Doctoral theses at NTNU, 2024:36

Nina Vibeche Skei

Incidence, case fatality and long-term outcomes in patients with sepsis

Nationwide registry studies of sepsis and COVID-19-related sepsis

Doctoral thesis

NTNU
Norwegian University of Science and Technology
Thesis for the Degree of
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Department of Circulation and Medical Imaging

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Norsk Sammendrag (Norwegian summary)***:***

Forekomst og prognose hos pasienter med sepsis

Sepsis er en alvorlig immunologisk reaksjon på en infeksjon som fører til svikt i kroppens organer, og en vanlig årsak til sykehusinnleggelse, sykelighet og død. Etter å ha overlevd sepsis lever mange med helseplager og redusert livskvalitet, som påvirker optimal helbredelse, inkludert mulighetene til å komme tilbake i jobb. Derfor er formålet med denne avhandlingen a) å undersøke forekomst og sykehusdødelighet av sepsis, b) å undersøke prognose for overlevelse av sepsis etter utskrivelse fra sykehus, og c) å undersøke om overlevere returnerer til arbeid etter sepsis.

I Studie 1 (2008-2021) undersøkte vi forekomst og sykehusdødelighet av sepsis og fant at aldersstandardisert forekomst var 352 per 100.000 innbygger og 13.7% døde i sykehus. Forekomsten av sepsis økte med 15%, mens sykehusdødeligheten ble redusert med hele 28%. Økningen i forekomst skyldtes i hovedsak at flere pasienter ble innlagt med sepsis gjentatte ganger, med en dobling blant pasienter med gjentatte sepsis episoder over 60 år. I 2020 og 2021 snudde denne trenden; forekomsten av sepsis gikk ned, samtidig som sykehusdødeligheten gikk opp. Sammenlignet med andre sepsis pasienter hadde pasienter med COVID-19 som årsak til sepsis i gjennomsnitt noe høyere sykehusdødelighet.

I Studie 2 (2008-2021) hvor vi undersøkte prognosen etter en innleggelse med sepsis fant vi at 17%, 24%, 34% og 59% ikke overlevde 30 dager, 90 dager, 1 år og 5 år. Vi fant at trenden i dødelighet var synkende, og størst var nedgangen hos pasienter med lungeinfeksjon som årsak til sepsis. Pasienter med tilleggssykdommer som kreft, kronisk lungesykdom, demens og kronisk leversykdom hadde større risiko for å dø sammenlignet med kronisk hjerte- og karsykdommer. Risikoen for å dø for pasienter som hadde behov for intensivbehandling sammenlignet med pasienter innlagt på sengepost var høyere til og med 1 år etter innleggelse, men utjevnet seg ved 5 år. Videre hadde pasienter med COVID-19 som årsak til sepsis omtrent samme risiko for å dø som andre sepsis pasienter.

I Studie 3 (2010-2021) undersøkte vi om de som overlevde sepsis kom tilbake i arbeid, og fant at ved ½, 1 og 2 år etter utskrivelse var henholdsvis 58%, 68% og 63% tilbake i jobb. Trenden i andelen som var i jobb var stabil (ved ½ og 1 år), bortsett fra ved 2 år hvor andelen i jobb ble redusert med hele 19%. Yngre pasienter, pasienter med færre kroniske tilleggssykdommer og færre akutte organsvikter hadde høyere sjanse for å komme tilbake i jobb. I tillegg fant vi at pasienter med COVID-19 som årsak til sepsis hadde høyere sjanse for å komme tilbake i jobb sammenlignet med andre sepsispasienter.

Avhandlingen baserer seg på data fra Norsk Pasientregister, Statistisk Sentralbyrå, Dødsårsaksregisteret, Norsk Intensivregister, og Norsk Arbeids- og Velferdsforvaltning.

Oppsummert viser denne avhandlingen at antallet pasienter som overlever sepsis er økende. Nedgangen i antall sepsis innleggelser under COVID-19 pandemien i kombinasjon med økt sykehusdødelighet gir grunn til bekymring, og de tiltak som ble gjort for å forhindre spredning av SARS-CoV-2 bør undersøkes nærmere. Den synkende utviklingen i antall pasienter som er i jobb ved 2 år etter en sepsis diagnose er urovekkende. Dette og identifisering av utsatte pasientgrupper, som gjør det mulig å forbedre prognoser med målrettede tiltak, kan være nyttig kunnskap for arbeidsgivere, i tillegg til politikere og helseledere som har ansvar for å planlegge fremtidens helsetjeneste.

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Paper I

Skei NV, Nilsen TIL, Knoop ST, Prescott H, Lydersen S, Mohus RM, Brkic A, Liyanarachi KV, Solligård E, Damås JK, Gustad LT. ***Long-term temporal trends in incidence rate and case fatality of sepsis and COVID-19-related sepsis in Norwegian hospitals, 2008-2021: a nationwide registry study***. BMJ Open. 2023 Aug 2;13(8):e071846. doi: 10.1136/bmjopen-2023-071846. PMID: 37532480; PMCID: PMC10401253.

Paper II

Skei NV**,** Nilsen TIL, Mohus RM, Prescott HC, Lydersen S, Solligård E, Damås JK, Gustad LT. ***Trends in mortality after a sepsis hospitalization: a nationwide prospective registry study from 2008 to 2021.*** Infection. 2023 Aug 12. doi: 10.1007/s15010-023-02082-z. Epub ahead of print. PMID: 37572240.

Paper III

Skei NV, Moe K, Nilsen TIL, Aasdahl L, Damås JK, Prescott HC, Gustad LT. ***Return to work after a sepsis hospitalization: A nationwide, register-based cohort study.***
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Abbreviations

ARDS	Acute respiratory distress syndrome
BCE	Before common era
CE	Common era
CFR	Case fatality risk
CI	Confidence interval
DÅR	The Norwegian Cause of Death Registry
HR	Hazard ratio
ICD-10	International classification of diseases, version 10
ICU	Intensive care unit
GBD	Global burden of disease
IR	Incidence rate
IRR	Incidence rate ratio
LOS	Length of stay
MERS	Middle East respiratory syndrome
NAV	The Norwegian Labour and Welfare Administration
NIR	The Norwegian Intensive Registry
NPR	The Norwegian Patient Registry
OR	Odds ratio
PIN	Personal identification number
q-SOFA	Quick sequential organ failure assessment
REK	Regional Ethical Committee
RTW	Return to work
SARS-CoV-2	Severe acute respiratory syndrome - corona virus
SIRS	Systemic response syndrome
SOFA	Sequential organ failure assessment
SSB	The Statistics of Norway
WHO	World Health Organization

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Nina Vibeche Skei, August 2023

Summary

Sepsis is a severe immune reaction to an infection that leads to acute organ dysfunction and is a common cause of hospitalization, morbidity, and death. After surviving sepsis, many patients experience health impairments and reduced quality of life, which affects successful recovery, including the ability to return to work. Even though most studies have found an increasing incidence of sepsis in the last decade, a recent global study suggests the opposite. Epidemiological studies that describe trends are sparse, and it is essential to increase our knowledge of the incidence and prognosis of sepsis to plan for future health services. Therefore, this thesis aims a) to investigate the incidence and in-hospital mortality of sepsis, b) to investigate the prognosis of sepsis after hospital discharge, and c) to investigate the ability of sepsis survivors to return to work.

Among 12,619,803 adult patients discharged from non-psychiatric hospitals in 2008-2021, 2.5% had a diagnostic code matching sepsis. This accounted for 317,705 hospitalizations with sepsis (Study 1), of which 222,282 (70%) were admitted with sepsis for the first time (Study 2). Further, of those admitted with a first sepsis episode, 12,260 (34%) were between 18 and 60 years old, working prior to hospitalization and discharged alive (Study 3).

In Study 1, we found that the incidence of sepsis increased by 15% during the study period, mainly because of an increase in recurrent sepsis episodes. Patients over 60 years of age were more likely to be admitted with recurrent sepsis episodes. The mean in-hospital death was 13.7%. During the study period, the in-hospital mortality was reduced by 28%, and the highest reduction was among patients admitted with a first sepsis episode with 43%. Fewer sepsis patients were admitted during the first two COVID-19 pandemic years, and in-hospital

mortality increased during this period. COVID-19-related sepsis accounted for 1 out of 10 hospitalizations with sepsis in this period. Compared to other sepsis patients, patients with COVID-19-related sepsis had a somewhat increased risk of in-hospital death.

In Study 2, we found that 17%, 24%, 34%, and 59% of the patients did not survive 30 days, 90 days, 1 year, and 5 years, respectively. During the study period, we found a 14% reduction in 30-day, 90-day, and 1-year mortality and a 9% reduction in 5-year mortality. The highest decrease was seen among patients with respiratory tract infection as the cause of sepsis, with 10% reductions in 30-day and 90-day mortality and 16% and 11% reductions in 1-year and 5-year mortality. In addition, patients with comorbidities such as cancer, chronic lung disease, dementia, and chronic liver disease had an increased risk of dying compared to those with chronic heart and vascular disease. The mortality for patients in need of intensive care treatment compared to patients admitted to the ward was 26% vs. 17% at 30-day, 32% vs. 24% at 90-day, and 41% vs. 34% at 1-year. This difference aligned at 5-years and was 61% in patients that needed intensive care treatment and 58% in patients admitted to wards. Further, patients with COVID-19-related sepsis had approximately the same risk of death as other sepsis patients.

In Study 3 (2010-2021), we found that 58% of sepsis patients had returned to work at ½ year, 68% at 1 year, and 63% at 2 years after hospitalization. The trends were stable during the study period (at ½ and 1 year), except at 2 years, where we found a 19% reduction in the proportion of patients that had returned to work between 2010 and 2019. Younger patients, patients with fewer comorbidities, and patients with fewer acute organ dysfunctions had an increased risk of returning to work. In addition, we found that patients discharged with

COVID-19-related sepsis had an increased probability of returning to work compared to other sepsis patients.

This thesis is based on individual-level data from 5 nationwide registries: The Norwegian Patient Registry (NPR), Statistic Norway (SSB), The Norwegian Cause of Death Registry (DÅR), The Norwegian Intensive Registry (NIR), and the Norwegian National Social Security System Registry (NAV). Diagnostic codes from NPR were used to identify sepsis in patients over 18 years of age hospitalized at all Norwegian public hospitals from 2008 through 2021. The extraction of diagnostic codes was in line with international standards and existed of one code with infection combined with a code of acute organ dysfunction, in addition to specific codes for sepsis. Patients` characteristics were retrieved from NPR, together with diagnostic codes for selected comorbidities. In Study 1, we used first and recurrent sepsis episodes from NPR and population data from SSB to calculate incidence and further the date of in-hospital death from NPR to calculate in-hospital mortality. In Study 2, we used the first sepsis episode from NPR and the death date from DÅR to estimate mortality. We linked the first sepsis episode from NPR to NIR in Study 2 and Study 3 to find patients needing intensive care treatment. Finally, to evaluate return to work in working-age patients discharged with a first sepsis episode in Study 3, we linked NPR with sick leave, work assessment, and disability data from NAV.

Summarized, this thesis shows that the number of sepsis survivors increases. The decrease in the number of sepsis admissions during the COVID-19 pandemic, combined with increased in-hospital mortality, is concerning, and efforts to prevent the spread of severe acute respiratory syndrome-coronavirus (SARS-CoV-2) should be investigated further. The decreasing trend in patients working at 2 years is worrying. This and identifying vulnerable

patient groups that warrant targeted interventions to improve long-term outcomes can be helpful knowledge for employers, politicians, and health leaders with responsibility for the future of health services.

1.0 Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Around 1-3 % of all hospitalizations are due to sepsis [2, 3], with a high rate of in-hospital death that varies between 15% to 56% [4-7]. Accounting for approximately 20% of all-cause global deaths [8], sepsis is a burden to public health. An increasing number of new infectious agents affecting humans [9] and increasing antibiotic resistance [10, 11] raise a concern that infectious diseases and sepsis will continue to represent a formidable challenge. In a report published in 2017, The World Health Organization (WHO) acknowledged sepsis as a significant health concern and underscored the need for research in its epidemiology [12].

Sepsis survivors often experience cognitive and functional impairments [13, 14], with a high risk of new infections and recurring sepsis episodes. This makes normal activities hard to resume and affects the ability to return to work [15]. Further, sepsis survivors have an elevated risk of death up to two years after discharge [16]. Moreover, sepsis became highly actual during the recent COVID-19 pandemic caused by the novel severe acute respiratory syndrome-coronavirus (SARS-CoV-2) that infected an unprecedented number of persons and caused a public health crisis with notable economic and social consequences [17]. To meet the elevated healthcare use [18] and delayed return to work, contemporary trends are needed to commission appropriate health services and work facilitations.

Sepsis can originate from bacterial, virus, and fungal infections, leading to failure in different organ systems [1, 19]. In patients where we suspect sepsis, we gather knowledge by performing clinical examinations, which we support by vital measures, imaging, and blood

tests [20]. Diagnosing sepsis is thorough work, and detection may be difficult because of the heterogeneity of the syndrome. As an experienced clinician in the intensive care units (ICUs), I can still be surprised by the diversity sepsis represents. Working with patients with sepsis has always fascinated me and became even more actual during the COVID-19 pandemic. Fortunately, this project started after the outbreak of SARS-CoV-2, and therefore, we could successfully integrate the novel virus into the investigation.

This thesis is based on three papers referred in the text by Roman numerals I-III. The three papers describe the understanding of the burden of sepsis in terms of incidence and case fatality rate while hospitalized for first and recurrent sepsis (Paper I), long-term mortality after survival of sepsis (Paper II),, and the ability to return to work within two years (Paper III) after hospitalization. Together, these three papers are an important contribution to sepsis epidemiology.

For centuries, infectious diseases, including sepsis, have been the leading cause of mortality and morbidity and continue to challenge our health security and human progress. In the next paragraph, I will summarize historical events leading up to our current understanding of sepsis.

2.0 Background

2.1 Understanding the history of sepsis and severe infectious diseases with high impact

Sepsis is a constant threat to the human population with seasonal and non-seasonal infectious diseases. Historically, this burden has peaked during the various pandemics, where “The Black Death” is an example of the deadliest and reduced the European population by one-third [21]. Historic influenza pandemics have been less lethal, and an example is the “Spanish Flue,” where 3-6% of the world’s population died [22].

The next section presents a description of our understanding of sepsis from ancient to modern times and some of the most important discoveries in medical history.

2.1.1 Sepsis

Over thousands of years, the meaning of the term sepsis has changed remarkably. The word “sepsis” [σηψις] is derived from the Greek verb form "sepo" [σηψις][23]. Translated sepo means "I rot." The first time we meet the word is in Homers` writings, a Greek author presumed to have lived in the 9th or 8th century Before the Common Era (BCE). In Hippocrates` work Corpus Hippocraticum (400 BCE), we can find the word "sepidon" [σηπεδών] in the meaning of "the decay of webs," and he viewed sepsis as dangerous biological decay that could potentially occur in the body. Sepsis was also later used in the same meaning by Aristoteles, Plutarch, and Galen [24].

Hippocrates (460-370 BCE) was one of the first to explore a cure for sepsis using different medical compounds, including alcohol [25]. Another medical authority fighting sepsis was

the Roman physician Galen (129-199 Common Era (CE)). He was known for his "apothecia," a collection of different substances used as medicine, and an expert on abscess drainage and bloodletting. Galen believed that pus formation was critical in the healing process of injured tissues, known as the putrefaction theory. This theory was unchallenged until the 19th-century, when the findings of Semmelweis, Pasteur, Lister, Davaine, and Koch contributed to influential developments and knowledge in the cause of sepsis [25]. The earliest of these men was the Hungarian Ignaz Semmelweis (1818-1865). He discovered that hand washing could prevent the passing of illness from physicians to patients and is credited for uncovering the role of hygiene in preventing disease outbreaks. The discoveries of Semmelweis were later vindicated by the theory that microbes cause infection (Germ Theory) and the intervention of antiseptic technique. The Germ Theory was proposed by the French chemist Louis Pasteur (1822-1895) in 1878, hypothesizing that putrefaction required living organisms, thus rejecting the putrefaction theory, which stated that putrefaction arises spontaneously. These new findings by Pasteur found their way to the British surgeon Joseph Lister (1827-1912), who managed to reduce post-operative infections using phenol by linking the Germ Theory to the origin of putrefaction in wounds [26]. Pasteur also created the first laboratory-produced vaccine against fowl cholera in chickens and later prevented rabies through post-exposure vaccination [27]. During the same era, the French physician Casimir-Joseph Davaine (1812-1882) injected rotten blood into 25 mise and observed that they died shortly. Thus, he managed to identify the causative organism but was unaware of its true etiology [24]. Further, the German physician Robert Koch (1843- 1910) managed to investigate the etiology of Bacillus anthracis, which was crucial in the development of an antitoxin, and formulated his famous postulate. The postulate is a medical concept with four generalized medical principles to determine the relationship of pathogens with specific diseases and is still a part of microbiological diagnostics [28]. The Germ Theory (Pasteur),

handwashing (Semmelweis), the invention of the antiseptic technique (Lister), and disease transmission (Koch) led to the discovery of Penicillin by Aleksander Fleming in 1929 [29-32]. The discovery of penicillin and the rapid development of new antibiotics from the 1940s was of utmost importance for sepsis survival [33], and almost nine decades later, antibiotics remain the cornerstone of sepsis treatment [20, 34, 35]. Moreover, influenza vaccine development became a priority during World War I, when the Spanish Flue killed 1 in 67 United States soldiers [27]. However, the first influenza vaccine approved for military use came as late as 1945, and the year later, it was approved for civilian use [27]. Today, infectious diseases are prevented through vaccine programs, and this has made infectious diseases less lethal.

With the advanced microscope and the discovery of bacteria, the first modern attempt to define sepsis was done was in 1914 by Hugo Schottmuller. He wrote ”sepsis is present if a focus has developed from a pathogenic bacteria, which constantly or periodically, invade the bloodstream in such way that this causes subjective and objective symptoms” [36]. At this time, the first iron lung was already in use to treat polio patients. However access to the patient was a problem, so respirator rooms with access through a door were developed to care for the patients [37]. When the polio epidemic reappeared in 1950, mortality went from 80 to 40 % by treating the polio patients with tracheostomy and positive pressure ventilation [37]. A high number of patients in need of mechanical ventilation at the same time approached a logistical challenge, and the first ICUs as we know them today were developed [37]. Providing support with assisted ventilation and a greater focus on oxygenation failure supported by improvements in blood gas measuring further led to the identification of acute respiratory distress syndrome (ARDS) in the 1960s [37]. Further, as sepsis is the leading

cause of ARDS, the development of ventilator strategies became a cornerstone of organ support in sepsis [38].

During the 18th and 19th-centuries, the term sepsis began to lose its connection to rottenness and became synonymous with infection and “blood poisoning.” Nevertheless, our understanding of the pathogenesis of sepsis changed, and early recognition of the source of infection, improved imaging techniques, new broad-spectrum antibiotics, better invasive hemodynamic monitoring, and better use of fluids and vasoactive agents represent today's key advances in modern medicine. However, despite advanced development in organ support therapy, the world still lacks targeted treatment against the dysregulated immune response that causes acute organ dysfunctions in sepsis patients.

Reviewed prehistoric definitions of widespread infectious diseases vary. In the following historical overview, we have named the worldwide outbreaks of infectious origin before and including “The Black Death” as plagues, while outbreaks after are named pandemics.

2.1.2 Historical plagues and pandemics with high impact

Historically, “plague” was used to describe a febrile disease causing a high mortality rate [39]. The use of the term has changed throughout history and is today limited to outbreaks caused by a bacteria named Yersinia pestis. Interestingly, the first use of the word pandemic as late as 1666 describes a continuously spreading disease in a country, which was further used synonymously with the term “epidemic” in the following 200 years [40]. The current definition of a pandemic is an epidemic caused by an infectious disease that occurs worldwide or over an extensive area, crossing international boundaries and usually affecting many people [41]. This modern definition excludes severity and level of mortality caused by

infectious disease and includes nothing about population immunity, virology, or disease severity [41]. Nevertheless, the fatalities seen during the plagues and pandemics are due to acute organ dysfunction and would have been diagnosed as sepsis in today's medicine. Throughout history, two revolutions have changed how humans live: the development of agriculture 10,000 years ago (Neolithic Revolution) and the Industrial Revolution starting in the 18th century. The Neolithic Revolution marked the transition from small, nomadic bands of hunter-gatherers to agricultural settlements. Through increased interactions between humans and animals, these early civilizations made it possible for contagious diseases to cross borders and cause plagues [39, 42]. Sometimes, during a short period, these plagues reduced the population by one-fifth, one-third, or even maybe by half. Because of these plagues, wars were lost, cities were depopulated, and economies ended. The various infectious diseases have influenced the world's history, and a prerequisite for spread has been trading between different countries. The first historical description of an infectious disease that spread over borders and had high mortality is from the Peloponnesian War, 430 BCE [22]. Agens of this first documented infection are uncertain, but some have postulated typhoid fever, others Ebola virus hemorrhagic fever [43]. After this, we find reports of "The Antonine Plague" (smallpox) in 165-80 CE and two plagues caused by Yersinia Pestis; "The Justinian Plague" in the mid-sixth century and "The Black Death," which originated from China in 1334 CE. "The Black Death" was the first plague caused by Yersinia Pestis in almost a thousand years and was followed by many other small outbreaks with high mortality. During "The Black Death," a theory about contagious air (miasma theory) developed, and soon it became clear that the smartest thing to do was to escape from the pest (a solution limited to privileged people only). Ships with sick crew members and passengers were not allowed to enter the docks, which is the first description of quarantine used in disease management [44], a solution that is in use even today. Further, the novel miasma

theory became the precursor for modern bacteriology. Since the 18th century, Yersinia Pestis epidemics in Europe have been absent, probably because of better hygiene and the extermination of black rats.

Influenza epidemics have been known in Europe since the 16th century [45]. An example is the “la russe” that revenged in East Europe in 1781-82 and later became a pandemic [45]. During World War I, when the population was weakened [46], “The Spanish Flue” caused by the influenza A virus [22] became the most lethal influenza pandemic in history, and 50 to 100 million people died. The Spanish Flue was the first true pandemic that epidemiologists and specialists in infectious diseases studied [47]. Less severe examples of the 20th-century pandemic are the “Asian Influenza” in 1957 and “Hong Kong Influenza” in 1968-69 caused by the influenza A virus [45]. While the mortality during Spanish flue was highest among 20-40 years-old , the Asian and Hong Kong influenza caused significant morbidity and mortality, especially among the elderly [45].

