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Association between hospital onset of infection and outcomes in sepsis patients – A propensity score matched cohort study based on health claims data in Germany

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ABSTRACT

Background: Hospital-acquired infections are a common source of sepsis. Hospital onset of sepsis was found to be associated with higher acute mortality and hospital costs, yet its impact on long-term patient-relevant outcomes and costs is unknown.
Objective: We aimed to assess the association between sepsis origin and acute and long-term outcomes based on a nationwide population-based cohort of sepsis patients in Germany.
Methods: This retrospective cohort study used nationwide health claims data from 23 million health insurance beneficiaries. Sepsis patients with hospital-acquired infections (HAI) were identified by ICD-10-codes in a cohort of adult patients with hospital-treated sepsis between 2013 and 2014. Cases without these ICD-10-codes were considered as sepsis cases with community-acquired infection (CAI) and were matched with HAI sepsis patients by propensity score matching. Outcomes included in-hospital/12-month mortality and costs, as well as readmissions and nursing care dependency until 12 months postsepsis.
Results: We matched 33,110 HAI sepsis patients with 28,614 CAI sepsis patients and 22,234 HAI sepsis hospital survivors with 19,364 CAI sepsis hospital survivors. HAI sepsis patients had a higher hospital mortality than CAI sepsis patients (32.8% vs. 25.4%, RR 1.3, $p < .001$). Similarly, 12-months postacute mortality was higher (37.2% vs. 30.1%, RR=1.2, $p < .001$). Hospital and 12-month health care costs were 178% and 22% higher in HAI patients than in CAI patients, respectively. Twelve months postsepsis, HAI sepsis survivors were more often newly dependent on nursing care (33.4% vs. 24.0%, RR=1.4, $p < .001$) and experienced 5% more hospital readmissions (mean number of readmissions: 2.1 vs. 2.0, $p < .001$).
Conclusions: HAI sepsis patients face an increased risk of adverse outcomes both during the acute sepsis episode and in the long-term. Measures to prevent HAI and its progression into sepsis may be an opportunity to mitigate the burden of long-term impairments and costs of sepsis, e.g., by early detection of HAI progressing into sepsis, particularly in normal wards; adequate sepsis management and adherence to sepsis bundles in hospital-acquired sepsis; and an improved infection prevention and control.

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1. Introduction

Every year, sepsis affects 49 million patients worldwide and is, therefore, considered a leading cause of health loss (Rudd et al., 2020). Despite increasing efforts toward prevention, hospital-acquired infections (HAI) are estimated to cause 24% of sepsis cases according to a recent systematic review and meta-analysis (Markwart et al., 2020). In up to one-third of hospital-acquired sepsis cases, the underlying infection is caused by drug-resistant pathogens such as ESBL-producing *Enterobacteriaceae*, Methicillin-resistant *Staphylococcus aureus*, and multidrug-resistant *Pseudomonas spp.* (World Health Organization, 2020). An estimated 9.3 per 1000 hospital patients have been affected by hospital-acquired sepsis (Markwart et al., 2020). The prevalence is particularly high in the intensive care units (ICU), with 56.5 (95% confidence interval (CI) 35.0–90.2) per 1000 ICU patients affected (Markwart et al., 2020).

Compared to community-acquired sepsis, which is mostly caused by respiratory or urinary tract infections (Henriksen et al., 2015), hospital-acquired sepsis has been found to affect younger patients with preexisting comorbidities and a higher severity of the acute disease in a cohort of US sepsis patients identified using electronic health records (Rhee et al., 2019). After adjusting for these differences, patients with hospital-acquired sepsis were twice as likely to die in the hospital as patients with community-acquired sepsis in this cohort (33.4% vs. 16.8%) (Rhee et al., 2019), Additionally, it has been shown that hospital-acquired sepsis patients have a longer hospital length of stay and higher hospitalizations costs compared to patients with community-acquired sepsis (Adrie et al., 2005; Page et al., 2015), particularly if the sepsis was ICU-acquired (Adrie et al., 2005).

Despite this prior research, we lack knowledge regarding whether the hospital origin of sepsis is associated with poorer long-term outcomes in sepsis survivors. After sepsis, patients often have long-term functional deficits, frequent readmissions for recurrent sepsis or cardiovascular diseases, and increased mortality (Prescott and Angus, 2018). Understanding how long-term outcomes are affected by the hospital origin of sepsis can help to identify modifiable factors to improve patient care and to reduce the burden of survivorship. Therefore, we sought to assess the association between sepsis origin and acute and long-term outcomes based on a nationwide population-based cohort of sepsis patients in Germany.

2. Methods

We conducted a retrospective propensity score-matched analysis of sepsis patients with hospital-acquired infections (HAI) vs. community-acquired infections (CAI). The study was approved by the Jena University Hospital Institutional Review Board (2019–1282-Daten).

