
\caption{Most frequent infectious diseases as a cause of death ≥365 days after the initial intensive care unit admission}
\end{table}

Abbreviation: COPD, chronic obstructive pulmonary disease.
However, we were able to reduce the probability of inter-group differences in mortality by using SAPS3 probability for death as a matching variable, which is an effective approach because the SAPS3 score predicts mortality in ICUs.9,19 We also believe that using severely ill ICU-treated patients as the control group is a strength of the present study, because this approach allowed us to examine differences in the causes of death that were specific to the sepsis itself.

Nevertheless, it is always difficult to design an adequate control group and we cannot exclude the possibility of unconsidered confounding of the matching process. Despite using SAPS3 score, which includes some comorbidities but not all, in the matching procedure, one confounding variable may be pre-existing diseases and comorbidities. Unfortunately, we were not able to include more detailed data on comorbidities, which is a limitation of this study.

Another obvious limitation in our study is that many of the sepsis cases could not be matched to non-sepsis cases in the ICU. The unmatched sepsis cases had higher SAPS3 predicted mortality and longer ICU stays, indicating more severe disease. This must be kept in mind when discussing the generalizability of our results. It is plausible that our findings may be generalized to other countries with similar healthcare systems and disease distributions. However, the generalizability to the most severely ill patients with sepsis may be questioned and further studies may be needed to study this population of sepsis patients.

Retrospective observational studies also have general limitations. For example, registry data may not correctly indicate the patient’s clinical condition. Severe sepsis is one of four key diagnoses in the SIR with updated and detailed guidelines that aim to improve coding accuracy and reliability. However, there is no external validation of the coding which is made by attending intensive care physicians at ICU discharge. It is also important to note that the diagnosis of severe sepsis was based on the 2001 consensus criteria, as the Sepsis-3 definition was not established before the study period ended. Misclassification is also possible in the Cause of Death Register, as it is impossible to determine whether the correct diagnosis is registered.20,21 In this context, it may be difficult or impossible to retrospectively verify causes of death, as many patients die outside of hospital (ie lack recent hospital record) and only 11% of deaths in Sweden during 2014 were examined using an autopsy.22 Furthermore, the reporting of causes of deaths may be influenced by the patient’s previous health record, ie patients recently treated for a specific disease (for example sepsis) may be more prone to have this diagnose also registered as a cause of death. This phenomenon is probably more common when there is short time between the ICU stay and death, and may not influence registration of causes of late mortality to the same extent. Another form of misclassification is lack of diagnoses. However, the Swedish Cause of Death Register is founded on a stepwise registration with the goal to include both acute diseases and underlying comorbidity that contribute to death (primary and secondary diagnoses).

When discussing proper diagnosis recording, it is also important to remember that sepsis is a complex clinical condition that can mirror a broad range of other diagnoses. There can also be a subtle difference between severe sepsis and infections without sepsis. For example, a study of ICD coding accuracy using a Swedish register of national hospital admissions (the Swedish National Patient Register) revealed that ICD codes at discharge had a high positive predictive value but a low sensitivity, compared to patient chart reviews.23 Furthermore, we have observed similar results, as only 55% of patients discharged after ICU treatment for sepsis were assigned ICD codes indicating sepsis.24 Thus, this limited accuracy may also apply to the Cause of Death Register, which relies on retrospective ICD coding.

In summary, our results indicate that infectious disease were a more frequent cause of death in patients previously treated for sepsis compared to the matched control group. The study has some limitations, as detailed above. Many of the limitations are general to register-based research, and the results of our study may be further investigated in prospective studies. The explanation for the finding that infectious diseases are more common as a cause of death in patients with a previous ICU-treated sepsis episode compared to ICU-treated patients without sepsis is unclear. Hypothetically, patients treated for sepsis may have persisting alterations in the immune response, warranting studies with longer follow-up periods as well as studies into potential underlying immunological mechanisms.

5 | CONCLUSIONS

The most common causes of late mortality among ICU-treated Swedish patients with and without sepsis were heart diseases and cancer. However, infectious diseases were a more frequent cause of death in the sepsis group, compared to the control group.

CONFLICT OF INTEREST

None.

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APPENDIX 1

International classification of disease codes

Diabetes: E10–14
COPD: J44
Cancer: C00–97
Renal failure: N17–19, N99.0, I13
Infection: A00–99, B00–99, J10–16, J18, J85, R57.2, R65.1
Heart diseases: I20–25, I30–52, R57.0