In modern times also other viruses like Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), Swine flu, and the latest severe acute respiratory syndrome-related coronavirus (SARS-CoV-2) have spread across borders and affected humanity [48]. The world experienced a surge in need of ICU treatment with the COVID-19 virus causing organ dysfunction [34]. Virus infection may further be complicated by co-infections and/or secondary infection [49], and treatment and recovery may thus be prolonged, or mortality may rise. During the COVID-19 pandemic, the vaccine development accentuated in technology, administrative routes, and vaccination strategies form a milestone in pandemics to come [50].

Common for all pandemics is that they have shaped and had profound and lasting effects on societies' economies, politics, and social aspects [45]. Without all the achievements described above, the progress seen during the Industrial Revolution would have been challenging. The Industrial Revolution shaped diverse research and educational societies, made it possible for the pharmaceutical industry to mass produce medicine and eased the distribution of findings through the development of infrastructure, and includes new knowledge and innovations during the recent pandemic [51, 52]. In the next section, we provide a detailed description of the past and current definition of sepsis and the burden sepsis represents.

2.2 Definition of Sepsis

Although diagnosing and treating infectious diseases and sepsis improved, the definition of sepsis was unchallenged until the end of the 20th century (Figure 1).

2.2.1 Past definitions

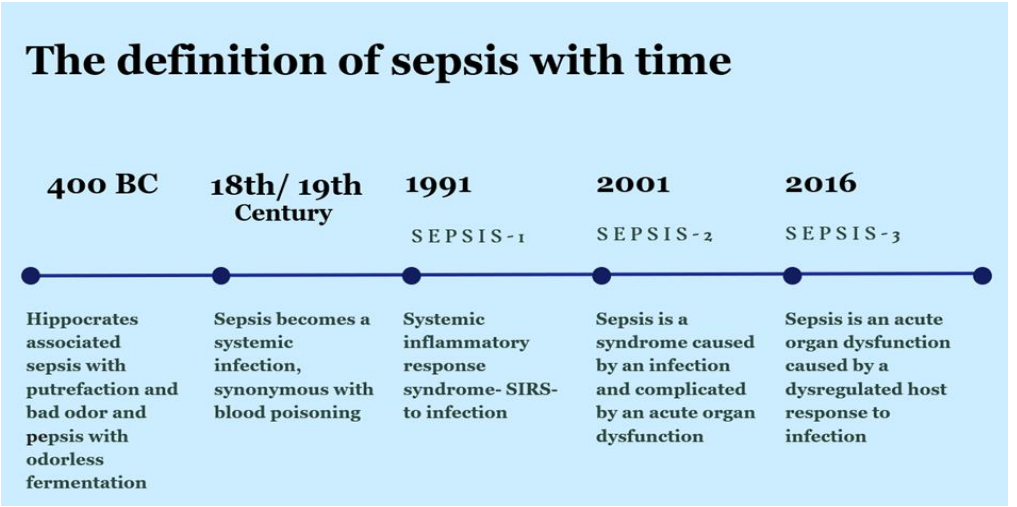

Figure 1. Timeline for the development of the meaning of the term sepsis

The first modern definition of sepsis (Sepsis-1) came after a consensus conference in 1991 that defined *sepsis* as a systemic inflammatory response syndrome (SIRS) to infection [53]. Two or more SIRS signs had to be present: temperature > 38°C or < 36°C, heart rate > 90 per minute, respiratory rate > 20 per minute or $PaCO_2$ < 32 mmHg (4.3kPa), and/or white blood cell count > 12 000/mm^3 or < 4000/mm^3 or >10 % immature band cells. Sepsis was then divided into three severity stages: sepsis, severe sepsis, and septic shock. Severe sepsis was present if the infection was complicated by organ dysfunction, and septic shock was present if hypotension persisted despite adequate fluid resuscitation.

In 2001, the second revision (Sepsis-2) pinpointed some limitations with the first definition. They stated that early organ dysfunction could indicate sepsis and facilitated bedside diagnostic warning signs of systematic inflammation, and in addition, general, inflammatory, hemodynamic, and tissue perfusion parameters were added [54].

2.2.2 Current definition

The Sepsis-2 definition was again challenged in 2016 by perspectives that claimed that the host response to sepsis is more complex and often involves concomitant, integrated antagonistic processes of exaggerated inflammation and immune response. Therefore, the term severe sepsis was considered redundant. Sepsis is currently defined as a dysregulated host response to infection that can lead to tissue damage, organ failure, and death (Sepsis-3) [1]. The need for vasopressors to maintain a mean arterial pressure of > 65 mmHg, despite adequate fluid resuscitation and lactate levels > 2 mmol per liter, was then used to define septic shock [1]. The SIRS criteria were still recognized by the Sepsis-3 definition as useful for identifying infection, however, combined with clinical symptoms to recognize the nature of the infection and its origin. To assess organ dysfunction in response to infection, the

Sepsis-3 definition required at least two points of deterioration on the Sequential Organ Failure Assessment Score (SOFA score) that assesses organ dysfunction in the respiratory-, cardiovascular-, hepatic, coagulation-, renal- and central nervous system. A quick Sequential Organ Failure Assessment Score (qSOFA) was also developed as a bedside tool to identify patients with acute organ dysfunctions due to sepsis. One point was scored for each of the following measures, where two or more qSOFA points should suspect sepsis: 1) respiratory frequency ≥22 per minute, 2) systolic blood pressure ≤100 mmHg, and 3) Glasgow Coma Scale <15.

2.3 Burden of sepsis

Sepsis is the leading cause of death [8], and the Global Burden of Disease Study (GBD) investigating sepsis found that the incidence was more than double that of previous calculations [8]. Of ICU patients, 25-40 % have sepsis [55, 56], and the prevalence of sepsis reported in ICU cohorts differs between 12% and 27% in the UK and USA, respectively [57]. Dividing results can partly be explained by the higher number of available ICU beds in the USA than in the UK [58, 59]. Sepsis contributes to one-third to one-half of the hospital deaths in the developed world [60]. In Norway, 12.9% of all hospital deaths in 2011 and 2012 were due to sepsis [3], which is lower than previous findings from the US [60].

Sepsis contributes to the highest hospital expenses compared to other medical conditions [61], and patients with sepsis admitted to wards contribute to most of the in-hospital costs [62]. However, 2/3 of the total economic burden occurs after discharge, including loss of productivity and other indirect medical costs following hospitalizations, with a high rate of recurring sepsis, readmissions, and considerable longer-term mortality [63-66]. Sepsis is

challenging to study and depends on the specific definition used, the study designs and the cohort investigated. In order to estimate the burden of sepsis, the knowledge of its incidence, prevalence, case fatality, and long-term outcomes is essential. In the next section, we summarize what we, to this point, know about the characteristics and burden of sepsis.

2.3.1 Characteristics

In hospitalized sepsis patients, respiratory tract infections are the most common site of infection causing sepsis, followed by abdomen, bloodstream, and genitourinary infections [55, 67, 68]. Sepsis also results in acute organ dysfunction that can be life-threatening [1]. All organs are at risk, and the organs most commonly affected are kidneys, liver, lungs, cardiovascular, and hematological systems [69].

2.3.2 Incidence

According to the GBD Study, there were 49 million sepsis cases worldwide in 2017 [8], with an incidence rate of 678 (95% CI, 536-876) per 100,000 citizens. This result is higher than a recent pooled estimate including low-income countries of 276 (95% CI, 189-403) per 100,000 hospital-treated sepsis patients [70], and also higher than two previous Norwegian studies with data from 1999 and 2011/2012 with estimated incidence rates among all age-groups of 149 and of 140 per 100,000, respectively [3, 71].

Incidence in subgroups of patients

Sepsis has a binominal age distribution with the highest incidence in neonates and elderly [8, 72]. In children <19 years, infants have the highest incidence rates (142 per 100,000), while the age group 5-14 years has the lowest (5 per 100,000), with an overall rate of 14 per

100,000 [73]. In adults, the incidence rates rise exponentially from the age of 50, with a rate in patients over the age of 80 of more than 1,500 per 100,000 [74].

Furthermore, men have been overrepresented in patients with sepsis in prior epidemiological studies [74, 75]. Increased sepsis incidence among men may be biased in high-income countries, as the recent global estimates have been estimated to be higher in females (767 [95 % CI, 560-921] than males (643 [95 % CI, 508-835]) per 100,000 citizens [8].

Patients with comorbidities are more prone to develop sepsis than others. Particularly in patients with cancer, the sepsis incidence is four- to tenfold higher compared to non-cancer patients and even higher in patients with certain malignancies, e.g., 65-fold increased risk for sepsis with myeloid leukemia [76-78]. The risk for sepsis hospitalization is 6 and 2-fold higher in diabetes Type 1 and Type 2, respectively, compared to the non-diabetic population [79]. In patients with hemodialysis access, one-third developed sepsis, corresponding to a crude incidence rate of 12,700 per 100,000 person-years [80].

According to WHO, transmissible pathogens of public health concern can also manifest as sepsis, where septic shock may be the final pathway [1, 12]. This description includes the novel SARS-CoV-2 virus, which induces a direct viral toxicity causing a dysregulated host response and sepsis [1, 81]. Respiratory dysfunction is the most common acute organ dysfunction in patients with COVID-19 with hypoxemia despite lungs with normal compliance and a coagulopathy resulting in large vessel thrombosis, which is rare in bacterial sepsis [17, 82, 83]. A meta-analysis, including studies from 2020 and 2021, reported COVID-19-related sepsis prevalence of 77.9% in adult ICU patients, with ARDS and septic shock as

the most common acute organ dysfunction and 33.3% prevalence in general ward patients [17].

Since the incidence of sepsis and age distribution are highly variable between regions[8, 70], and there are substantial knowledge gaps regarding data availability from low- and middle-income countries, we can conclude that the true magnitude of burden worldwide is unknown.

2.3.3 Case fatality

In 2017, 11 million sepsis-related in-hospital deaths were recorded worldwide [8]. The prognosis of sepsis is influenced by age, sex, preexisting comorbidities, infection site, sepsis severity, and infecting agent [3, 8, 74, 84]. The recent pooled global estimate of case fatality from 2020 was 26.7% [70], consistent with the latest overall Norwegian estimate of 26.4% from 2011 and 2012 [3].

Among children <19 years, the overall case fatality is 16.6% but varies and is highest in children <1 years old [73]. Among adults, the case fatality increases with increasing age and with the number of preexisting comorbidities [3, 74]. In addition, case fatality is higher and less dependent on age in patients with preexisting comorbidity than those without preexisting comorbidity [5, 74].

The case fatality also varies with sepsis severity and the level of care. The case fatality increases with the increasing number of acute organ dysfunctions. The recent pooled estimate of case fatality of ICU-treated sepsis was 42% [70] and higher than patients admitted to

wards [85]. This pooled ICU mortality is higher compared to previous Norwegian estimates of 35% [85].

2.3.4 Long-term outcomes

Advancements in clinical treatment protocols have resulted in decreased case fatality from sepsis [1]. Approximately half of the patients have a complete recovery. However one-sixth have persistent physical or cognitive sequela, and one-third die within one year [86]. The mortality risk is highest 3 months after discharge but remains increased for years after the acute episode of sepsis [16, 87, 88]. A study investigating patients ≥65 years found that 25% of those who survived a hospitalization with sepsis died within 2 years [16].

Interestingly, a recent study found that more than 20% of the patients discharged alive after a sepsis episode had a late death that could not be explained by preexisting comorbidities, suggesting that sepsis contributes to poor long-term outcomes [89]. There are conflicting reports on prognostic factors, including infection sites in sepsis survivors. While two ICU studies reported that all infection sites had higher long-term mortality than respiratory tract infections [90, 91], others reported the opposite [66, 92]. However, literature beyond 1 year regarding the impact of severity and origin of sepsis is limited. Nevertheless, the explanation for poor long-term outcomes is likely multifactorial and includes exacerbating of chronic medical conditions, remaining organ damage, and impaired immune function [86].

Readmissions are common after a sepsis admission [64, 65, 93]. Sepsis worsens already existing comorbidities and may generate new comorbidities. In addition, the immune system is altered after sepsis, and resulting in recurrent infections and readmissions [16, 65]. The majority of the readmissions within 90 days after discharge are due to recurrent sepsis [94].

The risk of recurrent sepsis is more than eightfold higher than developing sepsis for the first time [95]. This increased risk also existed across different levels of patient sociodemographic and comorbid burden, infection sites, and severity of illness in the first event [95]. In a matched control study investigating readmissions in 2,617 hospitalizations of severe sepsis who survived discharge, 43% were readmitted within 90 days [64]. In sepsis patients, 42% of the readmission diagnoses could potentially be prevented or treated early to avoid hospitalization, compared to 37% in matched acute medical conditions. Preventable causes of the readmissions included recurrent episodes of sepsis, congestive heart failure, pneumonia, acute renal failure, exacerbation of chronic pulmonary disease, and aspiration pneumonitis [86].

However, sepsis is not a disease reserved only for the elderly. A study investigating patients hospitalized with sepsis suggests that more than one-third of sepsis survivors are aged <65 years [96], thus in their working-age years. Due to long-term sequela, sepsis can hamper the return to normal living years after the sepsis event [13], including the ability to work. Work is recognized as important for health and well-being [97], thus, return to work (RTW) is a recommended measure of long-term functional level after disease. A previous administrative-based Danish study (2018) investigating a general ICU cohort found that among survivors receiving organ support therapy, 60% had returned to work at 1 year and 68% at 2 years after discharge [98]. In addition, they found that mechanical ventilation, cardiovascular support, an increasing length of stay (LOS), and increasing Simplified Acute Physiology Score II (SAPS II) were associated with a decreased chance of RTW. Prior studies suggest sepsis survivors have worse overall functional outcomes than other intensive care survivors [99, 100]. This is supported by a recent administrative-based German study (2023) covering 30% of the German population, which found that 55% and 65 % of ICU treated sepsis patients returned

to work 6 months and 1 year after discharge [15]. These findings are in line with a systematic review of ICU studies that suggest increasing rates of RTW over time [101], with a high degree of RTW variability [101-107]. Only 1 out of 52 included studies was based on administrative data, while the remaining studies were based on self-reported answers to questions in face-to-face or telephone interviews or mailed questionnaires to collect data.

In light of the recent pandemic, the research on reduced functioning after infection with COVID-19 is evolving, suggesting that 30% of survivors are affected [108-111]. Currently, limited research is available on RTW for patients with COVID-19-related sepsis, but RTW estimates at 6 months after a COVID-19 admission varies between 57% and 89% [112-115]. A Danish study investigating RTW in COVID-19 patients found that 6.6% of the patients hospitalized with COVID-19 did not work at 6 months after discharge, while 36% of those admitted to ICU did not work at 6 months [116]. They also found that female sex, older age, and comorbidity were associated with lower chance of returning to work. These estimates thus diverge from a study of 120 COVID-19 patients, which found no differences in self-reported RTW after 110 days between ward and ICU patients [117].

2.3.5 Changes over time.

Following The Surviving Sepsis Campaigns aiming at enhancing knowledge and description of evidence-based treatment bundles, one might anticipate increased recognition of sepsis followed by an increased incidence and some improvements in mortality over time [20, 34, 35, 118-120]. Nevertheless, the existing literature reveals conflicting results regarding trends in incidence and mortality. While some studies report a steady increase in incidence over time [72, 74, 75, 121], the recent GBD study reports a decreasing age-adjusted sepsis incidence of 37% from 1990 to 2017 [8].

Recent data suggest that sepsis-related mortality has substantially declined over the past two decades [8]. However, while the majority of the studies report decreasing case fatality over the past two decades [73], three recent observational studies have identified steady case fatality rates over time among patients admitted to the ICU [122-124]. Further, the pattern of the source of infection has changed over the past decades, where now chest infections succeed abdominal infections [125]. Increased use of mechanical ventilation and an aging population more prone to sepsis partly explain the increased incidence of chest infections and the stable case fatality found among sepsis patients admitted to the ICU. Furthermore, because of the increased use of broad-spectrum antibiotics, the number of antibiotic-resistant organisms is increasing [126-128]. Advancing ICU care for increasing elderly, immunosuppressed, and fragile individuals has resulted in a greater overall burden and complexity of nosocomial infections within modern ICUs and are important determinants of outcomes for patients in the ICU setting [129].

The increased sepsis incidence may also be related to a change in the recognition and coding of sepsis, with increased labeling of less severely ill patients as septic over time, also called stage migration, or the “Will Roger” phenomenon. This is related to the altered understanding of sepsis pathogenesis, but also studies with a stable sepsis definition find that the incidence of sepsis is rising over time, albeit more modestly [130, 131]. Increased incidence may also be related to better survival from other medical conditions such as cancer and increasing use of immunosuppressive therapies, which result in a greater number of patients at heightened risk for developing sepsis.

To summarize, the burden of sepsis is difficult to quantify due to its heterogeneity. The variance in worldwide incidence rates, from 90 to 1,000 per 100,000 citizens, reflects the

complexity of the syndrome [132]. Multiple factors are likely contributing to the observed changes in sepsis epidemiology, and since estimates on the incidence and mortality trends of sepsis in Norway are missing, accurate quantification of sepsis is warranted.

3.0 Aim of the thesis

3.1 General aims of the thesis

Our overall aim was to investigate the burden of sepsis, including incidence, case fatality, and long-term outcomes.

3.2 Specific aims of the studies

Paper I. To describe temporal trends in sepsis incidence rate and case fatality using nationwide data on all adult hospital admissions from 2008 through 2021, and examine changes in hospital admission and case fatality rates of sepsis during the first two COVID-19 pandemic years (2020 and 2021).

Paper II. To investigate trends in overall short and long-term all-cause mortality among patients admitted with sepsis during fourteen years, taking eventual deviations during the pandemic years 2020 and 2021 into consideration. In addition, to investigate factors associated with mortality.

Paper III. To investigate the return to work (RTW) rate among sepsis survivors working prior to sepsis admission Secondly, to examine whether the number of characteristics such as age, sex, comorbidities, and acute organ dysfunctions in sepsis survivors were associated with RTW.

4.0 Material and Methods

4.1 Study design

All three papers are descriptive epidemiological studies of longitudinal prospective design. Table 1 shows an overview of the study questions, outcome, data sources, design and study period, sample size, and inclusion criteria of the three papers.

Table 1. Overview of the methods used in Paper I-III

	Paper I	**Paper II**	**Paper III**
Study questions	What is the incidence and case fatality of sepsis and are there any temporal trends? Does the COVID-19 pandemic influence incidence and case fatality of sepsis?	What is the all-cause mortality and trends in mortality for patients admitted with sepsis during fourteen years, and is there any deviations during the pandemic years 2020 and 2021? What are the charachteristics associated with mortality?.	What is the RTW rate in patients priorly working after a first sepsis episode? What are the charachteristics associated with sustained RTW in prior working sepsis survivors?.
Outcome	Incidence In-hospital mortality	All-cause mortality	Return to work
Data sources	NPR, SSB	NPR, NIR, DÅR	NPR, NIR, DÅR, NAV
Design and period	Descriptive Prospective Longitudinal 2008-2021	Descriptive Prospective Longitudinal 2008-2021	Descriptive Prospective Longitudinal 2010-2021
Sample size	317,705	222,832	12,260
Inclusion criteria	Patients aged ≥ 18 with sepsis with first and recurrent sepsis	Patients aged ≥ 18 with first sepsis	Patients aged ≥ 18 and ≤ 60 with first sepsis working prior to the sepsis admission

Abbreviations : RTW= return to work, NPR= The Norwegian Patient Registry, SSB = The Statistics of Norway, NIR= The Norwegian Patient Registry, DÅR= The Norwegian Cause of Death Registry , NAV= The Norwegian Work and Welfare Administration

4.1.1 Study samples

All adult patients with a sepsis admission constitute 317,705 sepsis admissions, where 222,832 had a first sepsis admission. The preparation of the baseline sample selection in Paper I-III is presented in a flowchart below (Figure 2).

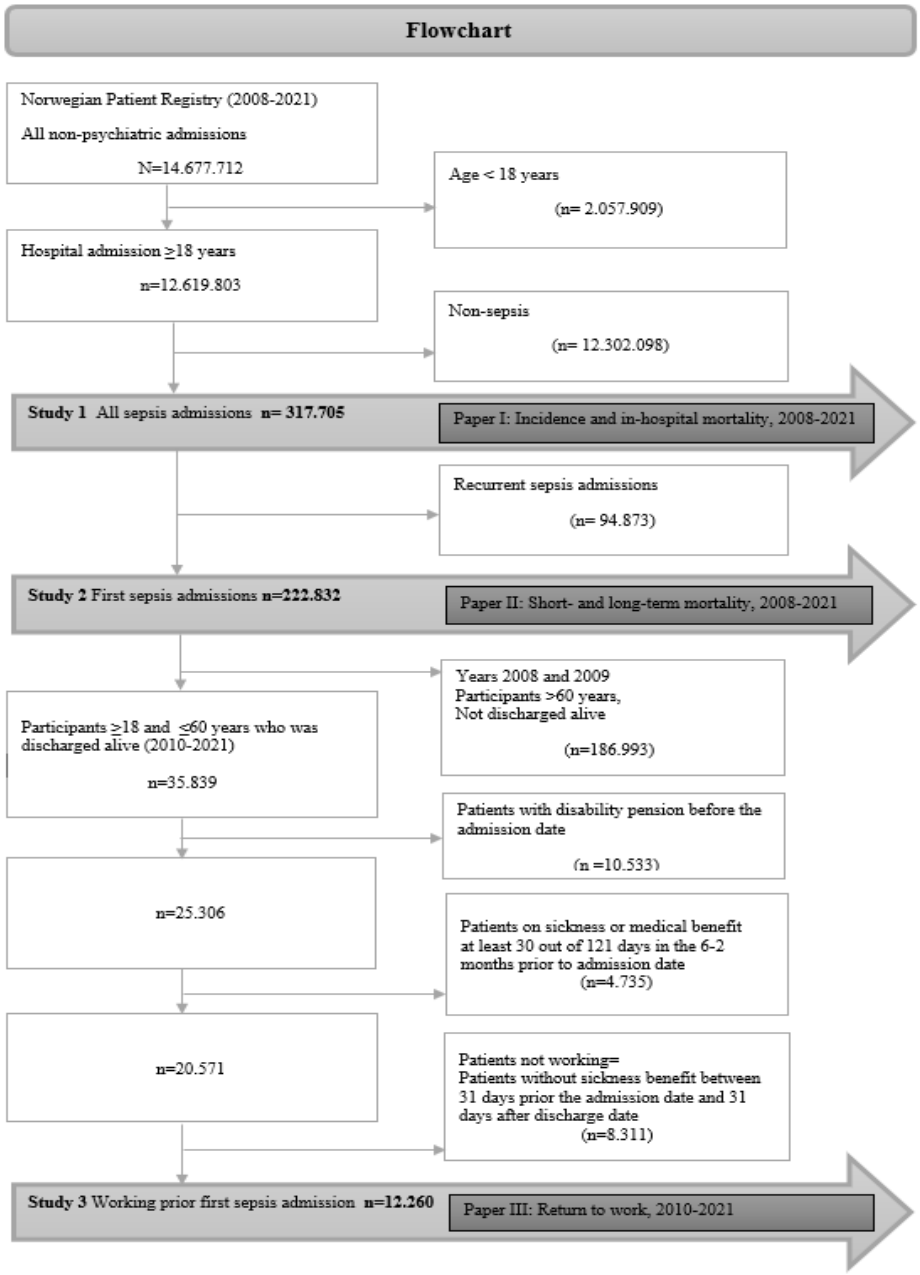

Figure 2. Flowchart showing the selection process of the data in Paper I-III.