2.1. Data source

We used population-based health claims data from the largest provider of health insurances in Germany (Allgemeine Ortskrankenkassen [AOK]), covering approximately 30% of the German population (26.7 million in 2013). Enrolment was unrestricted regarding age, health status, income, or employment. The national research institute of the AOK provided de-identified data of the years 2009–2017, including data on patient characteristics, hospitalizations and outpatient consultations, as well as rehabilitation and other therapies (e.g. occupational therapy), medication, nursing care levels and nursing home residence, as well as sickness benefits payments.

2.2. Study sample

A cohort of hospital-treated sepsis patients among all AOK beneficiaries >15 years discharged from 1/1/2013 through 12/31/2014 was identified using explicit sepsis ICD-10-GM codes (see Supplement), including ICD-10-GM codes for sepsis, severe sepsis and septic shock. In 2013–2014, sepsis was defined according to the sepsis-1/2 criteria (Bone et al., 1992; Levy et al., 2001) in the German coding guidelines. Sepsis cases comprised sepsis cases of all severities, including sepsis with and without organ dysfunction (severe sepsis), and septic shock. As subgroup, we identified patients with severe sepsis including septic shock by ICD-10-GM codes R65.1 (severe sepsis) and R57.2 (septic shock). The first hospital admission in the study time frame was identified as the index hospitalization. We excluded patients with sepsis 24 months prior to the index hospitalization and patients who were not continuously insured by AOK from 01/01/2009 through three years after the index hospitalization or until death. This time frame was chosen because this study was part of the SEPFROK study which includes a three-year follow-up after sepsis (Fleischmann-Struzek et al., 2021). To identify sepsis patients with HAI, we extracted ICD-9 and ICD-10 codes used in previous studies for HAI case identification (van Mourik et al., 2015; Goto et al). These diagnosis codes were mapped ICD-10-GM, after which a selection of HAI codes in the German ICD-10 was validated by two independent investigators. Discrepancies were resolved by discussion. The final HAI diagnoses were reviewed and approved by experts in infectious diseases and medical controlling. Sepsis patients with HAI were defined by at least one of the ICD-10-GM codes for HAI coded as either the primary or secondary hospital discharge code at the index hospitalization (see Supplement). Sepsis patients without these ICD-10-GM codes were considered to have CAI and served as the control group.

2.3. Outcomes

We collected patient demographics, preexisting comorbidities and clinical characteristics using ICD-10-GM codes and procedural codes as well administrative information from the index hospital stay (see Supplement). HAIs were classified as surgical site infections, catheter-associated blood-stream infections, catheter-associated urinary-tract infections, *Clostridium difficile* (*C. difficile*) infections, hospital-acquired pneumonia and other HAIs by using ICD-10-GM codes of primary and secondary hospital discharge diagnoses (see Supplement). Comparing HAI to CAI sepsis patients, we assessed the following acute outcomes: mean hospital length of stay, mean costs of hospital treatment and hospital mortality defined as the proportion of deaths among sepsis cases with HAI/CAI. We further assessed the following long-term outcomes in the 12 months after index hospital discharge: proportion of patients with nursing care dependency (nursing care level≥1 in the German nursing care level system [see Supplement], or nursing home residence), new nursing care dependency (among patients without prior nursing care dependency in the 12 months presepsis), the mean number of hospital readmissions, mean overall health care costs (costs for hospitalizations, outpatient consultations, medications, treatments (e.g. physical therapy, occupational therapy) and rehabilitation), and 12-month mortality (proportion of deaths in the 1–12 months after discharge among hospital survivors of sepsis with HAI/CAI).

2.4. Statistical analyses

We present patient characteristics and clinical features as numbers (percentages), means with standard deviations (SD), or medians with interquartile ranges (IQR). To compare the outcomes of sepsis patients with HAI and CAI after adjusting for potential confounders associated with the risk of HAI and adverse outcomes, we conducted a propensity score matching (PSM). We calculated propensity scores to predict the probability of an HAI given potential confounders. These potential confounders included age, sex, working status, admission category (emergency vs. nonemergency), health status (nursing care dependency, preexisting asplenia and comorbidities according to the Charlson and Elixhauser comorbidity indices, preexisting long-term dialysis and mechanical ventilation, preexisting psychological, cognitive and medical

diagnoses according to the SEPFROK definition) (Fleischmann-Struzek et al., 2021), outpatient care, hospital utilization, and costs for hospital and outpatient treatment, medication, rehabilitation, and other therapies (physical therapy, occupational therapy, etc.) in the 12 months prior to admission (see Supplement). To identify patients with asplenia, this timeframe was extended to up to five years. To match pairs, we used the one-to-one nearest neighbor within-caliper matching with replacement for two reasons. First, this method performs well for large samples with a large ratio of sample sizes of the reference and focus groups. Second, this method ensures that each patient with an HAI is matched to the closest patient in the reference group (CAI) (Leite, 2016). In our study the sample size ratio of CAI to HAI sepsis cases was 3.78:1. We chose a caliper = 0.2 SD, meaning that the matched pairs are not necessarily identical and can differ by up to 0.2 SD of the logit of the propensity score. Austin found that 98% of the bias in crude mean differences can be reduced by PSM with a caliper = 0.2 SD (Austin, 2011). .

We analyzed both the index hospitalization and 12-month outcomes of sepsis patients and the subgroup of severe sepsis patients. Therefore, we conducted four PSM procedures. The PSMs for index hospitalization outcomes included (i) all patients diagnosed with sepsis and (ii) all patients diagnosed with severe sepsis among AOK beneficiaries in 2013–2014. The PSMs for the 12-month outcomes included a subgroup of all index hospitalization survivors of patients with (i) sepsis and (ii) severe sepsis.

The matching with replacement technique permits sepsis cases with CAI to be matched to more than one HAI sepsis case by using case weights. For correct statistical inference with weighted data, statistical methods for complex data were used. For dichotomous outcomes, HAI and CAI sepsis cases were compared using the second-order corrected Rao-Scott F-statistic (Rao and Scott, 1984) with adjusted denominator degrees of freedom (Thomas and Rao, 1987). We provide risk estimates with 95% logit confidence intervals (CI) for both groups. The relative risks (RRs) with 95%-CIs were estimated based on robust quasi-Poisson regression models (Lumley, 2011). Risk differences with 95% Wald CIs were obtained using the Delta-method (Oehlert, 1992) based on the estimates from the binary logistic regression. As measures of practical significance of the group differences between HAI and CAI sepsis cases, we used the percentage change $\Delta_{binary} = (RR - 1) \bullet 100$.

Mean differences in at least interval-scaled outcomes were tested by linear regression models for complex data, which provide corrected standard errors using Taylor linearization (Lumley, 2011). An indicator variable I_{HAI} ($I_{HAI} = 1$ for sepsis patients with HAI, and $I_{HAI} = 0$ for sepsis patients with CAI) was the predictor in this regression of the general form $E(Y \mid I_{HAI}) = \alpha + \beta I_{HAI}$. Hence, the regression coefficient β is the mean difference $\widehat{\mu}_{HAI} - \widehat{\mu}_{CAI}$ between the matched samples. The mean percentage change in the outcome $\Delta_{metric} = 100 \bullet (\widehat{\mu}_{HAI} - \widehat{\mu}_{CAI}) / \widehat{\mu}_{CAI}$ is provided as an effect size measure to quantify practical significance. Δ_{metric} can be computed from the regression parameters: $\Delta_{metric} = 100 \bullet \beta / \alpha$.

All statistical analyses were conducted using R statistical software (R Core Team, 2021 The R package MatchIt was used for propensity score matching (Stuart et al., 2011). The R package survey was used for further statistical analyses of the matched samples with case weights (Lumley, 2011). .

3. Results

Of the 23.0 million beneficiaries > 15 years, we identified 159,684 index sepsis hospitalizations between 2013 and 2014 (Fig. 1).

A total of 69,956/159,684 (43.8%) had severe sepsis, including 20,589 (29.4%) with septic shock. A total of 20.9% (n = 33,399) of sepsis patients and 27.6% (n = 19,327) of severe sepsis patients had a HAI according to ICD-10-GM coded hospital discharge codes (74 and 43 per 100,000 beneficiaries, respectively). Among sepsis and severe sepsis patients, the most common HAIs were hospital-acquired pneumonia (45.1% and 52.2%, respectively), infections with *C. difficile* (20.8% and 19.6%, respectively) and catheter-associated bloodstream infections (17.9% and 17.4%, respectively, Table 1).

Sepsis patients with an underlying HAI were less often female (42.1% vs. 48.9%, $P < .001$) and were younger (mean age 72.6 vs. 74.2 years, $P < .001$) than sepsis patients with CAI. They had more comorbidities (mean Charlson Comorbidity Index 3.6 vs. 3.3, $P < .001$), but had been less dependent on nursing care in the 12 months prior to the index hospitalization (35.2% vs. 39.1% had a nursing care level ≥1, 9.2% vs. 12.3% were nursing home residents, each $P < .001$, Table 1). During the index hospitalization, patients with HAI received more frequent treatment in the ICU (57.2% vs. 27.9%, $P < .001$) and had more surgical procedures (62.7% vs. 28.2%, $P < .001$) than patients with CAI. Similar differences were found between severe sepsis patients with HAI and CAI.