4.1.2 Linkage

To link data between involved registries and our project, we used distributed linkage. This method involved a file with a personal identification number (PIN) and a specific serial number from NPR. This file was sent to the other registries, and our project received a file with a project-specific serial number and health information in return, in addition to a separate file from NPR (Figur 3).

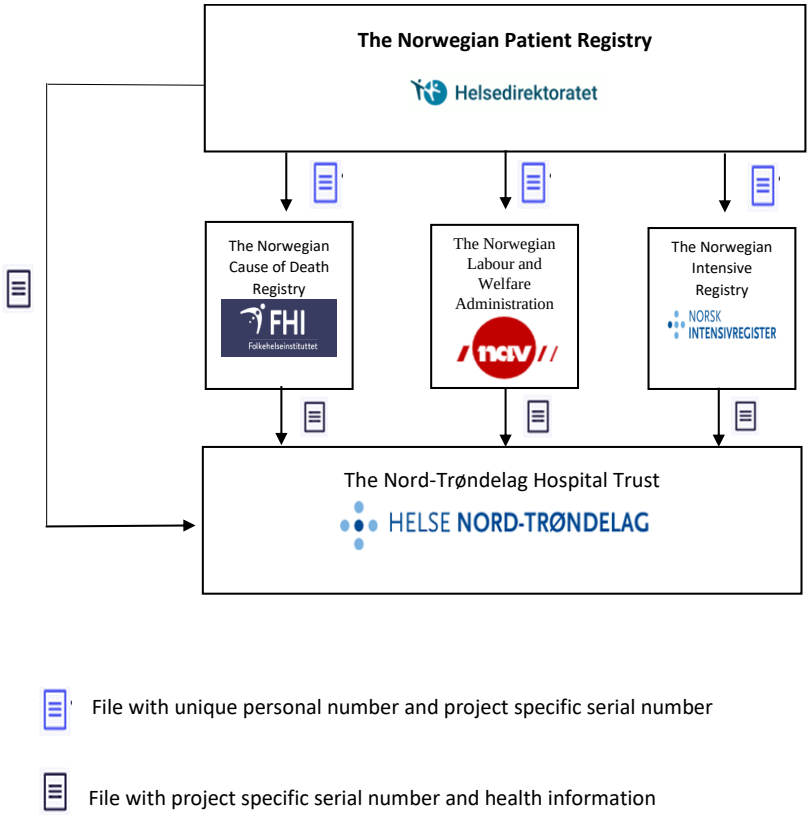

Figure 3. Overview of distributed linkage in the project.

In Paper II, we linked NPR to The Norwegian Cause of Death Registry (DÅR) and The Norwegian Intensive Registry (NIR), and in Paper III, we extended with data from The Norwegian Work and Welfare Administration (NAV).

4.3 Data sources

We conducted all three studies using nationwide administrative databases, and below is a detailed description of the data sources used in this thesis and the information we retrieved in each study.

4.2.1 The Norwegian Patient Registry (NPR, Paper I, II, III)

The NPR was established by a research institute (SINTEF) in 1997 and transferred to the Norwegian Directorate for Health in 2007. Before the transfer, the data did not include PIN, but from 2008, reporting with PIN is mandatory [133]. The registry covers all public specialist healthcare services in Norway, including private institutions and medical specialists contracted to the regional health authorities. The coded medical information is classified according to ICD-10 diagnostic codes in one primary diagnosis and up to twenty secondary diagnoses [134]. Reporting to the NPR is mandatory for all public Norwegian hospitals.

From NPR, we extracted ICD-10 codes defining sepsis and comorbidities (Paper I-III), see Chapter 4.5 for details regarding the codes. In addition, information regarding age, sex, admission and discharge date, readmission, number of hospital admissions with sepsis (Paper I and II), and LOS (Paper III).

4.2.2 Statistics Norway (SSB, Paper I)

As the central Norwegian office for official government statistics, SSB contains demographic data on all citizens of Norway [135]. SSB operates independently from all government agencies and relies extensively on data from registers.

In Paper I, we used population data from SSB of adults ≥18 years of age divided into age groups at the start of each calendar year between 2008 through 2021.

4.2.3 The Norwegian Cause of Death Registry (DÅR, Paper II, III)

The Norwegian Cause of Death Registry is mandatory and contains information on deaths and causes of death in Norway from 1951 until today. It collects death data by age, sex, cause of death [136]. The DÅR is managed by the Norwegian Institute of Public Health (NIPH). The registry collects death certificates for all deaths that occur in the country. It also registers the deaths of Norwegians who die abroad.

In Papers II and Paper III, we retrieved the death date from DÅR to investigate all-cause mortality. In Paper II, we collected death dates from 1 January, 2008 through 31 December, 2021, while in Paper III the start date of follow-up was set to 1 January, 2010.

4.2.4 The Norwegian Intensive Registry (NIR, Paper II, III)

The NIR covers all intensive care unit (ICU) admissions; data are available from 1 May, 2014[137]. NIR contains information on all patients treated at intensive care units in Norway, including patients admitted with COVID-19, and collects individual data from all

ICU admissions in Norway, recorded securely via a web-based platform. Inclusion criteria in the NIR include one of the following 5 criteria: a) >24 hours at ICU, b) respiratory support, c) dead within the first 24 hours, d) transfer to another ICU within 24 hours or e) in need of medication to help hemodynamics [137].

In Paper II and III we extracted admission and discharge date at ICUs from NIR.

4.2.5 The Norwegian Work and Welfare Administration (NAV, Paper III)

NAV runs the Norwegian National Social Security System Registry and operates all social benefits, which all Norwegian citizens can access through compulsory membership in The Norwegian National Insurance Scheme [138]. The Norwegian National Social Security System Registry contains information about all members` entry and exit dates and degrees of sickness and medical benefits. Medical benefit during illness is managed by medical doctors who need to send a sick leave application to NAV on behalf of the patient. All current medical benefits, including medical benefits, work assessments allowance, and permanent disability pensions, are available from 2010.

In Paper III, we used data from NAV containing start and stop dates and degree and type of medical benefit, work assessments allowance, and disability pension.

4.2 Study setting

The study was performed using Norwegian data. Norway had 4,737,171 inhabitants in 2008 and 5,393,369 inhabitants in 2021, with a primarily Caucasian population. The population of adults in Norway ≥18 years of age was 3,586,836 in 2008, which increased to 4,248,972 in 2021[135].

Norway has registered a positive net immigration each year since the late 1960s. The annual average net immigration increased considerably in 2004 and reached a peak in 2012, with an average of 40,500 for 2011–2015. In 2020, net immigration dropped considerably and was around 11,300, the lowest level since 2003 [139].

The Norwegian population is mainly served by public hospitals. The entire population in Norway is provided with public healthcare that covers all emergency incidents and is free at the point of delivery. Private hospitals in Norway are mainly for outpatients and non-emergencies and exclude severely ill patients, like those with sepsis needing acute hospitalization.

4.5 Study population

We retrieved detailed information on sepsis from NPR and defined eligible cases as patients ≥18 years of age with the ICD-10 diagnosis code(s) for sepsis consistent with the Angus implementation refined by Rudd and colleagues [8, 74]. Angus used an ICD-10 coding strategy to capture sepsis in administrative data consisting of a set of infection and acute organ dysfunction codes. These codes are in line with the later Sepsis-3 definition. Rudd expanded this strategy to include specific sepsis codes, named explicit codes. Figure 4 displays our ICD-10 coding strategy to capture sepsis in NPR.

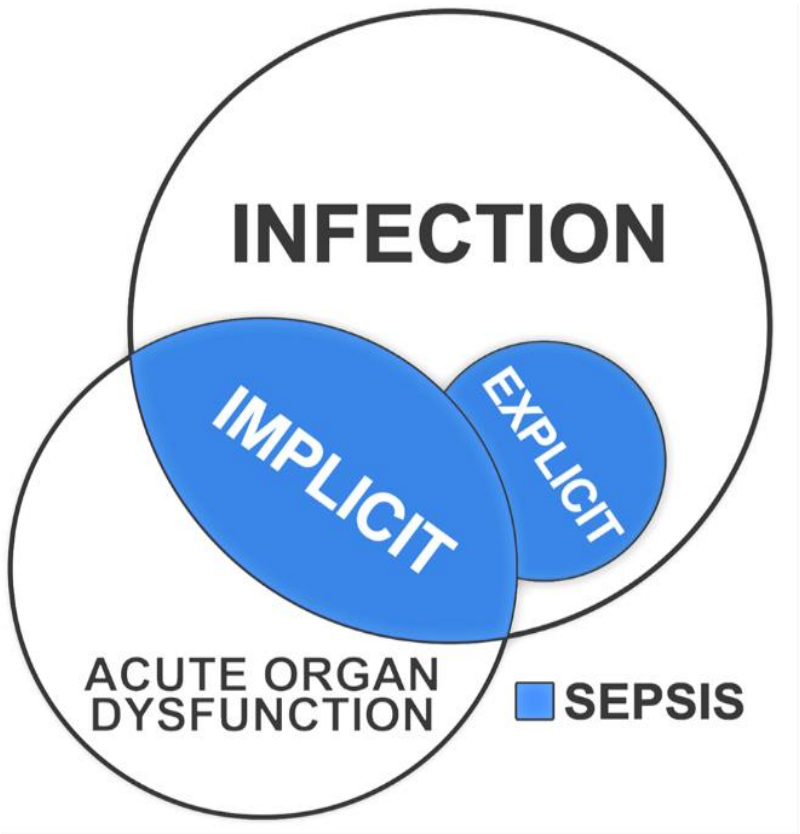

Figure 4. Illustration of the definition of implicit and explicit sepsis that guided our ICD-10 code strategy

For explicit sepsis, we used the presence of one code. For implicit sepsis, we used the combination of one infection code with the presence of an acute organ dysfunction code. This strategy was used for the primary and up to 20 secondary co-existing ICD-10 discharge codes since there is no obligatory order for the secondary codes. COVID-19-related sepsis was based on the presence of a diagnostic code for COVID-19 (U07.1, U07.2) and ≥one organ dysfunction code. Patients with a COVID-19-related sepsis code and an explicit sepsis code were categorized as explicit sepsis. Each hospitalization with sepsis was treated as an individual entry. Table 2 gives a detailed overview of ICD-10 codes and the combination of

ICD-10 codes used to define explicit and implicit sepsis, and appendix 4 gives a detailed description of the ICD-10 codes.

Table 2. Overview of ICD-10 codes identifying explicit and implicit sepsis[d]

Sepsis, Explicit code strategy	A02.1, A20.7, A21.7, A22.7, A24.1, A26.7, A28.2, A32.7, A39.2, A39.4, A40, A41, A42.7, B00.7, B37.7
Sepsis[a,b] Implicit code strategy	**Infection** A00/09, A19/28, A30/32, A36/39, A42/44, A46, A48/49, A54, A59, A69.0, A69.1, A69.9, A70, A74/75, A77/81, A83/89, A92/99, B00/09, B25/27, B33/34, B37/46, B48/50, B54/55, B57/58, B60, B64, B67, B95/97, B99, G00/08, H05.0, H60.2, H70.0, I00, I33, I38/40.0, J01/06, J09/22, J36, J39.0, J39.1, J85, J86, K35/37, K61, K63.0/63.1, K65, K75.0, K81.0, K83.0, L02/04, L08, M00/01, M72.6, M86, N10, N15.1, N30, N39.0, N41.0, N41.2, N41.3, N45, N70/74, N98.0, N49, O03.0, O03.5, O04.5, O08.0, O23, O75.3, O85/86, O88.3, O91, O98, T80.2, T81.4, T82.6/82.7, T83.5/83.6, T84.5/84.7, T85.7, T88.0, AND **Acute organ dysfunction** D65, D69.5, E87.2, G93.4, I46, I95.9, J80, J95.2, J96, K72.0, K72.9, N00, N17, N99.0, R02, R09.0, R09.2, R40.0/40.2, R41, R55, R57, R57.2, R65.1
COVID-19-related sepsis, code strategy[c]	U04, U07.1, U07.2 AND Acute organ dysfunction (same codes as for implicit sepsis) OR one code from Explicit code strategy

Abbreviation: ICD= International Classification of Diseases

[a] Implicit sepsis was defined if one code of infection was present with at least one acute organ dysfunction within same hospital entry. Total sepsis estimates are calculated from both explicit and implicit cases.

[b] Explicit codes are excluded from infection codes

[c] Covid-19 related sepsis was defined if identified cause of hospitalization were SARS (U04) identified coronavirus (U07.1) or unidentified coronavirus (U07.2) and the patient had at least one organ dysfunction

[d] Reprinted under CCBY 4.0 license agreement from Skei NV, Nilsen TIL, Knoop ST, *et al* Long-term temporal trends in incidence rate and case fatality of sepsis and COVID-19-related sepsis in Norwegian hospitals, 2008–2021: a nationwide registry study. *BMJ Open* 2023;**13:**e071846. doi: 10.1136/bmjopen-2023-071846

4.6 Outcomes

In the following we present an overview of the statistical analysis used in Paper I-III (Table 3) and describe the outcomes more in detail.

Table 3. Overview of statistical method, outcome and variable in Paper I-III.

	Paper I	Paper II	Paper III
Statistical analyses	Age-standardized IRs, Poisson regression to estimates changes in IRs across time, Logistic regression to estimate ORs for CFRs.	Age-standardized mortality including least-squares linear regression across years to estimate temporal trends Cox regression to investigate associations between charachteristics and mortality	Proportion of RTW, Age-standardized RTW with Least-squares linear regression across years to estimate temporal trends, Cox regression to investigate association between charachteristics
Outcomes	Incidence CFR	All cause short-and long - term mortality	RTW Sustained RTW
Other variables	Age, sex, comorbidities (no/type), infection-site (type), acute organ dysfunction (no/type), hospital stays with sepsis (no), readmission, explicit	Age, sex, comorbidities (no/type), infection-site (type), acute organ dysfunction (no/type), hospital stays with sepsis (no), readmission, ICU-stay, in-hospital death	Age, age-groups, sex, comorbidities (no/type), infection-site (type), acute organ dysfunction (no/type), readmission, ICU-stay, LOS (ICU/ward), COVID-19-related sepsis

Abbreviations: IR=Incidence Rate, OR= Odds Ratio, CFR= Case Fatality Rate, RTW= Return to work; ICU=Intensive Care Unit, LOS=Length of Stay

Paper I The outcomes in Paper I were incidence rate (IR) and case fatality rate (CFR). IR was defined as the number of sepsis admissions divided by the total inhabitants in Norway at the beginning of that year. CFR was defined as the number of sepsis admissions with a discharge status of in-hospital death divided by sepsis hospitalizations at the end of that same year.

Paper II The primary outcome in Paper II was all-cause mortality. Mortality was calculated as the proportion of deaths of any cause among those admitted with sepsis during a specific year.

Paper III Outcomes in Paper III were RTW and sustained RTW. Work status was categorized as RTW, ever RTW, never RTW, or dead. Patients without any medical or work

assessment allowance at the measurement point were categorized as RTW. Patients on sickness or medical benefit at all the measurement points were categorized as never RTW. Lastly, patients who had returned to work at an earlier time point but were back on medical or work assessment allowance were categorized as ever RTW. We also investigated sustainable RTW, defined as the absence of any medical benefit for at least 31 consecutive days after discharge from sepsis hospitalization. In Paper III, we investigated patients admitted with a first sepsis episode; thus, we limited the study cohort to patients of working age (18 to 60 years), which is 2 years before the earliest retirement possibility in Norway. The rationale for the upper age limit was to identify patients who stopped working due to sepsis, as opposed to patients who retired unrelated to sepsis. We also excluded patients with any disability pension prior to the sepsis hospitalization and patients who did not survive hospital discharge. In addition, we excluded the patients with no medical benefit 31 days before and 31 days after admission due to uncertain work status.

4.7 Definition of other variables

For sepsis admissions, we used ICD-10 codes to classify site(s) of infection into respiratory, genitourinary, gastrointestinal, intra-abdominal, endocarditis/myocarditis, soft tissue, infections following a procedure, and other (bone, joint, obstetric, ear, mouth, upper airway, central nervous system and unknown). The acute organ dysfunctions were classified by number and as circulatory, respiratory, renal, hepatic, coagulation, and/or other (acidosis, unspecific gangrene, central nervous system, and SIRS (R65.1) (Table 4). Acute neurological dysfunctions were not classified as a single dysfunction due to inconsistent practices in coding.

Table 4. ICD 10 codes identifying comorbidities, infection sites and acute organ dysfunctions[c].

Comorbidities	**ICD-10** code
Chronic heart- and vascular disease	G45, H34, I00/31, I34/37, I42/45, I47/95.8, I97/99
Cancer	C00/97, D32/33, D35.2/35.4, D42, D43, D44.3/44.5, D45/47
Chronic lung disease	J41/47, J84, J98
Chronic renal disease	N18.3/18.5
Diabetes	E10/11
Dementia	F00/03, G30, G31.0, G31.2, G31.8
Chronic immune disease	D80/84, Z94.0/94.4, Z94.8
Chronic liver disease	K70.4, K72
Infection sites[a]	
Respiratory	J09/18, J20/22, J85/86, U07.1, U07.2
Genitourinary	N10, N15.1, N30, N39.0, N41.0, N41.2/41.3, N45, N49, N70, N71/74, N98.0
Gastrointestinal	A00/09
Intra-abdominal	K35/37, K57, K61/61.1 K61.3, K63.0/63.1, K65, K75.0, K81.0, K83.0
Endocarditis/myocarditis	I32/33, I38/41
Skin/ Soft tissue	A46, B08/09, L02/04, L08, M72.6
Infection after procedure	T80.2, T81.4, T82.6/82.7, T83.5/83.6, T84.5/84.7, T85.7, T88
Other	A19/28, A30/32, A36/39, A42/44, A48/49, A54, A59, A69.0, A69.1, A69.9, A70, A74/75, A77/80, A81, A83/89, A92/B06, B25/27, B33/34, B37/46, B48/50, B54/55, B57/58, B60, B64, B67, B95/97, B99, G00/08, H05.0, H60.2, H70.0, J01/06, J36, J39.0/39.1, M00/01, M86, O03.0, O03.5, O04.5, O08.0, O23, O75.3, O85/86, O88.3, O91, O98
Acute organ dysfunction	
Respiratory	J80, J95.2, J96, R09.0, R09.2
Circulatory	I46, I95.9, R57, R57.2
Renal	N00, N17, N99.0
Hepatic	K72.0, K72.9
Coagulation	D65, D69.5
Other acute organ dysfunctions	G93.4, R40.0/40.2, R41, R55, E87.2, R02, R65.1[b]

[a] Explicit codes are excluded from other infection sites.

[b] R65.1 was excluded in the count of acute organ dysfunctions if present in combination with R57.2, according to the Norwegian ICD-10 coding rules.

[c] Reprinted using CCBY 4.0 license agreement from in Skei NV, Nilsen TIL, Knoop ST, *et al* Long-term temporal trends in incidence rate and case fatality of sepsis and COVID-19-related sepsis in Norwegian hospitals, 2008–2021: a nationwide registry study. *BMJ Open* 2023;**13:**e071846. doi: 10.1136/bmjopen-2023-071846

A sepsis admission was defined as a recurring sepsis admission if the patient was discharged with an explicit or implicit sepsis code, and after that, admitted with an explicit or implicit sepsis code, regardless of the time frame for the new admission. The number of sepsis

admissions was categorized from one to five or more. A readmission was defined as an admission within 30 days after discharge, regardless of cause. ICU stay was defined as an admission to the ICU during a hospital stay with a sepsis diagnosis. LOS was calculated in days from the admission date to the discharge date.

4.8 Statistical analyses

Contingency tables were conducted for each study of patients and clinical characteristics and are listed in Table 1. In Paper I, we described patients admitted with a first episode with sepsis (2008-2021) and for COVID-19-related sepsis (2020-2021). In Paper II, the contingency table included all patients with a first episode of sepsis (2008-2021), including three subgroups of sepsis: implicit, explicit, and COVID-19-related sepsis, while Paper III included a description of all patients working prior to the first sepsis admission in the period 2010 through 2021 and discharged alive. In all three papers, descriptive statistics are presented as frequencies, means, standard deviation, percent, and medians as appropriate, and all analyses were conducted using STATA version 16.1 (Stata Corp).

We wanted to treat each hospital admission as an individual entry. Thus, the study starts in Paper I and Paper II were set to 2008, consistent with the first available individual- level data from NPR. In Paper III, the study start was set to 2010 because of work assessment allowance data restrictions. Since a patient could have been admitted with sepsis before the study started, we assumed an increased possibility of a first episode being a recurrent episode in the first study year. Since this could inflate the incidence rate of a first sepsis episode, 2009 was used as a reference year for age-adjusting incidence per year in Paper I. Further, 2008 was included as an indicator variable in the regression analysis in Paper I and Cox regression in Paper II. In addition, we calculated the yearly age-adjusted mortality from 2009 paper II. In

Paper III, we first stratified the first sepsis episodes from 2008 but included the first episodes only from 2010 in the analysis due to data restrictions from NAV. This inclusion method lowered the possibility of including a recurrent episode, thus, no further considerations were taken.

Cox regression was conducted in Paper II and Paper III, and to meet the proportional hazard assumptions, all the Cox models were examined by visual inspection of log-log plots.

4.8.1 Paper I

The crude and age-standardized IRs of first and all sepsis episodes during the study period were calculated as the number of events divided by the total number of inhabitants in Norway ≥18 years of age at the beginning of that year, with 2009 as the reference year. The IRs for first and all sepsis were then standardized according to Segi's world standard population using ten-year age categories [140, 141] and reported per 100,000 citizens.

The crude and age-standardized CFR of first sepsis admission was calculated as the number of hospital deaths divided by the total number of first sepsis admissions at the end of each year, with 2009 as the reference year. Similarly, crude and age-standardized CFR of recurrent sepsis was calculated as the number of recurrent sepsis admissions with a discharge status of in-hospital death divided by all recurrent sepsis admissions in the same year. Age-standardized CFR was reported as mean CFR for both first and recurrent sepsis.

The crude sepsis IR of a first, recurrent, and overall sepsis episode was calculated according to year (2008–2021) and ten-year age groups and the number of sepsis admissions was divided by the total number of inhabitants in Norway at the beginning of the year. For the annual proportion of first, recurrent, and overall in-hospital deaths, we calculated crude CFR

according to year (2008–2021) and ten-year age groups at the end of each year, and divided by the number of first, recurrent, and overall sepsis admissions that year. During 2020 and 2021, we also calculated the quarterly CFR and compared CFR for COVID-19-related sepsis and sepsis.

Poisson regression was used to estimate incidence rate ratios (IRR) of sepsis using the number of sepsis admissions (first, recurrent or total) as the dependent variable, population as exposure, the years 2009 to 2019 as a continuous variable, and the years 2008, 2020 and 2021 as separate indicator variables to evaluate the temporal trends of sepsis incidence rates and the impact of the first year of observation (2008) as well as the COVID-19 pandemic (2020, 2021) on sepsis incidence rates. We adjusted for sex and age (10-year categories).

We used logistic regression to estimate odds ratios (ORs) for in-hospital death of a first and recurrent sepsis admission using the years 2009-2019 as a continuous variable, the years 2008, 2020, and 2021 as indicator variables, and adjusting for sex (man, woman) and age (10-year categories). We reported 95% confidence intervals (CI) where relevant to evaluate the trend of in-hospital mortality and the pandemic`s impact on hospital mortality.

4.8.2 Paper II

For each calendar year, we estimated 30-day, 90-day, 1-, 5-, and 10-year mortality by calculating the proportions of deaths from all causes, divided by the number of first sepsis admissions. The estimated mortality proportion was standardized according to 10-year age

groups (18-29, 30-39, 40-49, 50-59, 60-69, ≥80 years) using the age distribution in 2009 as the base.

Overall temporal trends in age-standardized mortality were estimated from least-squares linear regression across calendar years (2009-2021) and weighted by the inverse variance of the mortality proportion [142]. Similar analyses were conducted for subgroups of sepsis patients according to diagnosis (implicit and explicit), admission to ward or ICU, infection site, and comorbidity.

Cox regression was used to investigate clinical characteristics possibly associated with increased mortality. We adjusted for sex and age, the years 2009 to 2019 as a continuous covariate, and the years 2008, 2020, and 2021 as separate indicator variables. Factors explored were implicit, explicit, and COVID-19-related sepsis, type and number of comorbidities, infection site, number and type of acute organ dysfunction, and intensive treatment, yes versus no. Comorbidities, infection sites, and acute organ dysfunctions were analyzed as categorical variables, using the most frequent category as a reference. The categories were mutually exclusive, and the analyses were conducted on a restricted sample of patients with none or only one comorbidity, infection site, or acute organ dysfunction, respectively. Table 5 gives an overview of the Cox regression models' follow-up and censoring of events.

Table 5. Overview of the follow up time and censoring in the Cox regression models in Paper II and III.

Paper	Failure	Time of origin	Enter	Follow-up start	Follow-up end (cencored)
II	All-cause mortality	Admission date with a first sepsis episode	1 Jan 2008-31 Dec 2021	Admission date with a first sepsis episode	Date of death or end of study (31 Dec 2021)
II	All-cause mortality - sepsis patients admitted to ICU	Admission date with a first sepsis episode	1 May 2014-31 Dec 2021	Admission date with a first sepsis episode	Date of death or end of study (31 Dec 2021)
II	All-cause mortality - COVID-19-related sepsis	Admission date with a first sepsis episode	27 Febr 2020-31 Dec 2021	Admission date with a first sepsis episode	Date of death or end of study (31 Dec 2021)
III	Sustained RTW	Discharge date and alive after a first sepsis episode	1 July 2010 - 1 Oct 2021	Discharge date and alive after a first sepsis episode	The date when working at least 31 consecutive days, or 2 years after discharge, or death, or end of study (31 Dec 2021)
III	Sustained RTW -sepsis patients admitted to ICU	Discharge date and alive after a first sepsis episode	1 May 2014-1 Oct 2021	Discharge date and alive after a first sepsis episode	The date when working at least 31 consecutive days, or until 2 years after discharge, or death, or end of study (31 Dec 2021)
III	Sustained RTW -COVID-19-related sepsis	Discharge date and alive after a first sepsis episode	27 Febr 2020-1 Oct 2021	Discharge date and alive after a first sepsis episode	The date when working at least 31 consecutive days, death or end of study (31 Dec 2021)

Abbrevation: ICU= Intensive Care Unit, RTW= Return to work,

Sensitivity analysis was conducted to account for the late entry of COVID-19-related sepsis patients. We used a similar Cox model as described above but with follow-up time starting from February 27, 2020, for all patients with implicit, explicit, and COVID-19-related sepsis. The entry date corresponds with the first confirmed hospitalized COVID-19 case in Norway.

4.8.3 Paper III

To calculate the proportion of patients returning to work, we counted sepsis survivors from discharge date that had status as RTW, never RTW or dead at 6 months, and as RTW, never RTW, ever RTW or dead at 1 year, and 2 years, and divided by all patients working prior to admission, subtracting those who died between each measure point. We also completed

analyses stratified by treatment in the ICU vs. ward only and by COVID-19-related vs. non-COVID-19-related sepsis.

We calculated 6-month, 1-year, and 2-year RTW by calendar year to examine temporal trends in RTW. This was calculated as the proportions with RTW divided by the number of survivors after the index sepsis admission each year. To avoid potential bias of sepsis hospitalizations over time due to changing age distribution, the RTW proportion was standardized according to 10-year age groups (18-29, 30-39, 40-49, 50-60 years) using the age distribution in 2011 as the base for patients admitted to wards, and the age distribution in 2015 as the base for patients admitted to ICU. Temporal trends in age-standardized RTW were estimated from least-squares linear regression across calendar years and weighted by the inverse variance of the RTW proportion [142].

Clinical characteristics potentially associated with the probability of sustainable RTW were investigated using Cox regression to estimate crude and adjusted hazard ratios (HRs) with 95% CI. Association with age and sex were mutually adjusted, whereas all other associations were adjusted for both sex (male, female) and age (years). Comorbidities, site of infection, and acute organ dysfunctions were analyzed as categorical variables, using the most common category as the reference. The categories were mutually exclusive, and the analyses were conducted on a restricted sample of patients with none or only one infection site, comorbidity, or acute organ dysfunction, respectively. In all Cox regression models, the patients were followed for 2 years after the date of discharge with an index sepsis admission to ensure the follow-up time covered the time of possible sick leave and was within the first possible retirement age, see Table 5 for further information. Sensitivity analysis was conducted as many individuals go on and off medical benefits, where sustainable RTW was defined as at least 92 consecutive days without any medical benefit.

4.9 Patient and public involvement

Two patient representatives from the user group at Nord-Trøndelag Hospital Trust participated in the work with this study's research question and design. In general, they are positive to use health data for research purposes. They stress the importance of education regarding symptoms and signs of sepsis to prevent fatal outcomes and advised that research results and information about sepsis should be published in newspapers and social media to reach the patients and relatives. Accordingly, we plan to distribute our research results in plain language disseminated in general media to inform patients, sepsis charities, research funders and policy makers.

4.10 Ethical considerations

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK) in Eastern Norway (2019/ 42772) and the Data Access Committee in Nord-Trøndelag Hospital Trust (2021/184). In accordance with the approval from the REK and the Norwegian law on medical research, the project did not require written patient consent. This work was analyzed on TSD (Service for Sensitive Data) facilities owned by the University of Oslo, operated, and developed by the TSD service group at the University of Oslo, IT Department (USIT).

5.0 Main results

5.1 Paper I

Long-term temporal trends in incidence rate and case fatality of sepsis and COVID-19-related sepsis in Norwegian Hospitals, 2008-2021: A nationwide registry study.

Among 12,619,803 adult hospitalizations, 317,705 (2.5%) met the sepsis criteria; of these 222,832 (70%) had a first sepsis episode. In 2020 and 2021, 2,845 of 29,329 (9.7%) of the first sepsis episodes were identified as COVID-19-related sepsis. There were 53,9% men among those with sepsis and 65,5% men among those admitted with COVID-19-related sepsis. The sepsis patients were older than patients with COVID-19-related sepsis (mean age 71.1 vs 61.4). The sepsis patients experienced most often renal acute dysfunction (44.6%), while COVID-19-related patients naturally experienced most often respiratory failure (86.5%). Readmissions within 30 days occurred in 25% of the sepsis group and 16.7% of those in the COVID-19-related sepsis group.

The overall age-standardized IR of a first sepsis admission was 246 per 100,000 inhabitants (95% CI 245 to 247), whereas the age-standardized IR of all sepsis admissions was 352 per 100,000 inhabitants (95% CI 351 to 354).

In 2009-2019, the annual IR for first sepsis admissions was stable (IRR per year 0.999; 95% CI 0.994 to 1.004), whereas IR for recurrent sepsis increased with an IRR of 1.048 (95% CI 1.037 to 1.059) per year, with a total increase in overall IRs of 15.5%. Figure 5 shows the annual incidence for first and recurrent sepsis by 10-year age groups.

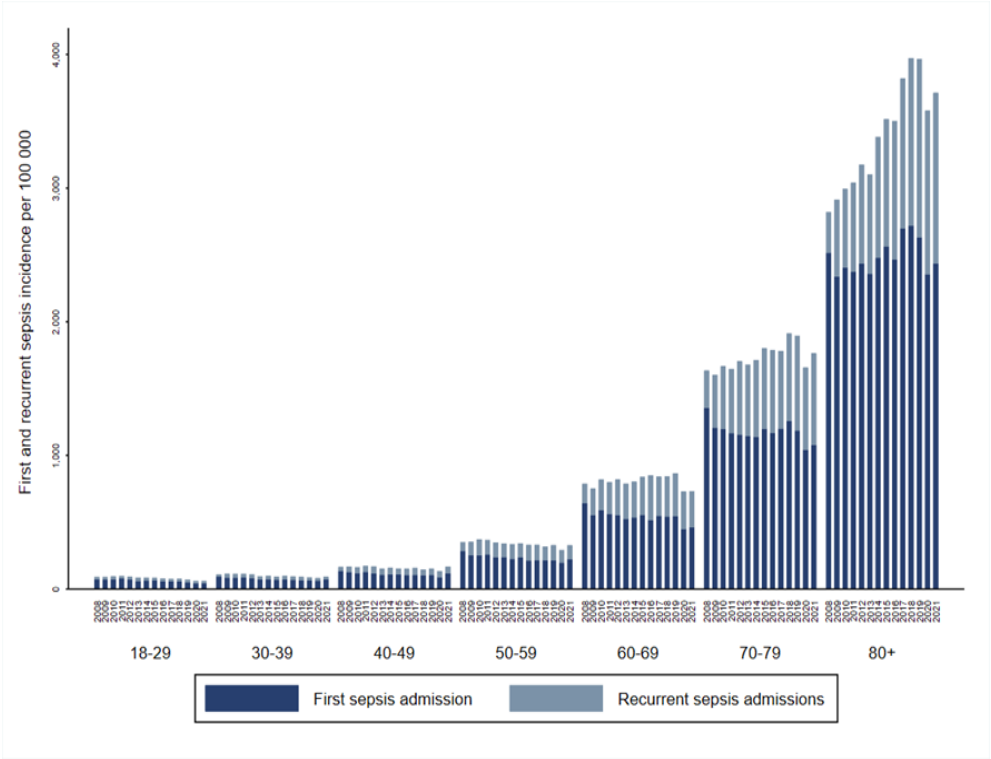

Figure 5. Annual first and recurrent sepsis incidence by 10-years age-group.

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The mean CFR was 13.7% for the first sepsis admissions during the study period and 12.6% among recurrent episodes. CFR declined for the first sepsis admissions in 2009-2019 (OR per year, 0.954 [95% CI,0.950 to 0.958]), with a total decline of 43.1%. The CFR for recurrent sepsis declined with an OR of 0.973 (95% CI 0.966 to 0.980) per year in the same period, with a total decline of 28.0%. Figure 6 displays the detailed annual CFR for first and recurrent sepsis admissions by 10-year age groups.

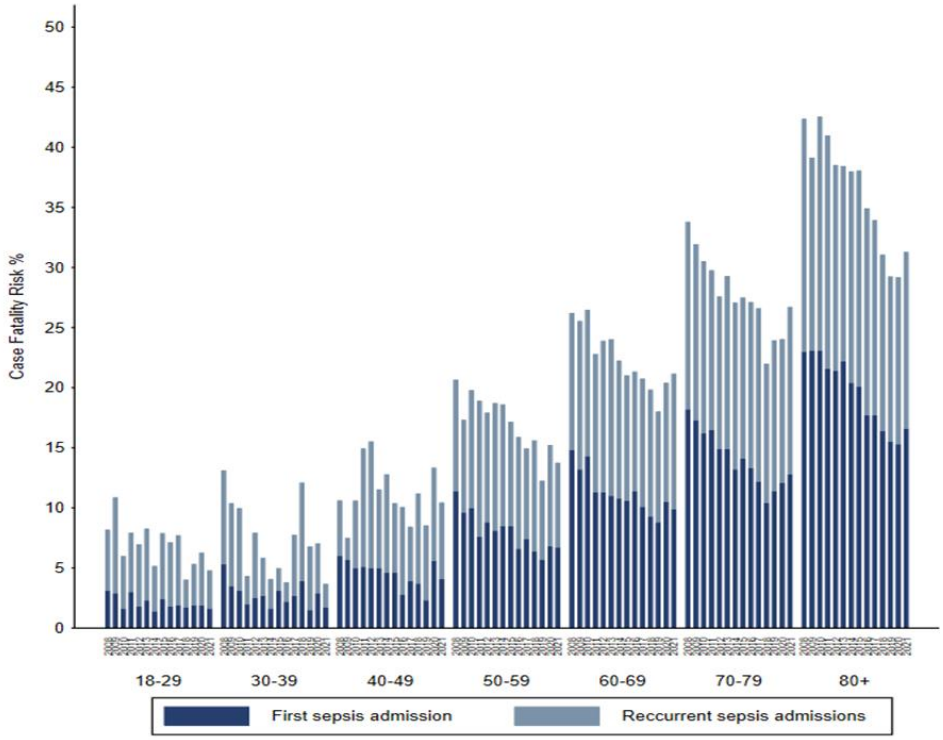

Figure 6. Annual Case fatality risk by 10-years age-groups for first and recurrent sepsis.

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During the two first pandemic years the IRR for a first sepsis was reduced compared with the previous 11-year period, with IRR of 0.877 (95% CI 0.829 to 0.927) in 2020 and 0.929 (95% CI 0.870 to 0.992) in 2021, and for all sepsis episodes it was 0.870 (95% CI 0.810 to 0.935) in 2020 and 0.908 (95% CI 0.840 to 0.980) in 2021. In the same period, the in-hospital deaths for first sepsis episodes increased with an OR of 1.061 (95% CI 1.001 to 1.124) in 2020 and an OR of 1.164 (95% CI 1.098 to 1.233) in 2021 and for recurrent sepsis admissions in 2021 with an OR of 1.112 (95% CI 1.027 to 1.205).

5.2 Paper II

Trends in mortality after a sepsis hospitalization: A nationwide prospective registry-study from 2008-2021.

Among 12,619,803 adult hospitalizations, 222,832 had a first episode of sepsis, and of these 127,059 (57.1%) had implicit sepsis, 92,928 (41.7%) had explicit sepsis, and 2,845 (1.3%) had COVID-19-related sepsis. The proportion of men was 54.1%, variating between 52.7% (implicit group), 55.6% (explicit group), and 65.5% (COVID-19-related sepsis group). The most frequent comorbidity was chronic heart and vascular disease, with 44.9% for all sepsis patients and 48.2%, 41.0%, and 24.7% in the implicit, explicit, and COVID-19-related sepsis group, respectively. Overall readmission proportion within 30 days was 24.9%, variating between groups, with 24.3% in the implicit group, 25.9% in the explicit group, and 16.7% in patients with COVID-19-related sepsis. Respiratory tract infections were the most common infection site with 36.8% for all sepsis patients, but varied and were diagnosed in 50.2% of the patients with implicit sepsis, 16.8% of the patients with explicit sepsis, and in 91.1% of the patients with COVID-19-related sepsis. 8.5% of all patients were admitted to ICU, and in the subgroups, 8.7% of the implicit, 7.7% of the explicit, and 11.1 % of the COVID-19-related sepsis patients needed ICU treatment.

Overall age-adjusted mortality showed that 16.9% (95% CI 16.7 to 17.0) and 23.9% (95% CI 23.7 to 24.1) did not survive 30 and 90 days, while 34.3% (95% CI 34.1 to 34.5) and 58.5% (95% CI 58.2 to 58.7) did not survive 1 year and 5 years. During the study period, we found a 14,0% (95% CI -14.2 to -13.8), 14.1% (95% CI -14.6 to -13.6), 13.8% (95% CI -13.9 to -13.5), and 8.6% (95% CI -8.7 to -8.5) reduction in 30-day, 90-day, 1-year, and 5-year mortality. The highest decrease was seen among patients with respiratory tract infection as

the cause of sepsis, with 10.0% (95% CI -9.8 to 10.1), 10.4% (95% CI -10.9 to -9.8), 15.7% (95% CI -15.9 to -15.6), and 11.08% (95% CI -11.07 to -11.08) reduction in 30-day, 90-day, 1-year, and 5-year mortality.

Explicit sepsis patients had a similar prognosis as implicit sepsis patients, HR =0.98 (95% CI 0.97 to 0.99). Cancer (HR 2.48, 95% CI 2.42 to 2.53), chronic lung disease (HR 1.21, 95% CI 1.18 to1.24), dementia (HR 1.58, 95% CI 1.52 to 1.65), and chronic liver disease (HR 3.44, 95% CI 3.09 to 3.83) had increased risk of dying than to chronic vascular disease. All infection sites had a lower risk of dying compared to respiratory tract infections. Circulatory (HR 1.05, 95% CI 1.02 to 1.08), coagulation (HR 1.33, 95% CI, 1.27 to 1.38), and hepatic acute organ dysfunction (HR 1.95, 95% CI 1.82 to 2.07) had increased risk of mortality compared to acute respiratory organ dysfunction.

5.3 Paper III

Return to work after a sepsis hospitalization: A nationwide, register-based cohort study.

Among 35,839 patients aged 18-60 who were discharged alive from an index sepsis hospitalization during 2010-2021, 12,260 (34.2 %) were confirmed to be working before sepsis hospitalization and included in this study. Disability pension prior to sepsis hospitalization led to the exclusion of 10,533 (29.3%) patients. Further, 4,735 (13.2%) patients were excluded for >30 days of sickness or long-term medical benefits in the months prior to sepsis hospitalization, indicating other illnesses than sepsis affecting RTW. Finally, 8,311 (23.1%) patients were excluded for lack of employment data prior to sepsis hospitalization, as inferred by no sickness or medical benefit surrounding sepsis hospitalization.

COVID-19-related sepsis patients had a higher probability of sustainable RTW (HR 1.31; 95% CI 1.15 to 1.49) than other sepsis patients. At 6 months, a higher proportion of COVID-19-related sepsis patients were at work (67.4% vs 58.4%), and at 1 year (77.8% vs. 66.9%), the longest we could follow COVID-19 patients. Beyond 1 year, the proportion of RTW in sepsis patients was 63.6% at 2 years and 53.9% at 5 year. During the study period, the trend in age-standardized RTW proportions was stable for ICU patients, while for ward patients, the RTW proportion decreased at 2 years (-1.32%; 95% CI, -2.14 to -0.49) (Figure 7).

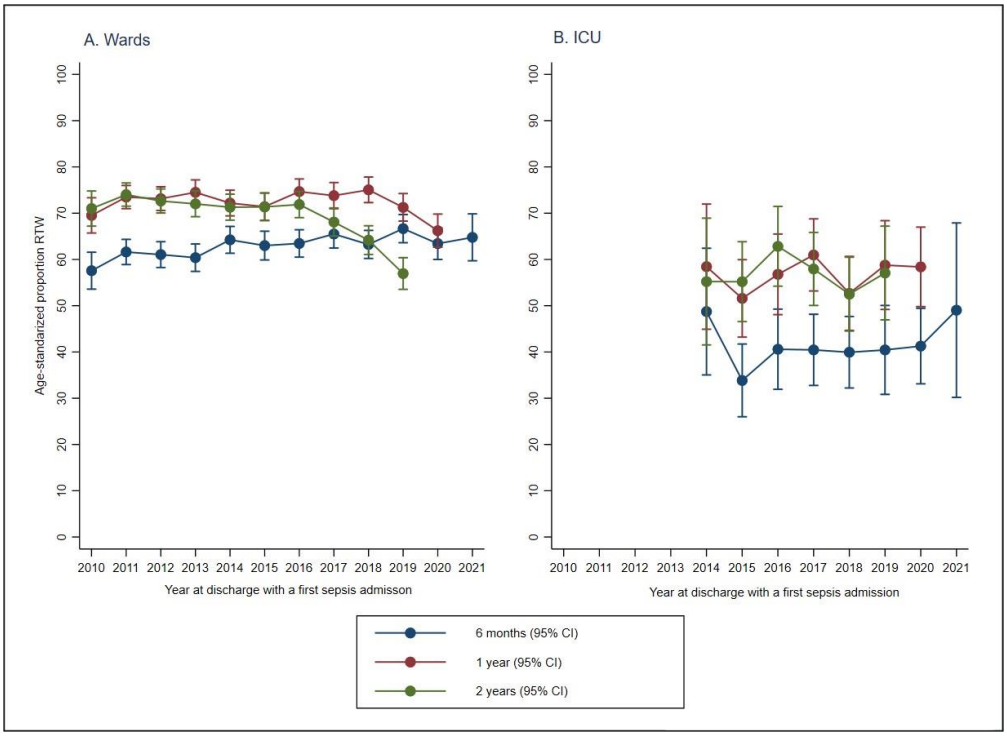

Figure 7. Age-standardized proportions RTW by discharge year for sepsis patients admitted A. wards (2010-2021) and B. ICU (2014-2021).