Prior to the PSM, we excluded 1029 (0.64%) of the cases due to missing values in the variable "admission category". The first PSM for the analyses of hospital outcomes included 158,655 cases. The number of matched HAI/CAI cases is reported in Fig. 1. Balance checks based on standardized mean differences indicated very good balancing with respect to all potentially confounding variables (Supplement Tables S1-S4). The maximum absolute standardized mean difference was < 0.02 in all four matched samples (Supplement Fig. S1A-D). In line with these findings, the propensity score distributions of the sepsis cases with HAI and the matched cases with CAI were almost identical (Supplement Fig. S2A-D).

3.1. Hospital outcomes of sepsis and severe sepsis patients with HAI vs. CAI.

Sepsis: The mean hospital length of stay was 18.0 days longer for sepsis patients with HAI than for sepsis patients with CAI (35.6 days vs. 17.6 days, Δ_{metric}=102%, $P < .001$, Table 2). Sepsis patients with HAI had 20,990 Euro higher mean hospital costs (32,788 vs. 11,798 Euro, Δ_{metric}=178%, $P < .001$) and were 29% more likely to die in the hospital (mortality rate: 32.8% vs. 25.4%, RR 1.3, $P < .001$).

Severe Sepsis: Severe sepsis patients with HAI also had longer mean hospital lengths of stay and hospital costs than severe sepsis patients with CAI (mean differences: 18.6 days and 23,588 Euro, Δ_{metric}=98% and Δ_{metric}=138%, respectively, each $P < .001$, Table 2), In-hospital mortality was 45% for both HAI and CAI sepsis patients ($P = 0.362$).

3.2. Long-term outcomes of sepsis and severe sepsis survivors with HAI vs. CAI.

Sepsis: In the 12 months after hospital discharge, nursing care dependency and new nursing care dependency were 16% and 39% more common in survivors of sepsis with HAI than in sepsis survivors with CAI (53.4% vs. 46.2%, RR=1.2, $P < .001$%, and 33.4% vs. 24.0%, RR=1.4, $P < .001$, respectively, Table 3). Survivors of sepsis with HAI had slightly more often hospital readmissions in the 12 months postsepsis (mean number of readmissions: 2.1 vs. 2.0 in survivors of sepsis with HAI vs. CAI, respectively, Δ_{metric}=5%, $P < .001$). Twelve-month mortality was 37.2% in sepsis survivors with HAI and 23% higher than in sepsis survivors with CAI, who had a 12-month mortality of 30.1% (RR=1.2, $P < .001$). One-year post-sepsis health care costs were 22% higher in survivors of sepsis with HAI compared to those with CAI (19,585 Euro vs. 16,123 Euro, $P < .001$).

Severe Sepsis: Seventeen percent and 34% more survivors of severe sepsis with HAI vs. CAI were dependent and newly dependent on nursing care (52.7% vs. 44.9%, RR 1.2, $P < .001$%, and 35.2% vs. 26.2%, RR=1.3, $P < .001$, respectively). In the 12 months after severe sepsis, we found similar differences in hospital readmissions and health care costs among severe sepsis survivors with HAI compared to survivors with CAI (Table 3). The 12-month mortality of survivors of sepsis with HAI was 37.8%, while 32.7% of survivors of sepsis with CAI died during this time (RR=1.2, Δ_{binary}=15%, $P < .001$).

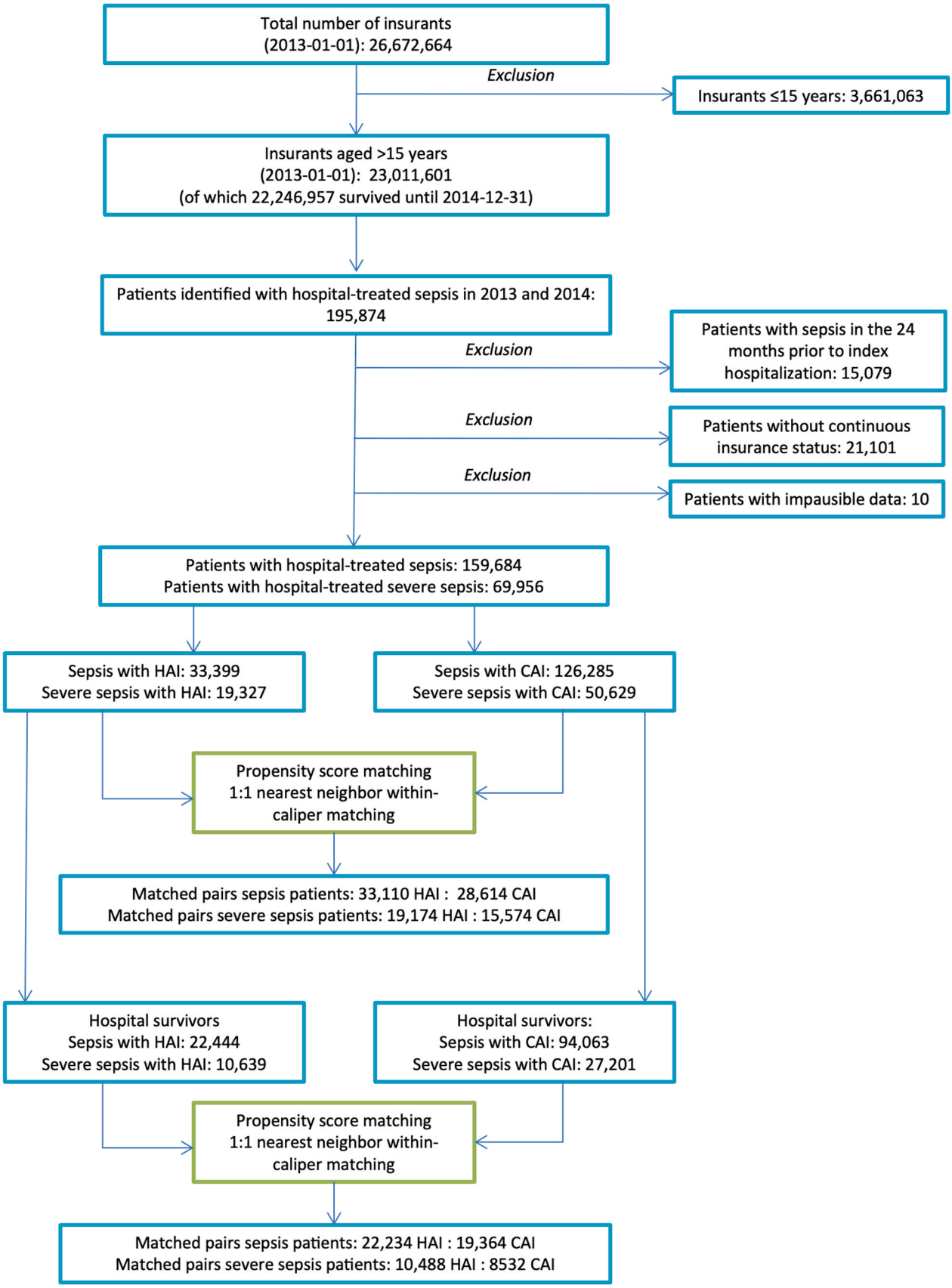

Fig. 1. Flow of study inclusion.

Table 1
Baseline characteristics and clinical features of sepsis patients with HAI (n = 33,399) and CAI (n = 126,285), unmatched cohorts.

Variable	Proportion in % (95%-CI)		p-value[a]
	CAI	HAI	
Index hospitalization			
Female sex	48.9 [48.6, 49.2]	42.1 [41.5, 42.6]	< 0.001
Admission as emergency	59.5 [59.2, 59.8]	53.5 [53.0, 54.1]	< 0.001
Surgical treatment	28.2 [28.0, 28.5]	62.7 [62.2, 63.2]	< 0.001
Occurrence of severe sepsis	40.1 [39.8, 40.4]	57.9 [57.3, 58.4]	< 0.001
Occurrence of septic shock	11.3 [11.1, 11.5]	18.9 [18.5, 19.3]	< 0.001
Underlying HAI			
- Surgical site infection	-	11.4 [11.0, 11.7]	-
- CABSI	-	17.9 [17.5, 18.4]	-
- CAUTI	-	7.6 [7.3, 7.9]	-
- C. difficile infection	-	20.8 [20.4, 21.3]	-
- Hospital-acquired pneumonia	-	45.1 [44.5, 45.6]	-
- Other HAI	-	17.2 [16.8, 17.6]	-
Intensive care treatment	27.9 [27.6, 28.1]	57.2 [56.6, 57.7]	< 0.001
Mechanical ventilation	20.2 [20.0, 20.4]	43.7 [43.2, 44.3]	< 0.001
Renal replacement therapy	7.8 [7.7, 8.0]	19.6 [19.2, 20.1]	< 0.001
Prior health status and occupation 12 months prior to hospital admission			
Employed persons	12.5 [12.3, 12.7]	13.2 [12.8, 13.5]	< 0.001
Nursing home residence	12.3 [12.1, 12.5]	9.2 [8.9, 9.5]	< 0.001
Nursing care level	39.1 [38.9, 39.4]	35.2 [34.6, 35.7]	< 0.001
Long-term ventilation	1.3 [1.2, 1.3]	1.7 [1.5, 1.8]	< 0.001
Long-term dialysis	3.6 [3.5, 3.7]	6.8 [6.5, 7.1]	< 0.001
	M (SD)		**p-value[b]**
	CAI	**HAI**	
Age at admission	74.2 (12.9)	72.6 (12.3)	< 0.001
Charlson-Comorbidity Index[c] 12 months prior to admission	3.3 (2.2)	3.6 (2.3)	< 0.001