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Compared with respiratory infection, sustainable RTW was higher in patients with genitourinary infection (HR 1.38; 95% CI 1.27 to 1.49), gastrointestinal infection (HR 1.63; 95% CI 1.49 to 1.77), and skin/soft-tissue infection (HR 1.28; 95% CI 1.14 to 1.45). Compared to acute respiratory dysfunction, renal dysfunction (HR 1.48; 95% CI 1.39 to 1.58) they had a higher probability of sustainable RTW. ICU patients had a lower probability of sustainable RTW (HR 0.56; 95% CI 0.52 to 0.60) than patients treated at the wards.

6.0 Discussion

This thesis has quantified sepsis incidence, case fatality, long-term mortality, and return to work after sepsis in a Norwegian nationwide register-based study with no loss to follow-up in the period 2008 through 2021. In the following sections, I present methodological considerations made in this thesis, identify errors, and discuss our findings against existing literature. Further, I highlight the strengths and limitations and provide possible clinical implications and future perspectives.

6.1 Methodological considerations

6.1.1 Study design

Epidemiological design and methods are valuable tools when the aim is to investigate and understand diseases and health events [145]. WHO defines epidemiology as : "*Epidemiology is the study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems. Various methods can be used to carry out epidemiological investigations: surveillance and descriptive studies can be used to study distribution; analytical studies are used to study determinants*" [146].

Importantly, this definition distinguishes between descriptive and analytic epidemiology by study aim. A descriptive approach is preferred if the study's aims to characterize the exposure in relation to the outcome. On the other hand, an analytical approach should be used if the study aims to measure the association between exposure and outcome. Since our study aim was descriptive, we have followed a descriptive epidemiological framework that highlights a) a well-defined research question, b) a defined target population, c) representative sampling,

d) a definition of outcome, e) a specified measure of occurrence, and f) describe the role of other variables [147].

However, in all scientific research, potential sources of error could influence the results. To assess the precision and validity of our findings, I will, in the following section, discuss our target population, definition of outcome, representative sampling, and the role of other variables and how possible errors due to this may have affected our measure of occurrence.

6.1.1 Precision (Random Error)

Errors in an estimate that occurs by chance are defined as random [148]. These errors depend on how the subjects are sampled and how the variables are measured. To quantify the impact of random errors in observational studies confidence intervals (CI) can provide an index of precision. High precision of the estimates measured by narrow CIs indicates a lower possibility for random error. Random error cannot be eliminated but can be reduced by increasing the sample size [148].

In Paper I-III, the precision of the estimates was examined using 95% CI. The study population was large in all three studies, and the estimates had narrow CIs in most analyses. However, there are few events and less precise estimates in some subcategories of the exposure variable, such as those with COVID-19-related sepsis, chronic liver disease, and acute liver dysfunction in Paper II and Paper III.

6.1.2 Internal validity (Systematic error)

In descriptive epidemiology, systematic errors include selection bias, information bias, and bias due to adjustments [148-150]. These errors represent important threats to the internal validity of any study and must be carefully considered before the interpretation of results [148]. Notably, CIs do not consider systematic errors, so estimates within a 95% CI must be interpreted cautiously regarding true associations [148].

Selection bias

Selection bias occurs at the stage of recruitment of participants and/or during follow-up. The consequence of selection bias is that the study population is not representative of the background population, which may affect internal and external validity.

Selection bias due to the extraction of codes in administrative data can considerably impact the incidence of the measure of interest. Representative sampling with a well-defined population is essential to capture the study subjects in descriptive epidemiology [150]. Studies based on administrative databases involves the selection of ICD codes. This is a challenge for sepsis due to its heterogeneity and great variability, involving multiple codes and combinations of these. The different ICD-code strategies used to identify sepsis in administrative data are greatly discussed and validated [151-155]. The latest pooled sensitivity estimate for sepsis ICD-10 codes was 35% (95% CI 22 to 48), whereas the pooled specificity was 98% (95% CI 98 to 99) [151]. A validation study of the sepsis code strategy of implicit and explicit sepsis codes has found that the explicit sepsis coding strategy causes an underestimation of sepsis. Thus, using both strategies most likely aligns the results [154]. We retrieved a combination of codes previously used by Rudd et al. and defined sepsis by implicit and explicit sepsis codes [8]. Implicit sepsis was defined as a combination of an infection and an acute organ dysfunction code. This may generate false positive implicit

sepsis cases since acute organ dysfunction concurrent to infection can be due to other medical conditions. On the other hand, organ dysfunction can also be inadequately documented and lead to false negatives. False-positive sepsis cases will inflate the incidence rate, while false-negative sepsis cases will have the opposite effect.

During the study period, the definition of sepsis and the recommended ICD-10 coding have changed. New specific codes for SIRS and septic shock were implemented in 2010 [134], and the latest definition of sepsis came in 2016 [1]. We used the same coding strategy for the whole study period, although changes in coding practices may have occurred during the study period. Our result for first sepsis incidence is consistent during the study period, however, we acknowledge these factors and consider them relevant.

The sample of sepsis patients used in all three studies was extracted from a complete nationwide registry covering all Norwegian public hospitals, thus considerably reducing the risk of bias due to non-response [148, 156]. Moreover, due to the reimbursement system and the robust qualitative coding-control procedures, discharges without ICD-10 codes are rare. Consequently, missing discharge codes are minimal in NPR [133]. Therefore, our extraction is without incomplete or unknown discharge codes, and selection bias due to missing is highly unlikely. In the follow-up of the study participants, we assessed mortality using NPR (Paper I) and DÅR (Paper II and Paper III), which both are nationwide population-based registries with a high degree of completeness and good quality [133, 157]. Additionally, Norway has experienced a positive net immigration, which reduces the likelihood of loss to follow-up [148].

Detailed knowledge of coding practices and changes is important when conducting a registry-based study because this can potentially affect data quality and completeness and influence results. We designed an extraction strategy in 1 primary and 20 secondary diagnosis fields, which is in line with recommendations where at least 15 fields are recommended to fully characterize clinical outcomes [158]. Increasing the number of fields when searching for ICD-10 codes improves the international and intra-national comparability of data for epidemiologic research. Further, the ICD 10 codes were extracted at both three and four-signs levels. A total of four-sign levels would have increased the detailed information about the sepsis phenotype but increased the risk of recognition of participants, which was a concern during the ethical approval process. Thus, we proceeded with a three-sign-level approach.

Since treating sepsis involves antibiotics and/or organ support therapy and surveillance [1], we can assume that most sepsis cases are admitted to hospitals. However, we cannot rule out that contact with healthcare is more frequent among certain patient groups (e.g., cancer), or physicians may be more attentive to early signs of infection in patients more prone to infection. However, due to the acute and fulminant clinical presentation of sepsis, we consider it less likely that the presence of sepsis in certain patient groups should have influenced patients' triage and clinical care. The implications would have overestimated the incidence in groups of patients with certain comorbidities and probably also mortality. However, we cannot preclude that a small proportion of patients were not captured if they died before being given a sepsis diagnosis. The implications would have overestimated the incidence and underestimated the mortality of sepsis patients.

Additionally, we did not have data on other healthcare facilities that may have treated some patients. Still, most people in Norway reside in common housing and probably use the acute care chain in case of a medical emergency like sepsis. Furthermore, when calculating in-hospital mortality in Paper I for COVID-19-related sepsis, we observed that we could only identify 30% of the patients nationally registered as having COVID-19 as the cause of death during the same period [159]. It is shown that Norway had a high threshold for hospitalization among older individuals aged over 70 years [160], which implies that many elderly patients infected with COVID-19 in Norway died outside the hospital, e.g. in other healthcare facilities. In Paper II, we investigated in-hospital deaths and acknowledge that both the incidence and the case fatality rate could have been higher if more older patients had been admitted. Including more older patients with COVID-19-related sepsis in the study would most likely increase the long-term mortality in this group.

Comorbidity was a prognostic factor in all three studies and based on ICD-10 extraction from NPR. The strategy we used was based on diagnostic groups and is found to be superior compared with the Charlson Index and the Elixhauser Comorbidities [161]. However, we must recognize that this strategy has limitations, and we acknowledge the relevance and consider them important for any definition of comorbidities.

Return to work (Paper III) was assessed using medical benefit data from NAV, a population-based registry. Applying for medical benefits when absent from work due to critical illness is not mandatory. However, a sick leave application from a physician to NAV is mandatory to cover the wage during sick leave. Employers often demand the sick leave application after the sick leave has extended the 16 days allowed to self-report absence due to sickness. During the selection process in Paper III, we observed that 40% of the sepsis patients were without

sickness benefits in the period surrounding their hospitalization. Due to our definition of working, we had to exclude these patients. The excluded patients were younger, and we thus find it more likely that this included a higher proportion of students.

In summary, we find it highly unlikely that mortality rates (Paper I and Paper II) are biased due to loss of follow-up. Further, we acknowledge that more information about the excluded patients in Paper III would have heightened the validity and that the RTW analysis might be biased. Additional information about the excluded patients might have led to a higher proportion of younger individuals with a higher probability of returning to work and potentially increased the likelihood of sustained RTW.

To conclude, we cannot entirely dismiss the presence of some selection bias in all three studies, some that may have led to an underestimation and some that may have led to an overestimation of the sepsis incidence. We acknowledge these biases and consider them relevant.

Information bias

Information bias refers to a measurement error of exposure and /or outcome or other variables among the already included subjects in the analysis [148]. Information bias occurs due to classification errors. The diagnoses in administrative data might be imprecise due to different coding practices, and the coding practices may have changed during the follow-up [162, 163]. Factors that may have induced bias due to more coding of sepsis during our study period are summarized in Figure 7.

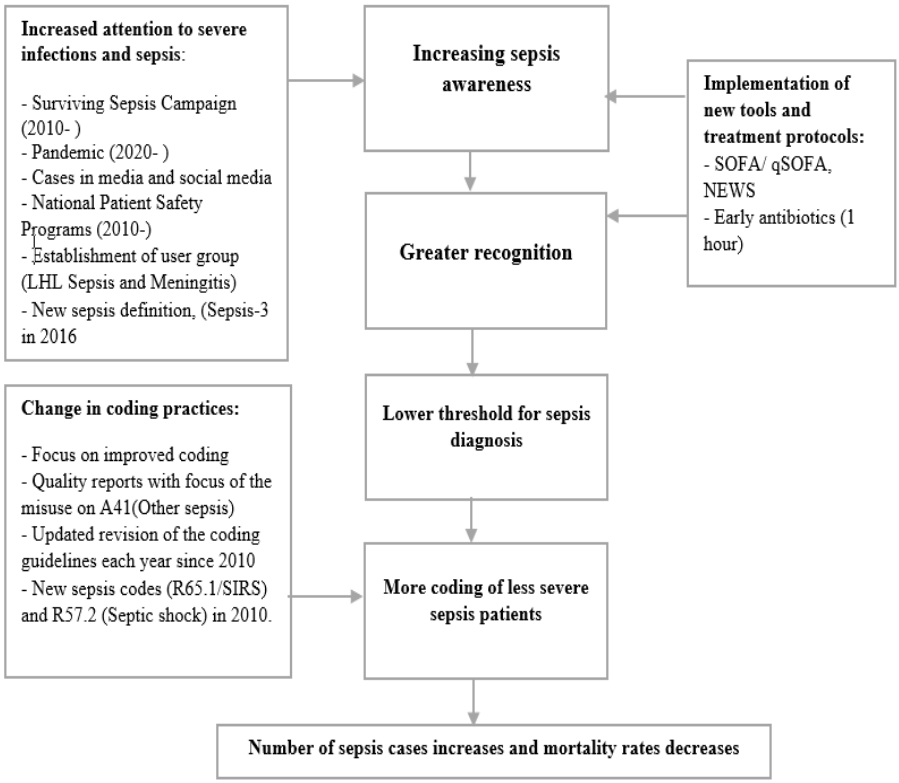

Figure 8. Summary of factors that may affect coding during the study period possibly introducing bias.

A lower threshold to diagnose and code for sepsis may increase sepsis incidence and decrease sepsis mortality rates. Nonetheless, our trends seem consistent throughout the follow-up period for first sepsis admissions. Moreover, reporting to NPR is mandatory and subject to annual quality assessments conducted by the Settlement Committee. These assessments advice about correct medical coding at a hospital level, and hospitals with incorrect coding

may be subject to fines [164]. This systematic quality improvement work lowers the risk for creative coding motivated by increased earnings.

Additionally, recent reports have found instances of over-coding of A00 (Cholera) within the discharge ICD-10 codes in NPR [165]. There are hypothesized that as this is the first code in the ICD-10 system, it is easy for clinicians to choose; therefore, many A00 codes most likely represent a mis-coding. With this new insight, we found 103 cases of A00, which represent 0,032% of our total admissions. Consequently, we can conclude that the presumed mis-coding of A00 does have minimal impact on our estimates. In sum, we acknowledge the factors related to more coding of less severe sepsis and mis-coding. However, we find it unlikely that they have affected our outcome measures.

The patients' characteristics were prospectively registered during hospital admission, reducing the risk of misclassification based on outcome measures and eliminating recall bias[148].

We observed minor deviations in 2008 and during the pandemic years. As we could not control that the sepsis episode in 2008 was the first, and pandemic years that are known to affect sepsis incidence and mortality [166], we incorporated adjustments for these specific years within our analysis. This adjustment enhances the validity of our findings from 2009 to 2019, as the regression line in that period otherwise would have been influenced by the extremes.

Late entry in survival analysis may affect hazards between those who enter early and those who enter later than the standard subjects [167]. The influence of the pandemic on trends in

Paper I and Paper II was calculated from January 2020, although the first COVID-19 sepsis case came in February the same year. This could have caused an underestimation of the reported incidence and in-hospital (Paper I) and all-cause mortality (Paper II). The COVID-19-related sepsis patients were included from 27 February 2020 (the first confirmed hospital case) and treated with delayed entry in the regression analysis in Paper II and Paper III. The same was done for patients needing intensive care treatment, with delayed entry from 1 May, 2014 (Paper II and Paper III). To assess possible error due to delayed entry in the regression analysis in Paper II, we conducted a sensitivity analysis with follow-up time from 27 February for all subgroups of sepsis patients (implicit, explicit, and COVID-19-related sepsis), and the results remained consistent. Therefore, we consider error due to late entry highly unlikely.

One way to report data quality and completeness is the percentage with PINs in records [148]. If the percentage of a PIN is high, then the possibility of linking data to other registries is elevated, thus, the probability of biased prevalence estimates is reduced. The reporting of the PIN to the NPR was nearly complete from the very beginning of the registry [133]. We linked all 5 registries used in Paper I. Paper II and Paper III by PINs, with complete linkage, thus minimizing the risk of measurement error. In addition, NPR undergoes yearly quality controls by the National Service for Validation and Completeness Analysis, which shows that in most diagnosis groups, the completeness is >95% [168]. However, the completeness of the sepsis codes for this study is unknown.

In sum, we consider measurement error due to data quality (completeness, loss-to-follow-up) and change in sepsis definition highly unlikely. However we cannot entirely rule out

measurement error due to index sepsis admission and earlier study start for COVID-19-related sepsis.

Adjusting for other variables

Our purpose was descriptive and did not aim to identify causal effects, thus, we avoided adjusting for covariates (which have a strong causal interpretation [150, 169]. However, we have adjusted for possible differences in age and sex since the age and sex distribution in the population changed somewhat over the years [135]. We acknowledge that this adjustment could mask possible age or sex-specific differences in incidence and case fatality rates.

To conclude, this study is not immune against selection, information, and adjusting bias, however, we have approached the most prominent biases with appropriate design, thus, we consider the study to have high internal validity.

6.1.3 External validity

External validity is to what degree the study results can be generalized to a broader context. When the sampling is for descriptive purposes, seeking representativeness of the study population is crucial for implementation [170]. Internal validity is a prerequisite for external validity, and the sample size and appropriate patient characteristics are important to warrant representativeness [148].

By including all Norwegian public hospitals, our sample is representative for those admitted to hospitals with sepsis in Norway. Since incidence and mortality are strongly associated with age, we conducted a yearly incidence rate per 100,000 citizens per 10-year age group, which makes our estimates highly representative for different age categories. Our estimates also

showed small differences in incidence, mortality, and RTW among males and females, which makes them representative for both sexes. However, our results are only representative for the adult population since we investigated only the adult population ≥18 years. In sum, we find our sample to have high generalizability for the whole adult Norwegian population.

Our use of Segi`s world population distribution in the standardization of incidence in Paper I increases the generalizability to adult populations in other countries with different age distributions [171]. Further, using this approach, we observe that our incidence estimates are in line with a recent pooled global estimate [70]. However, reported sepsis incidence is probably underestimated due to few studies from low-income countries that comprise 85% of the world's population and additionally have higher rates of infectious diseases per inhabitant [70]. We acknowledge considerable differences in sepsis incidence between high- and low-income countries [8, 70].

Moreover, generalizing the results is challenging because of the high variability between comparable studies [151]. Comparison of first and recurrent trends in sepsis incidence with other countries is problematic because most registry-based studies fail to extract sepsis cases by PID [72, 74, 75]. These studies have, however, shown an overall increase in yearly sepsis incidence, which is in line with our total incidence estimates, although our rise in incidence is more modest.

A systematic review identified considerable differences in RTW rate among countries, where studies from China had the highest RTW rate after COVID-19 with almost 100%, and the lowest RTW rates (10-28%) was seen in samples restricted to ICU patients [172]. This

suggests that variances in RTW rate depend on several factors, such as severity of sepsis episode, age differences between studies, presenteeism (i.e., working while sick), and differences in social infrastructure. To investigate the RTW among sepsis patients is challenging and has yet to be previously investigated using nationwide administrative data. However, a recent registry study based on health claims data from the German AOK health insurance found higher RTW in a study population covering 30% of the German population than our study [15]. The individuals with AOK insurance were in another study of patients undergoing revision for hip arthroplasty found to have different socio-economical backgrounds compared to all other German patients [15]. In contrast, we included all patients and thus are more generalizable across the socioeconomic. However, we also lack information on trajectories based on socioeconomic background.

Notably, the level of SARS-CoV-2 incidence in Norway was relatively low; therefore, the interpretation of findings in this subgroup is only relevant to countries with the same burden.

To conclude, our findings can be generalized to the whole adult Norwegian population hospitalized with sepsis and may be compared to other countries. There is, however, a need for research on other population-based cohorts on long-term mortality and RTW since such research is limited, and long-term outcomes in sepsis survivors are a global concern.

6.2 Discussions of main findings

This thesis aimed to describe the incidence and long-term outcomes after sepsis in a nationwide cohort with complete follow-up of all sepsis patients. Our main findings from Paper I-III will be discussed below:

6.2.1 Incidence

To date, adequate data on the incidence and mortality trends of sepsis in Norway have been lacking, and internationally, only a few have nationwide data with the ability to stratify by individual. Our findings show a stable trend in hospitalized first sepsis episodes in the Norwegian population between 2008 and 2021, which goes against the reported increasing trends in sepsis incidence [8, 72, 75, 121, 173-175]. However, our finding is in line with a US study (2015) that found a stable trend investigating sepsis by clinical criteria in electronic health records [163]. Most of the studies that report trends are based on ICD code extraction from administrative registries, thus, increased recognition followed by increased medical coding is hypothesized to cause an increased sepsis incidence [162].

Some of the studies that report increasing sepsis incidence report on cases [72, 75, 121, 173], thus can be compared to our overall increasing trend that includes recurrent admissions. This implies that the previously reported increasing trends could be related to the limited access to individual-level data in other registries. Nevertheless, our findings suggest an increasing overall sepsis incidence due to recurrent sepsis has more than doubled in patients over 60 years, and the explanation for this is probably multifactorial. An aging population with an age-related weakened immune function, better treatment of other medical conditions, and more patients on immunosuppressive medication due to, e.g. cancer treatment increases the number of patients at risk of developing more than one episode [70, 176, 177]. In addition, sepsis survivors are more prone to recurrent sepsis due to new and worsened comorbidities and recurrent infections [13, 65]. In sum, this increases the sepsis burden and underscores the need for reliable surveillance methods.

Our mean age-standardized incidence was in line with the recent pooled estimate from the last decade [70]. However, our overall incidence was higher than previous Norwegian estimates [3, 71], thus suggesting that the impact of sepsis is higher than previously assumed. Comparisons are complicated by using different sepsis definitions between the studies and different extraction of ICD codes. While our estimates give information on incidence using the updated Sepsis-3 definition with the extraction of implicit and explicit sepsis codes, previous Norwegian studies use a more narrow coding strategy [3, 71]. A Swedish study (2010) investigating three different ICD-coding strategies found divergent results between all three [175]. While explicit coding strategies underestimate sepsis, the opposite is found for implicit sepsis strategies [154]. In sum, the different approaches are all hampered by methodological shortcomings and errors must be considered.

The decreasing trend in incidence during the pandemic is also observed in Denmark [166]. Possible explanations can be a lower incidence of other infections because of social distancing during lockdowns [166, 178], vaccination strategies (prioritizing the elderly first), and cancelation of elective surgeries [179]. Interestingly, it is shown that Norway had a high threshold for hospitalization among older (over 70 years) during the first pandemic years [160], making it possible to avoid capacity problems. With the high threshold for hospitalization combined with the fact that we could only identify 30% of those who had COVID-19 as a cause of death [159], we must assume that many died outside the hospital.