Note: [a] The p-value refers to the χ^2-Test with the Null-hypothesis of equal distributions of the categorical variables in sepsis cases with HAI versus CAI.
[b] The p-value refers to the Welch-Test with the Null-hypothesis of no mean differences in the metric variables between sepsis cases with HAI versus CAI.
[c] Unweighted Charlson-Comorbidity Index
Abbreviations:
CAI = community-acquired infection
HAI = hospital-acquired infection
M = Mean
SD = Standard deviation
CABSI = catheter-associated blood-stream infection
CAUTI = catheter-associated urinary tract infection
C. difficile infection = Clostridium difficile infection

4. Discussion

In this population-based cohort of 159,684 sepsis patients identified in German health claims data, we found that hospital-acquired sepsis affected every fifth sepsis patient and 74 per 100,000 beneficiaries per year (severe sepsis: 43 per 100,000). Hospital-acquired sepsis was associated with poor acute and long-term outcomes in survivors of sepsis. After adjusting for differences in patient and treatment characteristics, sepsis patients with HAI were 20–30% more likely to die in the hospital or during the first year after discharge than sepsis patients with CAI. Remarkably, survivors were 39% more often affected by new nursing care dependency after HAI. Due to higher consumption of health care resources, costs were substantially increased for acute care and overall health care in the year postsepsis in sepsis patients with HAI compared to CAI, underscoring the economic burden HAI sepsis poses to modern health care systems.

Our findings are similar to those of previous studies, which reported a hospital origin in approximately 23% of sepsis cases (Markwart et al., 2020). HAIs patients were more often male, previously ill patients, with pre-existing chronic organ replacement procedures, whereas the age differences between HAI and CAI sepsis patients were rather small. While the positive association between HAI sepsis and increased hospital length of stay and costs is consistent with other studies (Rhee et al., 2019; Page et al., 2015; Martin et al), differences in mortality have been previously reported for severe sepsis patients with HAI vs. CAI (Rhee et al., 2019). A recent US study found an odds ratio of 2.1 for in-hospital death comparing hospital with community onset severe sepsis after adjusting for differences in patient characteristics (RR 0.99 in our study) (Rhee et al., 2019). These discrepancies may arise from methodological differences (e.g. different databases, sepsis identification methods or variables used for adjustment) but further research is needed to understand this observation.

Our results expand current knowledge and provide evidence for the negative long-term impact of HAI sepsis origin on nursing care needs, readmissions and costs. There may be different reasons for this observation. On the one hand, patients with HAI sepsis had higher frequencies of septic shock and more often required mechanical ventilation or renal replacement therapy in our cohort, which likely impacts their risk of death and adverse long-term outcomes. On the other hand, previous studies found that patients with hospital- or ICU-acquired sepsis more often received inadequate antibiotic therapy - defined as an escalation of antibiotic therapy within five days – than sepsis patients with community-acquired sepsis; and sepsis patients with inadequate antibiotic therapy are more likely to die (Bloos et al., 2014). One reason for this finding may be the higher proportion of sepsis patients with infections due to drug-resistant bacteria, who receive inadequate empiric antibiotic therapy four times more frequently than patients with nonresistant pathogens according to a recent US study (Rhee et al., 2020). Furthermore, patients on regular wards who develop sepsis during their hospitalization may receive less timely diagnostics. For example, it was shown that compliance with the recommended early lactate measurement as part of the sepsis bundle strategy was highest in the emergency department setting (Han et al., 2018). In contrast, only a minority of nonmedical ward patients or patients with hospital-onset sepsis received this testing (Rhee et al). Delays in sepsis diagnostics and treatment have been found to be associated with poorer acute outcomes, increased long-term mortality (Peltan et al., 2019) and poorer cognitive outcomes (Calsavara et al., Mar 14 2018). This may provide potential opportunities for the prevention of HAI sepsis and associated long-term consequences. On the one hand, a priority must be early detection and guideline-based treatment of sepsis cases, particularly on normal wards, e.g. supported by the implementation of rapid response teams (Hyun et al., 2022). In addition, infection prevention and control (IPC) measures are of particular importance. This includes, among others, IPC programs with trained IPC teams, development and implementation of evidence-based IPC guidelines, IPC education for all health care workers, facility-based HAI surveillance and audits with feedback systems, and optimized staff-to-patient ratios (Storr et al., 2017).

To the best of our knowledge, this is the first study examining the impact of hospital origin on long-term outcomes after sepsis. For this purpose, we chose patient-relevant outcomes, including nursing care dependency and hospital readmissions, that are compensated by the health insurance and, thus, are fully represented in our data. We applied a comprehensive adjustment methodology for between-group differences, including health status, health care utilization and costs in the

Table 2
In-hospital outcomes of sepsis and severe sepsis patients with HAI and CAI after propensity score matching (n = 33,110 HAI sepsis patients and n = 28,614 CAI sepsis patients; n = 19,174 HAI severe sepsis patients and n = 15,574 CAI severe sepsis patients).