6.2.2 Case Fatality

Previous reported trends in hospital death show a decreasing trend [5, 173, 180] and are consistent with our findings. Explanations for this decreasing trend are increased attention to sepsis, with surviving sepsis campaigns and new and updated treatment protocols [1, 20, 35], assisting clinicians in timely and accurate treatment, preventing illness severity from developing, and further preventing mortality. Another explanation for the decreasing trend is the increasing sepsis incidence due to increased coding of less severe sepsis [162]. Increasing the nominator without changing the denominator will decrease in-hospital mortality. However, this plausible explanation is less relevant for our decreasing case fatality since we found a stable trend in incidence. During the COVID-19 pandemic, the mortality increased, most prominently in 2021. Increased mortality during the pandemic was also found in Denmark [166]. The fatality of the new SARS-CoV-2 virus can explain the higher in-hospital mortality we found among COVID-19-related sepsis admissions. However, only 1 out of 10 sepsis admissions were due to COVID-19-related sepsis during the first two pandemic years. Further concerns are negligence of symptoms and hesitancy to seek healthcare due to the perceived risk of contracting COVID-19 infection. The implication could be that those admitted to hospitals had higher baseline mortality risk since they were more severely ill.

6.2.3 Long-term mortality

This thesis shows a declining trend in all-cause mortality rates beyond hospital discharge over time, which is in line with two meta-analyses investigating patients with severe sepsis and septic shock [181, 182]. However, all-cause mortality rates are challenging to investigate because they may be attributed to the sepsis episode itself or represent an event that would have occurred independently of the sepsis episode [183-185].

To our knowledge, we are the first nationwide study investigating long-term all-cause mortality, encompassing both ward and ICU patients. Surprisingly, we found that although ICU patients had higher mortality rates at 1 year, this disparity diminished at 5 years, with a 61% mortality rate for patients requiring intensive care treatment and a 58% mortality rate for those admitted to wards. In a matched-cohort study, sepsis patients had a 2.2-fold relative increase in long-term mortality compared to adults not currently in the hospital [16], which suggests that 20% of the patients die as a consequence of sepsis. One plausible biological explanation is epigenetic regulation causing immunosuppression after sepsis and atherosclerosis [186], which explains the observed elevated rates of recurring infection, cancer, and cardiovascular deaths among those who survive sepsis [65, 187].

High long-term mortality rates in sepsis survivors are likely multifactorial. A previous study found that severe comorbidities, respiratory tract infection, and an increased number of acute organ dysfunctions during admission was associated with long-term mortality [66], which is in line with our result. In addition, we found that long-term mortality were associated with various acute organ dysfunctions, with the strongest association in patients with acute liver dysfunction compared to other acute dysfunctions. Others have found similar associations [188, 189]. However, their estimates were smaller than ours, which can be explained by smaller and different study populations. Additionally, we did not have the opportunity to exclude end-stage comorbidity diseases, possibly contributing to a stronger association between acute organ dysfunction and mortality. Since all aforementioned studies investigated causal relationships, and ours were descriptive, comparisons must be done cautiously.

This thesis showed the highest decline in mortality among patients with respiratory tract infections. The literature on infection sites among sepsis patients and trends in long-term mortality are non-existent. However, a study investigating infection sites and trends in hospital mortality found that the decline was highest among sepsis patients with skin infections, primary bacteremia, and catheter-related bloodstream infections [190]. For comparison, our study had a higher number of respiratory tract infections, fewer skin infections, and a longer follow-up. To some extent, our decline in the incidence of respiratory tract infections can be explained by pneumococcus vaccinations and the relatively low mortality may explained by low bacterial resistance in Norway [191].

A recent English study (2019) of ICU survivors, using the Sepsis-3 definition, reported mortality rates of 15% at 1 year and 38% at 5 years following hospital discharge [66]. These findings contrast with our study, where 41% of the patients needing intensive care treatment had died within 1 year and 61% at 5 years after discharge. A possible explanation of the diverging result may be the exclusion of in-hospital deaths in the English study. Notably, including only sepsis survivors when assessing long-term mortality can cause an underestimation of the severity of sepsis and affect the association between clinical characterization and mortality. Therefore, this aspect must be considered when making comparisons between studies. Another contributing factor is that NIR includes stays at the ICU with a duration >24 hours [137], while the English study included participants in the first 24 hours at the ICU. This may also have led to a sample of less severe sepsis patients than ours. However, our estimates are in line with overall 1-year mortality measured in two recent studies from Island and Sweden [122, 123].

We found a similar prognosis in patients with explicit than implicit sepsis, in contrast to two other studies, which reported a higher risk among patients with explicit sepsis [4, 192]. A key factor contributing to these diverging result are different ICD-code abstraction and search in a lower number of diagnosis fields to find secondary codes than recommended [158], which can cause an underestimation of implicit sepsis. Considering the widespread media coverage of COVID-19, it is noteworthy that we observed a similar risk of death among patients with implicit and COVID-19-related sepsis. In sensitivity analyses restricted to the two first pandemic years, we found a slightly lower risk of death in COVID-19-related sepsis patients. These three subgroups of sepsis patients also had a higher proportion of preexisting comorbidities than to the prevalence previously reported in the general population [193]. These findings emphasize the need to discuss follow-up of all sepsis patients, also after the recent COVID-19 pandemic.

6.2.4 Return to work

Being out of work can harm health and is recognized as an important factor for well-being [194]. Resuming normal activity, including return to work, is considered an indicator of recovery. Thus, we estimated RTW to investigate long-term outcomes among sepsis survivors further. RTW is a relatively new long-term outcome used to estimate both physical and mental impairments after illness. Most of the previous studies on RTW are hampered by loss to follow-up bias and small sample size [101]. We are the first to use complete nationwide registries to calculate RTW and found that RTW is a challenge even 2 years after discharge. Only one recent German study (2023) has used administrative data and ICD-10 code extraction to investigate RTW in sepsis survivors [15] and found a higher proportion of patients with RTW at 6 months and 1 year compared to our estimates. A possible explanation for the diverging result is the extraction of only explicit codes found to underestimate sepsis

[154]. In addition, the German study covered only 30% of the total population. Thus, due to possible demographic and sociodemographic differences between the included and excluded patients, their results must be cautiously generalized [195].

Decreasing trends in RTW are previously well described among patients surviving cancer [196]. However, to our knowledge, trends in RTW have not previously been described among sepsis survivors. This thesis shows that the trends of RTW were stable among patients admitted at wards during the study period (at ½ and 1 year), except at 2 years, where the trend decreased by one-fifth. However, the RTW trend was stable for patients admitted to the ICU. A possible explanation of the decreasing trend among patients admitted at wards is increased short and long-term survival, which points to a higher proportion of ill patients with less ability to RTW being discharged. The stable trend in RTW among ICU sepsis patients can similarly be explained by the observed stable trend in case fatality and long-term mortality.

An administrative-based Danish study (2018) found that increasing numbers of organ failures needing support therapies were associated with a decreased chance of RTW [98]. Two other studies found that increasing age and preexisting comorbidities were associated with work status in patients admitted with ARDS [102] and patients with acute kidney injury [103]. However, compared to our study, these studies are small and based on self-report. Characteristics associated with sustained RTW in both ward and ICU patients are not previously described in a nationwide population-based study, and early identification of factors associated with increased probability of non-assuming work offers opportunities to reduce the burden associated with sepsis.

The literature is limited regarding the RTW rate in hospitalized COVID-19 patients beyond 6 months and patients with COVID-19-related sepsis. Up to 6 months, RTW rates vary between 10 to 100%, increase with follow-up time, and vary strongly between countries [172]. For comparison, a Danish register-based study found that 6.6% had not returned to work at 3 months, which gives a much higher estimate in RTW than ours [116]. Including patients with more severely ill patients in our group may explain the diverging result. Moreover, we found that patients with COVID-19-related sepsis had a higher probability of sustained RTW than other sepsis patients. This estimate includes both ward and ICU patients in both groups and due to the heterogeneity of the sepsis syndrome, must be interpreted cautiously.

6.3 Strength and limitations

We are the first study to describe the burden of sepsis in patients admitted to wards and ICU, including the recent pandemic. The major strength is that we have used complete nationwide register data, thus reducing the probability of systematic error due to missing and non-response bias. To capture all patients hospitalized for sepsis, we have extracted discharge codes that are internationally recognized and validated. Another strength is that the extensive number of cases over fourteen years allows us to describe incidence, mortality, and RTW trends. For incidence and mortality, we could also account for possible changes during the pandemic, including index and subsequent episodes of sepsis.

Further, we report age-adjusted estimates according to age-groups, which allows comparisons between age groups and other studies. In addition, we standardized the incidence to Segi`s world population, which increased our generalizability to countries with different age

distributions. To our knowledge, we are the first study that reports RTW using nationwide register data, thus avoiding recall bias and loss of follow-up, which is frequent in self-reported RTW. Further, nationwide inclusion is a strength in terms of reducing selection bias. We describe characteristics associated with RTW for at least 31 consecutive days, which is a strength because these results give a more sustained image of assuming work than previous results that report RTW at a specific time-

There are some limitations to this thesis. First, we used ICD-10 codes to define sepsis, including administrative discharge codes to capture sepsis, thus, the diagnosis is not clinically validated. Our sample was extracted from a nationwide registry and depends on the extraction strategy, the register's quality, and possible changes in coding practices during the study period. Although the quality of the registers we have used is good [133, 136], using ICD-10 codes in other studies has been found to underestimate sepsis [151]. However, using both explicit and implicit codes to capture sepsis will mostly align the results since implicit codes are found to overestimate sepsis, and explicit sepsis codes underestimate sepsis [154]. During the study period, the sepsis definition changed, and we used the Sepsis-3 definition, albeit this came first in 2016 [1]. However, our results seem persistent over the study years, which is reassuring. In study 3, we had to exclude 40 % of the patients of working age as we lacked information on sick leave benefits to indicate work. We found that the participants we had to exclude were younger and probably students not working at that time. If this assumption holds, we have underestimated the RTW rate.

6.4 Conclusions of main findings

Based on our results and the subsequent evaluation of the methodology applied in the three studies, the following main conclusions were drawn:

Paper I

Incidence of first sepsis admissions was stable in the period 2008 through 2021. A 15% increase in overall sepsis incidence was mainly due to recurring sepsis, with a more than doubling in patients above 60 years. The mean in-hospital case fatality rate was 13.7%. The in-hospital case fatality was reduced by 28% in all age groups, regardless of first or recurrent sepsis episode. The incidence of sepsis decreased in the first two COVID-19 pandemic years, while in-hospital mortality increased. COVID-19-related sepsis accounted for 1 out of 10 hospitalizations with sepsis in 2020 and 2021. Compared to other sepsis patients, patients with COVID-19-related sepsis had a somewhat increased risk of in-hospital death.

Paper II

We found that 17%, 24%, 34%, and 59% of the patients did not survive 30 days, 90 days, 1 year, and 5 years, respectively. During the study period, we found a reduction in mortality of 14% in 30-day, 90-day, and 1-year mortality, and 9% at 5-years. The highest mortality reduction was seen among patients with respiratory tract infections as the cause of sepsis. In addition, patients with comorbidities such as cancer, chronic lung disease, dementia, and chronic liver disease had an increased risk of dying compared to those with chronic heart and vascular disease. The mortality in patients needing ICU treatment compared to patients admitted to the ward was 26% vs. 17% at 30-day, 32% vs. 24% at 90-day, and 41% vs. 34% at 1-year. This mortality difference aligned at 5 years and was 61% in patients that needed ICU treatment and 58% in patients admitted to wards. Further, patients with COVID-19-related sepsis had approximately the same mortality risk as other sepsis patients.

Paper III

In this study, we found 58%, 68%, and 63% RTW at ½, 1, and 2 years after discharge with a sepsis diagnosis. The trends were stable during the study period (at ½ and 1 year), except at 2 years, where we found a 19% reduction in the proportion of patients that had returned to work between 2010 and 2019. Younger patients, patients with fewer comorbidities, and patients with fewer acute organ dysfunctions had an increased risk of returning to work. In addition, we found that patients discharged with COVID-19-related sepsis had an increased risk of returning to work compared to other sepsis patients.

6.5 Clinical implications and perspective

We present reliable and up-to-date estimates of incidence, in-hospital mortality, long-term mortality, and return to work of all hospitalized sepsis patients in Norway. Our estimates ensure a fully skilled sepsis dimension that is important to commission appropriate health services and work facilitation. At a patient level, our findings allow informed discussions and shared decision-making about treatment options, advanced care planning, and work facilitation [197]. This new knowledge is of interest to politicians, health leaders, clinicians, and employers. In addition, we provide a systematic approach to identifying patients with sepsis using of administrative data that can be useful for future research, surveillance purposes, and for quality improvement.

It is important that work with sepsis patient`s safety continues through the Patient Safety Programs initiated by the Norwegian Directorate of Health [198] and that the hospitals facilitate the nationwide learning networks [199]. With the increasing antibiotic resistance, a systematic approach and continuously updated guidelines for the use of antibiotics in hospital

and primary care have to be prioritized [200, 201]. These must be implemented through the antibiotic stewardship programs [202].

To be sure of improvements, we have to measure. However, it is important what we measure. With this in mind, sepsis statistics should become a standard component of national public health reports to better understand the epidemiology of sepsis. Further, the sepsis statistics should be mandatory to report at hospital levels to facilitate quality improvements. Better understanding, improved monitoring, detection, and treatment of sepsis across all age groups would benefit to the Norwegian population.

This thesis has clearly shown a paradox: with quality improvements and reduced mortality increased workload follows. This is a challenge for the future health care service. Therefore, a systematic approach to post-sepsis care and further research to better understand the impact of recurrent sepsis are warranted.

Future research that is needed :

- Sepsis in primary care to understand the complexity of the diagnosis and management in the community.
- Sepsis during the pandemic to better understand the changes observed during the first pandemic years in incidence and case fatality.
- Sepsis and rehabilitation programs to better understand and facilitate recovery.
- Sepsis and work facilitation programs to better understand and improve well-being.
- Sepsis in ICU to better understand the lack of improvements in long-term outcomes.
- Sepsis and national guidelines of the use of antibiotics, both in hospital and primary care.

- Cause-specific mortality in sepsis patients.
- Recurring sepsis, to better understand the increased incidence among this group of patients.
- Sepsis and sociodemographic factors to better understand and prevent sepsis among groups of patients.
- Sepsis in children <18 years.

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201. **Antibiotika i sykehus** [https://www.helsedirektoratet.no/retningslinjer/antibiotika-i-sykehus]
202. **Antibiotikastyring i sykehus** [https://www.antibiotika.no/antibiotikastyringsprogram-2/]

Appendix

1. Paper I

- Main document, including figures and tables
- Supplementary File, including figures and tables

2. Paper II

- Main document, including figures and tables
- Supplementary File, including figures and tables

3. Paper III

- Main document, including figures and tables
- Supplementary File, including tables

4. File with description of ICD-10 codes used to identify sepsis

PAPER I

BMJ Open

Long-term temporal trends in incidence rate and case fatality of sepsis and COVID-19-related sepsis in Norwegian hospitals, 2008–2021: a nationwide registry study

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ABSTRACT

Objectives To estimate temporal trends in incidence rate (IR) and case fatality during a 14-year period from 2008 to 2021, and to assess possible shifts in these trends during the COVID-19 pandemic.

Setting All Norwegian hospitals 2008–2021.

Participants 317 705 patients ≥18 year with a sepsis International Classification of Diseases 10th revision code retrieved from The Norwegian Patient Registry.

Primary and secondary measures Annual age-standardised IRs with 95% CIs. Poisson regression was used to estimate changes in IRs across time, and logistic regression was used to estimate ORs for in-hospital death.

Results Among 12 619 803 adult hospitalisations, a total of 317 705 (2.5%) hospitalisations in 222 832 (70.0%) unique patients met the sepsis criteria. The overall age-standardised IR of a first sepsis admission was 246/100 000 (95% CI 245 to 247), whereas the age-standardised IR of all sepsis admissions was 352/100 000 (95% CI 351 to 354). In the period 2009–2019, the annual IR for a first sepsis episode was stable (IR ratio (IRR) per year, 0.999; 95% CI 0.994 to 1.004), whereas for recurrent sepsis the IR increased (annual IRR, 1.048; 95% CI 1.037 to 1.059). During the COVID-19 pandemic, the IRR for a first sepsis was 0.877 (95% CI 0.829 to 0.927) in 2020 and 0.929 (95% CI 0.870 to 0.992) in 2021, and for all sepsis it was 0.870 (95% CI 0.810 to 0.935) in 2020 and 0.908 (95% CI 0.840 to 0.980) in 2021, compared with the previous 11-year period. Case fatality among first sepsis admissions declined in the period 2009–2019 (annual OR 0.954 (95% CI 0.950 to 0.958)), whereas case fatality increased during the COVID-19 pandemic in 2020 (OR 1.061 (95% CI 1.001 to 1.124) and in 2021 (OR 1.164 (95% CI 1.098 to 1.233)).

Conclusion The overall IR of sepsis increased from 2009 to 2019, due to an increasing IR of recurrent sepsis, and indicates that sepsis awareness with updated guidelines and education must continue.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is based on complete data from all Norwegian hospitals during 14 years.
⇒ Sepsis was identified using the primary International Classification of Diseases 10th revision (ICD-10) discharge diagnosis and up to 20 secondary ICD-10 diagnosis codes at discharge.
⇒ We used individual patient data enabling age-adjusted and sex-adjusted estimates and identification of first and recurrent sepsis.
⇒ Implicit identification of sepsis based on diagnostic codes for acute organ dysfunction and infection may result in overdetection of sepsis in instances where acute organ dysfunction is unrelated to infection.

INTRODUCTION

Sepsis is a dysfunctional immune response to infection that leads to acute life-threatening tissue damage and organ dysfunction.[1] With an estimated 50 million cases and 11 million sepsis-related deaths in 2017, sepsis remains a major cause of worldwide morbidity and mortality.[2] While sepsis may result from any infection, the majority of adult sepsis cases before the COVID-19 pandemic were attributed to bacterial infections, and viral sepsis was thought to be rare.[3–5] During the COVID-19 pandemic, however, an unprecedented number of patients were diagnosed with viral sepsis (hereafter labelled COVID-19-related sepsis),[6–9] with a high risk of coinfections and secondary infections that can aggravate the outcome.[10 11] It is likely that public health efforts to reduce the spread of SARS-CoV-2, such as lockdowns, may also have influenced the spread of other communicable diseases contributing to the risk of

sepsis.[12 13] However, few studies have assessed the impact of the pandemic on sepsis incidence rate (IR) and case fatality risk (CFR), using a few selected sepsis codes.[14] No previous study has focused exclusively on sepsis IR using all sepsis codes,[2] and compared sepsis IR and case fatality during the two first years of the COVID-19 pandemic with long-term historic trends.

Previous research on the incidence of sepsis before the COVID-19 pandemic has shown conflicting results.[2 15–17] However, precise incidence and mortality rates are difficult to measure, and a more accurate quantification (ie, correct identification and diagnosis coding) of sepsis is warranted.[18 19]

Therefore, the overall aim of this study is to describe temporal trends in sepsis IR and case fatality using nationwide Norwegian data on all adult hospital admissions from 2008 to 2021, and second to examine changes in hospital admission and mortality rates of sepsis during the first two COVID-19 pandemic years.

METHODS

Data source and study population

This nationwide longitudinal study used data from the Norwegian Patient Registry (NPR) and Statistics Norway.[20 21] NPR is an administrative database maintained by the Norwegian Directorate of Health that contains data with unique patient identifiers that allow longitudinal follow-up of individual patients for every admission to public hospitals in Norway from 2008 onward. In addition, NPR contains admission and discharge dates, and the International Classification of Diseases 10th revision (ICD-10) discharge codes, while Statistics Norway contains demographic data on all citizens of Norway. In NPR, we identified all hospitalisations to public hospitals in Norway (2008–2021) aged ≥18 years with the ICD-10 discharge diagnosis code(s) for sepsis consistent with the Angus implementation refined by Rudd *et al*.[2 22]

We treated each hospitalisation as an individual entry, and within this entry, sepsis was defined as explicit or implicit sepsis. For explicit sepsis, we used the presence of one code (see online supplemental table 1) for an overview of all ICD-10 codes to define explicit and implicit sepsis). For implicit sepsis, we used the combination of an infection code with the presence of an acute organ dysfunction code. The strategy was used for the primary and up to 20 secondary coexisting ICD-10 discharge codes since there is no obligatory order for the secondary codes. We added COVID-19-related sepsis to the implicit sepsis category based on the presence of a diagnostic code for COVID-19 (U07.1, U07.2) and ≥1 organ dysfunction code. Patients with a COVID-19 sepsis code and an explicit sepsis code were categorised as explicit sepsis. Online supplemental figure 1 shows the flow chart of the selection of patients into the study.

Characteristics of study population

Patient characteristics were extracted from NPR, including sex, age, ICD codes for selected comorbidities based on diagnostic groups,[23] as well as numbers of hospital stays from sepsis, readmissions and in-hospital deaths (for details, see online supplemental table 2 ICD 10 codes identifying comorbidities and infection sites). For sepsis admissions, we used ICD-10 codes to classify site(s) of infection into respiratory, genitourinary, intra-abdominal, extra-abdominal, endocarditis/myocarditis, soft tissue, infections following a procedure and other (bone, joint, obstetric, ear, mouth, upper airway, central nervous system and unknown). The acute organ dysfunctions were classified by number and as circulatory, respiratory, renal, hepatic, coagulation and/or other (acidosis, unspecific gangrene, central nervous system and systemic inflammatory response syndrome of infectious origin with organ dysfunction (R65.1)). A sepsis admission was defined as recurring sepsis admission if the patient was discharged with an explicit or implicit sepsis code and thereafter admitted with an explicit or implicit sepsis code, regardless of the time frame for the new admission. The number of sepsis admissions was categorised from one to five or more.

Statistical analysis

Descriptive statistics are presented as frequencies, means, SD, per cent and medians as appropriate, and are reported by sepsis or COVID-19-related sepsis. We calculated the crude sepsis IR of a first, recurrent and all sepsis episode according to year (2008–2021) and 10-year age groups as the number of sepsis admissions divided by the total number of inhabitants in Norway at the beginning of the year. The IRs for first and all sepsis were then standardised according to Segi's world standard population using 10-year age categories,[24 25] and reported per 100 000 person years.

To evaluate the temporal trends of sepsis IRs and the impact of the COVID-19 pandemic on sepsis IRs, we used Poisson regression to estimate IR ratios (IRR) of sepsis using the number of sepsis admissions (total, recurrent or first) as the dependent variable, population as exposure, the years 2009–2019 as a continuous variable, and the years 2008, 2020 and 2021 as separate indicator variables. Since our purpose was descriptive, we only adjusted for sex (man, woman) and age (10-year categories) in the analysis. Since 2008 was the first observation year, we could not differentiate between a first and a recurrent episode, and 2008 thus was included as an indicator variable to account for a possibly inflated IR of first sepsis. To account for overdispersion, we used the robust variance estimator.

CFR of a first sepsis admission was calculated as the number of first sepsis admissions with a discharge status of in-hospital death divided by all first sepsis hospitalisations. Similarly, CFR for recurrent sepsis was calculated as the number of recurrent sepsis admissions with a discharge status of in-hospital death divided by all

recurrent sepsis hospitalisations. The calculation was performed on annual cases for first and recurrent sepsis admissions from 2008 to 2021 and by 10-year age groups in the same period. During 2020 and 2021, we also calculated the quarterly CFR and compared CFR for COVID-19-related sepsis and sepsis.[14] To evaluate the trend of in-hospital mortality and the pandemic's impact on hospital mortality, we used logistic regression to estimate ORs for in-hospital death using the years 2009–2019 as a continuous variable, the years 2008, 2020 and 2021 as indicator variables, and adjusting for sex (man, woman) and age (10-year categories). We report 95% CIs where relevant.

All analyses were conducted by using STATA V.16.1 (StataCorp).

Patient and public involvement

Two patient representatives from the user group at Nord-Trondelag Hospital Trust participated in developing the research question and design of this study and were supportive of the use of health data for research purposes. They stressed the importance of education regarding symptoms and signs of sepsis to prevent fatal outcome and gave advice that research results and information about sepsis should be published in newspapers and social media in order to reach the patients and relatives. According to this, we plan to distribute this research results on our social media to inform patients, sepsis charities, research funders and policy-makers.

RESULTS

Characteristics of study population

Among 12 619 803 non-psychiatric adult hospitalisations during the study period (2008–2021), 317 705 (2.5%) met the criteria for sepsis, and of these, 222 832 (70%) were first hospitalisations with sepsis. Patient characteristics according to a first episode of sepsis and COVID-19-related sepsis are presented in table 1.

In 2020 and 2021, 2845 of 29 329 (9.7%) of first sepsis cases were identified as COVID-19 related sepsis. Men were over-represented among patients with sepsis (53.9%) and COVID-19-related sepsis (65.5%). The sepsis patients were older than patients with COVID-19-related sepsis (mean age 71.1 vs 61.4). The sepsis patients experienced renal acute organ dysfunction most often (44.6%), followed by respiratory failure (39.7%). The COVID-19-related sepsis patients experienced naturally most frequent respiratory failure (86.5%), followed by renal failure (15.6%). In total, 25.0% and 16.7% of the patients were readmitted within 30 days in the sepsis and COVID-19-related sepsis group, respectively. During the total study period (2008–2021), 24.2% of sepsis patients had ≥2 recurring sepsis hospitalisation.

Sepsis IRs and temporal trends

Table 2 shows that from 2009 to 2019, the annual age-standardised IRR of first sepsis episode was stable (IRR per year, 0.999; 95% CI 0.994 to 1.004), whereas the IR per year for recurrent sepsis increased with an IRR 1.048 (95% CI 1.037 to 1.059) per year, with a total increase in overall IRs of 15.5%. This is clearly illustrated in figure 1. During the COVID-19 pandemic, the IR was reduced compared with the previous 11-year period, with IRR of 0.877 (95% CI 0.829 to 0.927) in 2020 and 0.929 (95% CI 0.870 to 0.992) in 2021 for first sepsis cases, and 0.870 (95% CI 0.810 to 0.935) in 2020 and 0.908 (95% CI 0.840 to 0.980) in 2021 for all sepsis cases. The IR for both first and recurrent sepsis increased exponentially from ages 50 and beyond, and in individuals aged 80+ the IRs with recurrent sepsis were fivefold higher in 2021 than in 2008 (see figure 2 for first and recurrent sepsis and online supplemental figure 2 for more detailed first sepsis incidence).

The overall age-standardised IR of a first sepsis admission was 246/100 000 (95% CI 245 to 247), whereas the age-standardised IR of all sepsis admissions was 352/100 000 (95% CI 351 to 354) during the study period (online supplemental table 3).

Case fatality and temporal trends

The mean CFR was 13.7% for first sepsis admissions over the 14 years study period and 12.6% among recurrent sepsis admissions. In-hospital deaths for patients with a first sepsis admission declined during 2009–2019 (OR per year, 0.954 (95% CI 0.950 to 0.958)), with a total decline of 43.1% (table 3 and online supplemental figure 3). Online supplemental figure 4 shows that this decline in CFR over the study period occurred in all 10-year age groups. The CFR for recurrent sepsis declined with an OR of 0.973 (95% CI 0.966 to 0.980) per year in the same period, with a total decline of 28.0% (table 3). Online supplemental table 4 displays the details for age standardises CFR (%) for both first and recurrent sepsis episode per year.

Hospital death increased during the COVID-19 pandemic with an OR 1.061 (95% CI 1.001 to 1.124) in 2020 and an OR of 1.164 (95% CI 1.098 to 1.233) in 2021 for first sepsis admissions, and for recurrent sepsis admissions in 2021 with an OR of 1.112 (95% CI 1.027 to 1.205) (table 3).

Quarterly calculations for the years 2020 and 2021 are given in online supplemental table 5 and online supplemental figure 5, illustrating that the hospital outcome in COVID-19-related sepsis varied across the pandemic. In contrast, patients with first sepsis admission experienced more stable outcomes over the same period.

DISCUSSION

In this nationwide longitudinal registry study using all hospital data over 14 years (2008–2021), we demonstrate a stable trend in the IR of a first sepsis admission, while the recurrent sepsis IR has at least doubled in all individuals aged 60 or above. Overall, the sepsis case fatality rates have declined substantially by approximately one-third in all age groups, regardless of first or recurrent sepsis

Table 1 Characteristics of the study population at first sepsis admission (2008–2021) and COVID-19-related sepsis (2020–2021)

Characteristics	Sepsis*	COVID-19-related sepsis†	All first sepsis admissions
First admission (% of all sepsis admissions)	219 987 (69.0)	2845 (1.0)	222 832 (70.0)
Sex			
Male	118 580 (53.9)	1862 (65.5)	120 442 (54.1)
Female	101 407 (46.1)	983 (34.5)	102 390 (45.9)
Age (years)			
Mean±SD (median)	71.2±16.6 (74.4)	61.4±16.1 (61.8)	71.1±16.6 (74.3)
No of comorbidities			
0	66 869 (30.4)	1 581 (55.6)	68 450 (31.7)
1	97 894 (44.5)	909 (32.0)	98 803 (44 .3)
2	45 052 (20.5)	300 (10.5)	45 352 (20.4)
≥3	10 172 (4.6)	55 (1.9)	10 227 (4.6)
Comorbidities§§			
Heart and vascular	99 360 (64.9)	702 (55.5)	100 062 (64.8)
Cancer	39 243 (25.6)	125 (9.9)	39 368 (25.5)
Lung	35 859 (23.4)	306 (24.2)	36 165 (23.4)
Renal	8 873 (5.8)	76 (6.0)	8 949 (5.8)
Diabetes	24 030 (15.7)	386 (30.5)	24 416 (15.8)
Dementia	8068 (5.3)	32 (2.5)	8100 (5.3)
Immune	3091 (2.0)	49 (3.9)	3140 (2.0)
Liver	991 (0.7)	NA	994 (0.6)
Site of infection§			
Respiratory	79 290 (48.7)	2528 (97.9)	81 818 (49.5)
Genitourinary	44 700 (27.5)	82 (3.2)	44 782 (27.1)
Skin and soft tissue	8260 (5.1)	5 (0.2)	8265 (5.0)
Intra-abdominal	8841 (5.4)	29 (1.1)	8870 (5.4)
Extra-abdominal	12 318 (7.6)	22 (0.9)	12 340 (7.5)
Infections following a procedure	8277 (5.1)	13 (0.5)	8290 (5.0)
Endocarditis/Myocarditis	2522 (1.6)	8 (0.3)	2530 (1.5)
Other¶	28 836 (17.7)	152 (5.9)	28 997 (17.5)
Explicit sepsis	77 240 (35.1)	90 (3.2)	77 330 (34.7)
No of acute organ dysfunctions			
1	126 928 (84.5)	2252 (81.2)	28 928 (84.4)
2	17 869 (11.9)	427 (15.4)	18 296 (12.0)
3	3988 (2.7)	70 (2.5)	4058 (2.7)
≥4	1466 (1.0)	24 (0.9)	1490 (1.0)
Organ system with acute organ dysfunction**			
Respiratory	59 465 (39.7)	2399 (86.5)	61 864 (40.5)
Circulatory	14 824 (9.9)	68 (2.5)	14 892 (9.8)
Renal	66 809 (44.6)	433 (15.6)	67 242 (44.1)
Hepatic	3192 (2.1)	17 (0.6)	3209 (2.1)
Coagulation	6428 (4.3)	43 (1.6)	6471 (4.2)
Other¶	31 303 (20.9)	284 (10.3)	31 587 (20.7)
No of hospital admissions for sepsis††			
1	168 904 (76.8)	2714 (95.4)	171 618 (77.0)
2	33 097 (15.0)	4125 (4.4)	33 222 (14.9)
3	10 125 (4.6)	NA	10 129 (4.6)

Continued

Table 1 Continued

Characteristics	Sepsis*	COVID-19-related sepsis†	All first sepsis admissions
4	40 010 (1.8)	NA	4011 (1.8)
≥5	3851 (1.8)	NA	3852 (1.7)
Readmission‡‡	54 967 (25.0)	474 (16.7)	55 441 (24.9)

If not mentioned otherwise, the percentage (%) is calculated from available data from the first admission with sepsis or COVID-19-related sepsis. Estimates represent N (%) unless otherwise stated.
*Sepsis included patients with implicit and/or explicit sepsis, but not patients with an ICD-10 code for COVID-19.
†COVID-19-related sepsis included patients with COVID-19 combined with organ dysfunction or explicit code. The proportion of all comorbidities is calculated as number of particular comorbidity over total number of comorbidities.
‡The proportion of all infections sites is calculated as number of individuals with particular infection site over total number of infections sites.
§Other infection sites=bone, obstetric, upper airway, central nervous system and unknown.
¶The proportion of organ dysfunctions is calculated based on n with any organ dysfunctions.
**Other acute organ dysfunction=acidosis, unspecific gangrene, central nervous system dysfunctions and systemic inflammatory respons syndrome.
††Number of hospital admissions=calculated as new sepsis admission if admission with ICD-10 codes defining sepsis, regardless of time frame for the new sepsis admission. Follow-up=14 years.
‡‡Readmission=admission within 30 days after discharge regardless of cause.
§§ The proportion of all comorbidities is calculated as number of particular comorbidity over total number of comorbidities.
ICD-10, International Classification of Diseases 10th revision; NA, Not Applicable (used when the number of admissions was≤5).

episode. During the COVID-19 pandemic in 2020 and 2021, the IR of a first sepsis admissions decreased moderately compared with the prepandemic years, meanwhile the case fatality increased, most prominent in 2021.

Previously, 'The Global burden of Disease Study' by Rudd *et al*[2] registered an estimated reduction of 37% in the age-standardised IR of sepsis from 1990 to 2017,[2] and the differences to our study could be due to heterogeneity between regions, the inclusion of low-ncome and middle-income countries with less access to healthcare, inclusion of persons aged <18 and longer follow-up. Similarities with our study are the use of individual-level data and similar extraction of ICD-10 codes. Several other articles report increasing sepsis IRs,[15 17 22 26 27] that is, the opposite of what we and Rudd *et al* found. Martin *et al*[26] found an annual 8.7% increase in sepsis IR using claimed-based data between 1979 and 2000.[26] Dombrovskiy *et al*[17] found almost doubled hospitalisations of severe sepsis from 1992 to 2003,[17] and Kumar *et al*[15] calculated an increase in sepsis IR of 200/100 000 inhabitants from 2000 to 2007.[15] These results are difficult to compare with our analysis regarding first sepsis episodes because they report on all sepsis admissions not first sepsis admissions. However, their results can be compared with our analysis

Table 2 Poisson regression* for trends of first, recurrent and all sepsis episodes

	First sepsis admissions		Recurrent sepsis admissions		All sepsis admissions	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
Per year 2009–2019	0.999	0.994 to 1.004	1.048	1.037 to 1.059	1.013	1.007 to 1.019
2008	1.110	1.021 to 1.210	0.649	0.535 to 0.789	1.007	0.920 to 1.102
2020	0.877	0.829 to 0.927	0.844	0.746 to 0.964	0.870	0.810 to 0.935
2021	0.929	0.870 to 0.992	0.848	0.746 to 0.964	0.908	0.840 to 0.980
Female sex§	0.688	0.669 to 0.707	0.652	0.615 to 0.691	0.677	0.656 to 0.699
Age group, years						
18–29	0.023	0.021 to 0.026	0.020	0.018 to 0.023	0.023	0.020 to 0.025
30–39	0.029	0.026 to 0.031	0.025	0.022 to 0.029	0.028	0.025 to 0.030
40–49	0.043	0.041 to 0.046	0.046	0.041 to 0.051	0.044	0.041 to 0.047
50–59	0.089	0.085 to 0.093	0.107	0.095 to 0.121	0.094	0.088 to 0.100
60–69	0.207	0.200 to 0.214	0.273	0.249 to 0.300	0.225	0.215 to 0.235
70–79	0.457	0.441 to 0.473	0.581	0.536 to 0.631	0.491	0.470 to 0.512
≥80	1.000	Reference	1.000	Reference	1.000	Reference
Constant†	0.031	0.030 to 0.033	0.000‡	0.000-0.000‡	0.040	0.038 to 0.042

*The Poisson regression model was set up with cases as dependent variable, population as exposure, per year 2009–2019 as continuous covariate, and indicator variables as covariates for the years 2008, 2020 and 2021, and female sex and age groups.
†Constant=estimated incidence rate for men≥80 in 2009.
‡IRR=9.20e-44, 95% CI (5.09e-53 to 1.55e-34).
§ Male sex as reference
IRR, incidence rate ratio.

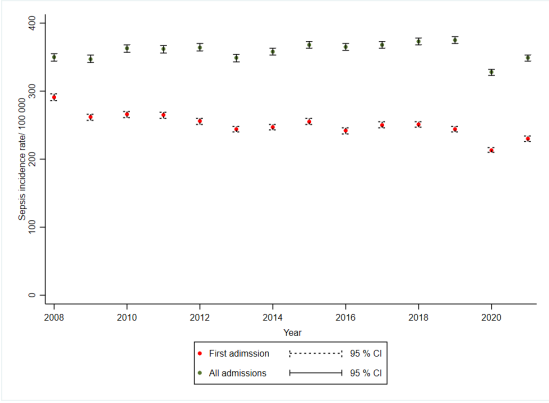

Figure 1 Annual all and first sepsis incidence per 100 000 inhabitants.

of all sepsis admissions, where we found an increased age-adjusted and sex-adjusted IRR before the current pandemic. Studies that include all sepsis admissions will naturally increase IRs because each person may be admitted multiple times, thus increasing the numerator without changing the denominator. Both Rudd *et al* and our study go against the myth that the increase in sepsis IRs primarily is driven by more liberal practices in sepsis coding over time. It is more likely that previously reported increased IRs are caused by the failure to treat each case as an individual entry.

The incidence of sepsis is higher among patients in the older age categories. Angus *et al*[22] investigated incidence of severe sepsis in the USA in 1995 and reported that the incidence of sepsis increased exponentially from ages 50 years and beyond.[22] This was also confirmed in later studies,[15 17] and is in line with the data in our study. Plausible explanations include increased prevalence of comorbidities by age that make patients more prone to sepsis and age-related weakening in immune function.[28] In addition, better treatment of medical conditions

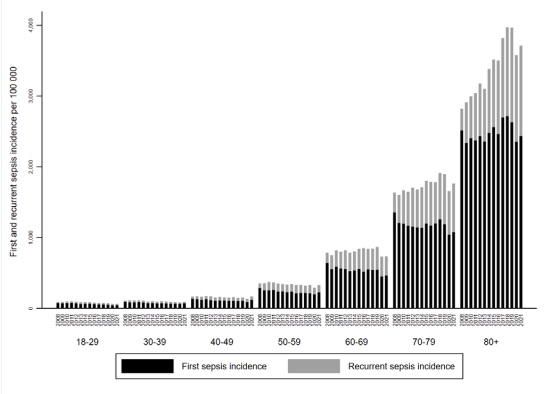

Figure 2 Annual first and recurrent sepsis incidence rates by 10-year age groups.

such as cancer and chronic diseases with increased use of immunosuppressives and invasive procedures[29 30] increases the number of patients at risk of developing more than one sepsis episode.[28] Further, sepsis survivors are prone to recurring sepsis due to new or worsened comorbidities and repeated infections and will thus drive the sepsis nominator.[31]

Previous studies of in-hospital sepsis mortality show in general a decreasing trend. Kaukonen *et al*[32] conducted a retrospective observational study over 12 years of sepsis patients admitted to Intensive Care Units (ICUs).[32] They reported annually decline in mortality throughout the study period with an OR of 0.49 in 2012, with year 2000 as reference. In a European registry-based study of ICU sepsis patients, Yébenes *et al*[27] reported an OR in 2012 with 2008 as reference of 0.77 in a multivariate analysis.[27] The higher decline than we observed can possible be due to different inclusion criteria of sepsis cases. While both Yebenes *et al* and Kaukonen *et al* stratified on all sepsis cases, the current study stratified on both first and all sepsis admissions. Other plausible explanations include different inclusion criteria regarding sepsis severity, and that new and updated guidelines, and more attention to the sepsis diagnosis have improved the recognition of the diagnosis, thus assisting clinicians in accurate and timely treatment of infections (ie, early blood culture sampling and antibiotics), preventing illness severity and therefore reducing mortality.[33–37]

The sepsis IR during the pandemic is previously studied by Bodilsen *et al*.[14] They compared hospital admissions for several diagnoses, 1 year prior to and 11 months after the COVID-19 pandemic and reported a significant reduction in sepsis IR using a few selected sepsis codes and found elevated 30 days mortality.[14] These previous results are in line with our results. Explanations for the observed lower incidence of sepsis after the pandemic can be the lower incidence of other infections with lockdowns,[14 38] in addition to vaccination strategies prioritising the elderly first and cancelling elective surgeries.[39] Moreover, our study could only identify one-fourth of the reported deaths due to COVID-19 in Norway at the end of 2021, which suggest that the majority of deaths due to COVID-19 occurred outside the hospitals. A possible explanation for the low proportion of in-hospital deaths due to COVID-19-related sepsis could be a higher threshold for hospitalisation during the pandemic in order to avoid an overflow of ill patients to hospitals.[40]

In the above-mentioned Danish study, the 30 days mortality for sepsis under and between the lockdowns was in line with our results.[14] The increased case fatality in first sepsis admission after the pandemic lockdown can be explained by the fatality of the novel SARS-CoV-2 virus. Further concerns are reluctance to seek healthcare because of the perceived risk of COVID-19 infection and negligence to report severe symptoms. Probably implications of these explanations are higher in-hospital mortality as those who were admitted with sepsis were more severely ill and thus had a higher baseline mortality risk.

Table 3 Logistic regression* with in-hospital deaths as dependent variable, 2008–2021

	First sepsis admission		Recurrent sepsis admission	
	OR	95% CI	OR	95% CI
Per year 2009–2019	0.954	0.950 to 0.958	0.973	0.966 to 0.980
2008	1.003	0.954 to 1.055	0.938	0.833 to 1.056
2020	1.061	1.001 to 1.124	0.985	0.909 to 1.067
2021	1.164	1.098 to 1.233	1.112	1.027 to 1.205
Female sex	0.898	0.876 to 0.920	0.863	0.830 to 0.900
Age group, years				
18–29	0.087	0.074 to 0.103	0.251	0.206 to 0.306
30–39	0.115	0.100 to 0.132	0.236	0.194 to 0.288
40–49	0.189	0.173 to 0.207	0.387	0.344 to 0.435
50–59	0.351	0.333 to 0.370	0.487	0.451 to 0.527
60–69	0.523	0.505 to 0.541	0.635	0.601 to 0.670
70–79	0.680	0.660 to 0.701	0.781	0.745 to 0.819
≥80	1.000	Reference	1.000	Reference
Constant†	0.327	0.317 to 0.338	0.247	0.234 to 0.261

*The logistic regression is modelled with in-hospital death in as dependent variable, per year 2009–2019 as continuous covariate and indicator variables as covariates for the years 2008, 2020 and 2021, and female sex and age groups.
†Constant=estimated odds for men≥80 in 2009.