Outcome	All Sepsis Cases				
	Proportion in % (95%-CI)		RR (95%-CI)	Δ_{binary} (95%-CI)	*P*-value[a]
	CAI	HAI			
In-hospital mortality	25.4 [24.9, 26.0]	32.8 [32.3, 33.4]	1.29 [1.26, 1.33]	29.1 [25.8, 32.5]	< 0.001
	M (SD)		Mean Diff. (95%-CI)	Δ_{metric} (95%-CI)	*P*-value[b]
	CAI	HAI			
Hospital LOS	17.6 (17,4)	35.6 (29.7)	18.0 [17.6, 18.4]	102.4 [99.2, 105.7]	< 0.001
Hospital costs	11,797.7 (23,179.5)	32,788.0 (45,932.8)	20,990.4 [20,419.3, 21,561.4]	177.9 [170.0, 185.8]	< 0.001
	Severe Sepsis Cases Only				
	Proportion in % (95%-CI)		RR (95%-CI)	Δ_{binary} (95%-CI)	*P*-value[a]
	CAI	HAI			
In-hospital mortality	45.5 [44.7, 46.4]	45.0 [44.3, 45.7]	0.99 [0.97, 1.01]	-1.1 [−3.5, 1.3]	0.362
	M (SD)		Mean Diff. (95%-CI)	Δ_{metric} (95%-CI)	*P*-value[b]
	CAI	HAI			
Hospital LOS	19.1 (18,7)	37.7 (31,2)	18.6 [18.1, 19.2]	97.5 [93.5, 101.5]	< 0.001
Hospital costs	17,068.7 (29,624.6)	40,657.3 (52,010.7)	23,588.7 [22,710.1, 24,467.2]	138.2 [130.2, 146.2]	< 0.001

Note: [a] The *P*-value refers to the second-order corrected Rao-Scott Test for contingency tables of complex data, with the Null-hypothesis of no adjusted differences in the outcome variables between sepsis cases with HAI versus CAI.
[b] The *P*-value refers to the Test of the Null-hypothesis of no adjusted mean differences in the metric variables between sepsis cases with HAI versus CAI.
Abbreviations:
CAI = community-acquired infections
HAI = hospital-acquired infections
LOS = length of stay
RR = Relative risk
M = Mean
SD = Standard deviation

year presepsis (five years for asplenia). Another major strength of our study is the population-based design using complete inpatient and outpatient health claims data of the six years surrounding the index hospitalization is another major strength of our study. Furthermore, our large patient sample that covered 30% of the German population and had a broad geographical representation to allow us to generate the first estimates on the population burden of HAI sepsis in Germany.

Our study also has a series of important limitations. First, we identified sepsis patients with HAI in health claims data using explicit ICD-10-GM codes, which were selected and adapted from international studies. This method was chosen because, in Germany, no specific "present-on-admission flag" is available in health claims data. We, therefore, selected ICD-10-GM codes that clearly indicated infections of nosocomial origin (e.g., hospital-acquired pneumonia, infections following a medical procedure). However, the validity of these codes for the detection of hospital-acquired infections is currently unknown and does not allow us to distinguish hospital-acquired from health care-associated infections. Additionally, it must be considered that health claims data are generated for reimbursement purposes and may be prone to external incentives. To detect incorrect coding, hospital reimbursement data are thoroughly checked by the Medical Review Board of the Health Insurance Funds in Germany and returned to hospitals for correction, if necessary. Increasingly, hospital discharge diagnoses are also used as quality indicators in the nationwide mandatory external inpatient quality assurance of the Federal Office for Quality Assurance (e.g., for community-acquired pneumonia [defined by the absence of hospital-acquired pneumonia ICD-codes]) (Busse et al., 2009) or in the program "quality assurance with administrative data" of the health insurance provider AOK (e.g., for infection following a medical procedure) (Jeschke et al., 2015). A previous study that assessed the accuracy of the coding of hospital-acquired pneumonia for quality management purposes found an underestimation of cases in the hospital discharge data in Switzerland (Wolfensberger et al., 2018). Second, the issue of coding accuracy also applies to sepsis case identification and preexisting illnesses included in the propensity score matching. Sepsis case identification using ICD-coding has lower sensitivity compared to the gold standard of manual chart review (Iwashyna et al., 2014; Fleischmann-Struzek et al., 2018). The validity of comorbidity coding seems to vary between comorbidities with a tendency for the under-representation of the comorbidity burden in administrative data (Quan et al). Therefore, we included inpatient and outpatient data to use the most available information to assess the prior health status. Third, we are unable to further explore the underlying mechanisms of the observed differences and have no detailed information on the causative pathogens and their antimicrobial susceptibility. Fourth, although we used a comprehensive adjustment, a residual confounding cannot be fully ruled out. Fifth, the sample of AOK patients may not be fully representative of the German population, although previous studies have suggested only minor differences between AOK and non-AOK beneficiaries in Germany (Jeschke et al., 2019).

5. Conclusion

Hospital-acquired infections are a common cause of sepsis and are associated with poorer acute and long-term outcomes than community-acquired sepsis. There are opportunities to reduce poor acute long-term outcomes of sepsis patients, by early detection of HAI progressing into sepsis, particularly in normal wards; adequate sepsis management and adherence to sepsis bundles in hospital-acquired sepsis; and an improved infection prevention and control.

CRediT authorship contribution statement

NR and CFS conceptualized the study and drafted the study protocol. All other authors contributed to the study conceptualization, protocol and data analysis plan. AF and JS defined the calculation of the applied costs of care variables. MS, LW and JS prepared and checked the data. NR conducted the statistical analyses. All authors interpreted the data. NR and CFS wrote the first draft of the manuscript. All authors revised the manuscript for important intellectual content and approved the final manuscript.

Table 3
Twelve-month outcomes of sepsis and severe sepsis survivors with HAI and CAI after propensity score matching (n = 22,234 HAI sepsis hospital survivors and n = 19,364 CAI sepsis hospital survivors; n = 10,488 HAI severe sepsis hospital survivors and n = 8532 CAI severe sepsis survivors).

Outcome	All Sepsis Cases				
	Proportion in % (95%-CI)		RR (95%-CI)	Δ_{binary} (95%-CI)	*P*-value[a]
	CAI	HAI			
Nursing care dependency	46.2 [45.5, 46.9]	53.4 [52.8, 54.1]	1.16 [1.13, 1.18]	15.7 [13.3, 18.0]	< 0.001
New nursing care dependency*	24.0 [23.3, 24.6]	33.4 [32.8, 34.0]	1.39 [1.35, 1.44]	39.4 [35.0, 44.0]	< 0.001
12-month mortality	30.1 [29.5, 30.8]	37.2 [36.5, 37.8]	1.23 [1.20, 1.27]	23.3 [19.9, 26.9]	< 0.001
	M (SD)		Mean Diff. (95%-CI)	Δ_{metric} (95%-CI)	*P*-value[b]
	CAI	HAI			
Number of hospital readmissions	2.0 (2.7)	2.1 (2.6)	0.1 [0.1, 0.2]	5.1 [2.4, 7.8]	< 0.001
Overall health care costs in Euro	16,122.8 (26129.1)	19,585.4 (29837.1)	3462.6 [2898.3, 4026.8]	21.5 [17.6, 25.4]	< 0.001
	Severe Sepsis Cases Only				
	Proportion in % (95%-CI)		RR (95%-CI)	Δ_{binary} (95%-CI)	*P*-value[a]
	CAI	HAI			
Nursing care dependency	44.9 [43.8, 46.1]	52.7 [51.7, 53.6]	1.17 [1.14, 1.21]	17.3 [13.7, 21.0]	< 0.001
New nursing care dependency*	26.2 [25.2, 27.3]	35.2 [34.3, 36.1]	1.34 [1.28, 1.41]	34.2 [28.1, 40.6]	< 0.001
12-month mortality	32.7 [31.6, 33.8]	37.8 [36.8, 38.7]	1.15 [1.11, 1.20]	15.5 [10.8, 20.3]	< 0.001
	M (SD)		Mean Diff. (95%-CI)	Δ_{metric} (95%-CI)	*P*-value[b]
	CAI	HAI			
Number of hospital readmissions	1.9 (2.3)	2.0 (2.3)	0.1 [0.0, 0.2]	5.9 [2.1, 9.7]	0.002
Overall health care costs in Euro	16,000.0 (26441.0)	19,322.3 (28480.1)	3322.3 [2499.8, 4144.7]	20.8 [15.0, 26.5]	< 0.001

Note: [a] The *P*-value refers to the second-order corrected Rao-Scott Test for contingency tables of complex data, with the Null-hypothesis of no adjusted differences in the outcome variables between sepsis cases with HAI versus CAI.
[b] The *P*-value refers to the Test of the Null-hypothesis of no adjusted mean differences in the metric variables between sepsis cases with HAI versus CAI.
* among survivors without pre-existing nursing care dependency
Abbreviations:
CAI = community-acquired infections
HAI = hospital-acquired infections
LOS = length of stay
RR = Relative risk
M = Mean
SD = Standard deviation

Conflicts of Interest

The authors declare no competing interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ijmm.2023.151593.

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