There are several limitations to our study. First, the use of registry-based study design is dependent on ICD-code abstraction and the characteristics of registries.[41] However, it is mandatory for all Norwegian hospitals to report all activity to NPR and the NPR is a complete and unselected national hospital registry. Our study identified and extracted sepsis by ICD-10 discharge codes, first used in registry-based studies by Angus *et al*,[22] and later modified by Rudd *et al* to reflect the modern understanding of sepsis pathophysiology.[2] In Norway, ICD-10 code reporting to NPR is mandatory and undergoes quality controls by the National Service of Validation and completeness analysis, therefore, our extraction of ICD-10 codes have minimal missing, incomplete or unknown discharge codes.[42] Different study designs have been investigated to find the most fitted design, with dividing results.[43–46] The selection strategies for ICD-10 codes used by Rudd *et al*[2] have been criticised for causing an overestimation of sepsis.[47] Further, recommended ICD-10 coding has changed throughout the period as new specific codes for SIRS and septic shock were implemented in 2010[48] and the Sepsis-3 definition was implemented in 2016.[1] However, the trends seem to be consistent across the follow-up period except for 2008 and the pandemic years. Second, the IR of first episodes is probably inflated in 2008, but we included 2008 as an indicator variable in the regression models to account for this. Third, the use of implicit sepsis can generate false-positive identification of sepsis since organ dysfunction concurrent to infection could be driven by other causes. On the other hand, false-negative results can occur if the organ dysfunction is inadequately documented. Fourth, as this was a descriptive study we did not adjust for illness severity, or other characteristics and pathogenesis that could affect the association between sepsis, COVID-19-related sepsis and death. As we presented, age-adjusted and sex-adjusted results could mask possible age or sex specific differences in incidence and CFRs. Finally, the influence of the pandemic was calculated from January 2020, although the first COVID-19 patients were first admitted in late February 2020, and thus, the estimated drop in the IR related to COVID-19 could be underestimated. It is important to note that the level of SARS-CoV-2 incidence in Norway has been relatively low, and therefore, the interpretation of the analysis is primarily relevant to countries with the same burden.

The study also has several strengths, including the large sample size, nationwide data including all public hospitals, the use of individual-based data, and a timespan of 14 years, which makes it possible to detect trends over time. Another strength is that we, in one joint paper, report the burden and case fatality of first sepsis admissions, recurrent and all sepsis admissions, including age-separated analyses. Since the patients at first admission are likely to be younger, have fewer comorbidities, and thus have less morbidity and mortality risk, stratifying on the first admission will avoid migrating the patient to the next stage, also known as Will Rogers Phenomenon,' or stage migration.[41] To the best of our knowledge, this is the first study that provides nationwide hospital admissions-based epidemiological characteristics over 14 years for sepsis and includes data outside the ICU as well as for severe COVID-19-related sepsis. Our findings argue against the view that sepsis IR is declining and that reports of increasing sepsis incidence could largely reflect methodological difficulties and ICD-10 code attribution issues.

Our results have implications for health policy-makers, clinicians and researchers. The burden of sepsis is higher than previously described in comparable studies and requires further attention. More sepsis survivors put more pressure on skilled nursing facilities and in-home care. There are few studies on longer-term recovery in sepsis patients, and more needs to be done to prevent recurring sepsis, including early physical and cognitive rehabilitation, transition of care and follow-up care.[31] Surveillance and prevention should be assessed and implemented in primary healthcare. Side effects of the pandemic, with a pressured healthcare system and a changed threshold for seeking healthcare, must be evaluated.

CONCLUSION

This nationwide register-based study over 14 years reveals that the burden of sepsis still is high, with increasing IRs of recurrent sepsis. Furthermore, the high IRs and decreasing mortality cause an increased number of sepsis survivors, with a growing impact on the healthcare system. Notably, the decreased IRs of sepsis hospitalisations together with increased mortality during the pandemics give a concern regarding different efforts that were made to stop the spread of SARS-CoV-2.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the Regional Committee for Medical and Health Research Ethics (REK) in Eastern Norway (2019/42772) and the Data Access Committee in Nord-Trøndelag Hospital Trust (2021/184). In accordance with the approval from the REK and the Norwegian law on medical research, the project did not require a written patient consent. This work was performed on TSD (Service for Sensitive Data) facilities owned by the University of Oslo, operated and developed by the TSD service group at the University of Oslo, IT Department (USIT). TSD is designed to store and post-process sensitive data in compliance with the Norwegian 'Personal Data Act' and 'Health Research Act'.

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Supplementary File Paper I

Supplementary Table 1 Standardized incidence rates for first and all sepsis admissions 2008-2021

Year	No. of persons	Incidence rate first sepsis admission per 100 000 person years		Incidence rate all sepsis admissions per 100 000 person years	
		Crude	Adjusted (95% CI)	Crude	Adjusted (95% CI)
2008	3 637 892	445	286 (281-291)	526	344 (338-350)
2009	3 697 780	401	257 (253-262)	544	342 (336-347)
2010	3 749 043	407	261 (257-266)	546	357 (351-362)
2011	3 805 931	402	260 (256-265)	545	356 (351-361)
2012	3 867 645	395	252 (247-256)	553	358 (353-364)
2013	3 928 378	380	240 (236-244)	533	343 (337-348)
2014	3 983 895	386	243 (238-247)	555	352 (346-357)
2015	4 040 198	401	250 (246-254)	576	361 (355-366)
2016	4 086 583	385	237 (233-241)	577	359 (353-364)
2017	4 127 266	409	246 (242-250)	599	361 (356-366)
2018	4 166 612	417	246 (242-250)	622	367 (362-372)
2019	4 205 704	409	240 (236-244)	631	368 (363-373)
2020	4 248 972	364	210 (206-213)	561	322 (317-326)
2021	4 279 679	390	226 (222-230)	602	343 (338-348)
Total	55 825 578	399	246 (245-247)	569	352 (351-354)

Abbrevation: CI = confidence interval

[a] Crude and age adjusted sepsis incidence rate was calculated by year (2008–2021) for first and all sepsis admissions by dividing sepsis admissions by the total number of inhabitants in Norway at beginning of the same years, using direct standardization weighted by 'Segi's world standard population.

Supplementary Table 2 Age-standardized case fatality risks (%) for first and recurrent sepsis admissions 2008-2021

Year	CFR First sepsis admission			CFR Recurrent sepsis admission		
	N	Crude	Adjusted (95% CI)	N	Crude	Adjusted (95% CI)
2008	16 176	17.1	17.4 (16.8-18.0)	2 953	13.2	14.2 (12.9-15.6)
2009	14 993	16.1	16.3 (15.8-16.9)	4 398	13.1	13.9 (12.8-14.9)
2010	15 263	16.0	16.2 (15.6-16.8)	5 196	13.4	14.1 (13.1-15.1)
2011	15 309	14.5	15.0 (14.4-15.5)	5 426	13.5	13.9 (13.0-14.8)
2012	15 265	14.4	14.6 (14.0-15.1)	6 130	12.9	13.2 (12.3-14.0)
2013	14 887	14.6	14.7 (14.2-15.3)	6 055	13.2	13.4 (12.6-14.3)
2014	15 390	13.6	13.6 (13.1-14.2)	6 724	13.2	13.3 (12.5-14.1)
2015	16 205	13.8	13.8 (13.3-14.3)	7 056	12.8	12.8 (12.0-13.6)
2016	15 720	12.6	12.6 (12.1-13.1)	7 597	13.1	13.1 (12.3-13.8)
2017	16 873	12.3	12.2 (11.7-12.7)	8 026	12.5	12.3 (11.6-13.1)
2018	17 380	11.8	11.6 (11.1-12.0)	8 524	11.8	11.6 (10.9-12.2)
2019	17 217	10.9	10.7 (10.2-11.2)	9 312	11.2	10.9 (10.3-11.5)
2020	15 447	11.7	11.5 (11.0-12.0)	8 417	11.5	11.2 (10.5-11.8)
2021	16 707	12.0	11.9 (11.4-12.4)	9 050	12.5	12.0 (11.3-12.6)
Total	222 832	13.6	13.7 (13.5-13.8)	94 873	12.6	12.6 (12.4-12.8)

Abbrevation: CI = confidence interval, CFR= Case Fatality Risk

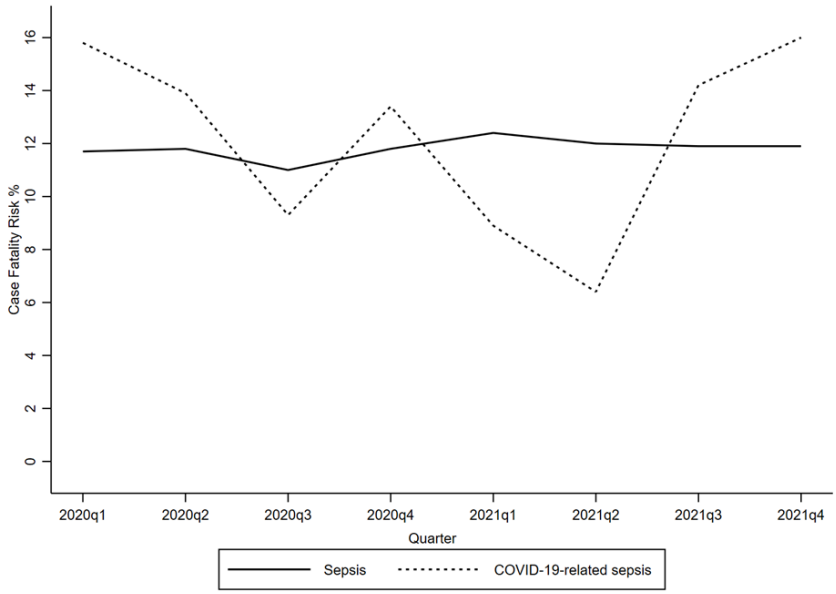
[a] Crude and age adjusted CFR was calculated by year (2008–2021) for first and recurrent sepsis admissions by dividing first and recurrent sepsis admissions by the total number of first and recurrent admissions of sepsis, using direct standardization.

Supplementary Table 3 First admissions, deaths, and CFR for sepsis and COVID-19-related sepsis patients in 2020 and 2021

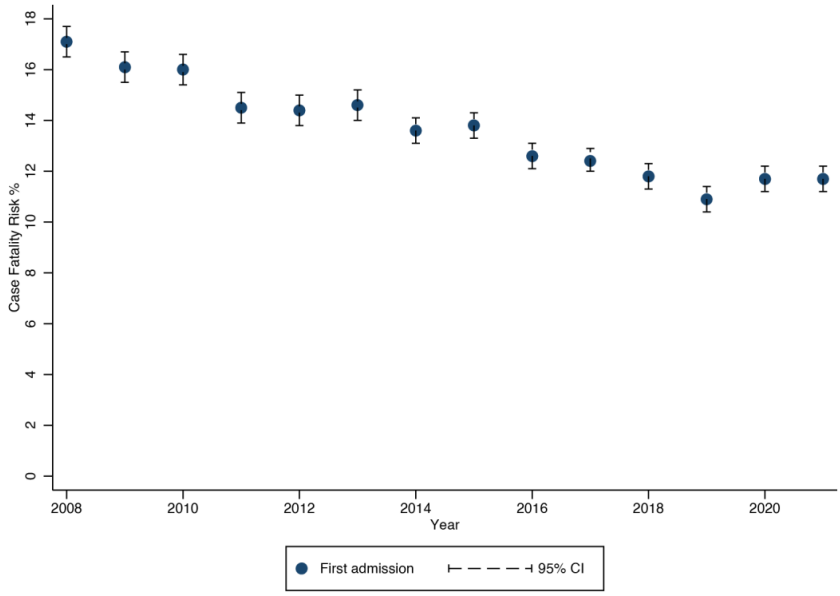
	2020						2021					
	Sepsis[a]			COVID-19-related sepsis[b]			Sepsis[a]			COVID-19-related sepsis[b]		
	N	Deaths	CFR %	N	Deaths	CFR %	N	Deaths	CFR %	N	Deaths	CFR %
Q1	4310	505	11.7	266	42	15.8	3335	415	12.4	655	58	8.9
Q2	3140	371	11.8	166	23	13.9	3336	401	12.0	389	25	6.4
Q3	3501	384	11.0	54	5	9.3	3734	446	11.9	225	32	14.2
Q4	3720	438	11.8	290	39	13.4	4233	505	11.9	800	128	16.0

Abbreviations: N = Number of cases, CFR= Case Fatality Risk calculated as in-hospital death divided by first sepsis admission in the quarter (Q). Q1 (January, February, March), Q2 (April, May, June), Q3 July, August; September, Q4 (October, November, December).
[a] Sepsis included patients with implicit and/or explicit sepsis, but not patients with an ICD-10 code for COVID-19
[b] COVID-19-related sepsis included patients with ICD-10 code for COVID-19 combined with organ dysfunction or explicit code.

Note: Calculated as **Q1** (January 2020, February 2020, March 2020), **Q2** (April 2020, May 2020, June 2020), **Q3** (July 2020, August 2020, September 2020), **Q4** (October 2020, November 2020, December 2020), **Q1** (January 2021, February 2021, March 2021), **Q2** (April 2021, May 2021, June 2021), **Q3** (July 2021, August 2021, September 2021), **Q4** (October 2021, November 2021, December 2021).



Supplementary Fig. 1 Quarterly mean case fatality risk (in %) in sepsis and COVID-19-related sepsis for first admission(2020 and 2021)



Supplementary Fig.2 Annual case fatality risk (CFR) in % for first sepsis admission

PAPER II

Infection
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RESEARCH

Trends in mortality after a sepsis hospitalization: a nationwide prospective registry study from 2008 to 2021

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Abstract

Background Few studies have reported on mortality beyond one year after sepsis. We aim to describe trends in short- and long-term mortality among patients admitted with sepsis, and to describe the association between clinical characteristics and mortality for improved monitoring, treatment and prognosis.

Methods Patients ≥ 18 years admitted to all Norwegian hospitals (2008–2021) with a first sepsis episode were identified using Norwegian Patient Registry and International Classification of Diseases 10th Revision codes. Sepsis was classified as implicit (known infection site plus organ dysfunction), explicit (unknown infection site), or COVID-19-related sepsis. The outcome was all-cause mortality. We describe age-standardized 30-day, 90-day, 1-, 5- and 10-year mortality for each admission year and estimated the annual percentage change with 95% confidence interval (CI). The association between clinical characteristics and all-cause mortality is reported as hazard ratios (HRs) adjusted for age, sex and calendar year in Cox regression.

Results The study included 222,832 patients, of whom 127,059 (57.1%) had implicit, 92,928 (41.7%) had explicit, and 2,845 (1.3%) had COVID-19-related sepsis (data from 2020 and 2021). Trends in overall age-standardized 30-day, 90-day, 1- and 5-year mortality decreased by 0.29 (95% CI − 0.39 to − 0.19), 0.43 (95% CI − 0.56 to − 0.29), 0.61 (95% CI − 0.73 to − 0.49) and 0.66 (95% CI − 0.84 to − 0.48) percent per year, respectively. The decrease was observed for all infections sites but was largest among patients with respiratory tract infections. Implicit, explicit and COVID-19-related sepsis had largely similar overall mortality, with explicit sepsis having an adjusted HR of 0.980 (95% CI 0.969 to 0.991) and COVID-19-related sepsis an adjusted HR of 0.916 (95% CI 0.836 to 1.003) compared to implicit sepsis. Patients with respiratory tract infections have somewhat higher mortality than those with other infection sites. Number of comorbidities was positively associated with mortality, but mortality varied considerably between different comorbidities. Similarly, number of acute organ dysfunctions was strongly associated with mortality, whereas the risk varied for each type of organ dysfunction.

Conclusion Overall mortality has declined over the past 14 years among patients with a first sepsis admission. Comorbidity, site of infection, and acute organ dysfunction are patient characteristics that are associated with mortality. This could inform health care workers and raise the awareness toward subgroups of patients that needs particular attention to improve long-term mortality.

Keywords Mortality · Sepsis · COVID-19 · Intensive care

Background

Sepsis occurs when a dysregulated immune response to infection leads to tissue damage and organ dysfunction [1]. This heterogeneous syndrome is associated with a high risk of death and is estimated to cause 20% of all global deaths [2]. While mortality up to 1 year and declining case fatality trends are well documented among sepsis patients [3–7], two recent studies report no change in short- and long-term mortality trends in sepsis patients admitted to intensive care units (ICU) with sepsis [8, 9]. Information on trends in long-term mortality beyond one-year among all hospitalized sepsis patients, including those admitted to the wards, is limited [10, 11]. Further, to commission appropriate health services, contemporary trends are needed to meet the increased use of healthcare [12].

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Identifying the site of infection is one of the keys in the management of sepsis [13]. Respiratory tract infections being the most common site, followed by abdomen, bloodstream, and genitourinary infections [12–14]. During the recent pandemic, an unprecedented number of patients were admitted with respiratory tract infection due to the novel SARS-CoV-2 virus and developed sepsis [14–16]. Thus, the pathogen and infection site in these cases were known, limited targeted treatment could be offered [17], and the long-term outcomes beyond 1 year of COVID-19-related sepsis is limited.

In-hospital mortality trends based on the site of infection in sepsis patients are declining for all sites [18]; however, little is known about mortality trends beyond hospital discharge. Moreover, there are conflicting results regarding the prognostic impact of infection sites on long-term mortality, with two studies conducted on ICU patients estimating that all infection sites had higher long-term mortality than respiratory tract infections [19, 20], while others reported the opposite [4, 21]. It is well known that worsen and new comorbidity contributes to higher mortality in sepsis patients [22]. Interestingly, a recent study found that more than 20% of the patients who survived sepsis had a late death that not could be explained by health status before sepsis and suggests that the sepsis itself contributes to poor long-term outcomes [23]. However, little is known about the impact of infection sites on long-term mortality in hospitalized sepsis patients beyond ICU cohorts and short-term follow-up.

Sepsis patients develop acute organ dysfunction, and the organs most often affected are kidneys, liver, lungs, cardiovascular and hematological system [24]. An increasing number of acute organ dysfunctions has been associated with an increased risk of early death in sepsis survivors [4]. A two-year follow-up multicenter study of sepsis patients found that neurologic dysfunction had the strongest adverse impact on long-term mortality, whereas other types of organ dysfunctions had a relatively modest impact [25]. Studies estimating the association between acute organ dysfunction and long-term mortality are few and restricted to specific sepsis diagnosis or have only included patients in ICUs or emergency departments [25, 26]. These studies may not fully capture the broader population of hospitalized sepsis patients or those who acquire sepsis during the hospital stay for other medical conditions [27].

In this nationwide study, we describe temporal trends in short- (30-day) and long-term (90-day, 1-, 5-, and 10-year) mortality over the past 14 years, including the recent COVID-19 pandemic, among patients admitted with a first-time sepsis, both overall and for subgroups of sepsis patients. Lastly, we investigate clinical characteristics associated with long-term mortality.

Methods

Study design and population

We conducted a prospective nationwide registry study, using data on all patients ≥ 18 years with ICD-10 discharge codes for sepsis admitted to Norwegian hospitals in the period January 1, 2008, through.

December 31, 2021. The data were provided by The Norwegian Patient Registry on an individual level using the personal identification number [28]. Reporting to the Norwegian Patient Registry is mandatory and NPR data is shown to have high level of completeness [28]. The Norwegian Patient Registry data were also linked to the Norwegian Intensive Registry [29], which covers all intensive care admissions since May 1, 2014.

We included the first admissions for sepsis during the period 2008 through 2021. We used the Sepsis-3 definition (2016) to define sepsis (presence of acute infection and acute new organ dysfunction)[1].We followed the approach used by Rudd et al. and extracted codes for implicit and explicit sepsis [2]. Implicit sepsis cases were those recognized with an ICD-10 discharge code for infection plus acute organ dysfunction, while explicit sepsis cases were those recognized with an specific sepsis ICD-10 discharge code. COVID-19-related sepsis was included based on the presence of a discharge code for COVID-19 (U07.1, U07.2) and ≥ one organ dysfunction code and/or explicit code. We used this strategy in the primary and up to 20 secondary co-existing ICD-10 discharge codes. We report estimates for all sepsis cases combined (implicit, explicit and COVID-19-related sepsis) and for each subgroup. The patient was classified as an implicit sepsis case only if the patient did not meet the criteria for an explicit sepsis or COVID-19-related sepsis, similar to the code extraction strategy of Rudd et al. (2020). In addition, we categorized infection, comorbidities and acute organ dysfunctions by ICD-10 discharge codes. Acute neurological dysfunction was not characterized as a single acute organ dysfunction but included in the category of other acute dysfunctions. ICD-10 discharge codes for selected comorbidities were based on diagnostic groups [30]. We provide an overview of the ICD-10 codes in the Supplemental Files, Supplemental Methods. Among 12,619,803 adult hospital admissions ≥ 18 years, 317,705 (2.5%) patients met the criteria for sepsis, and of these 222,832 were hospitalized with a first episode of sepsis in the study period (Fig. 1).

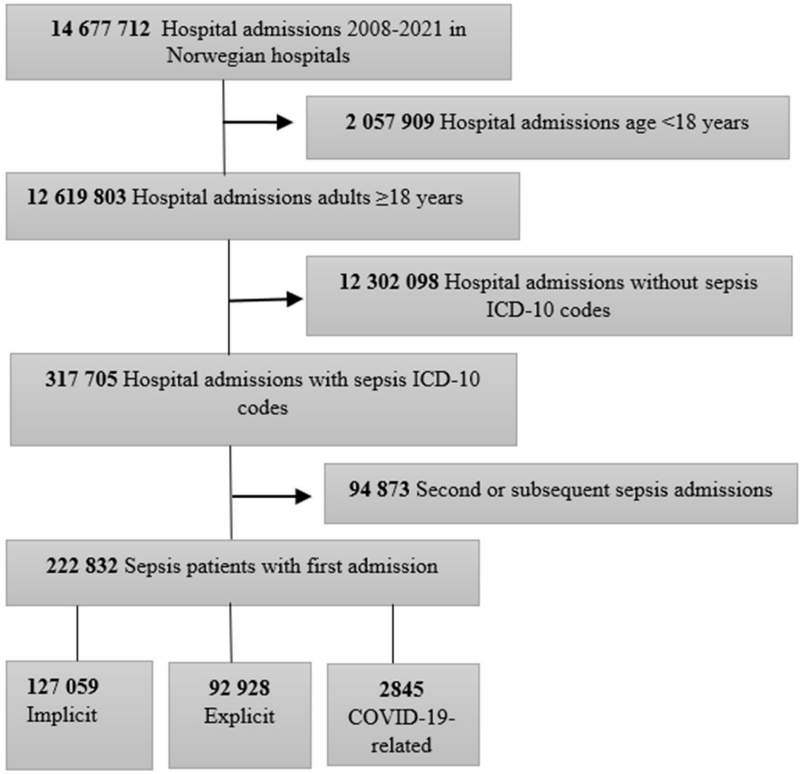

Fig. 1 Flowchart of the selection process

Outcomes

The primary outcome was all-cause mortality obtained from a linkage between the NPR records and The Norwegian Cause of Death Registry, covering all Norwegian citizens [31]. Mortality was calculated as the proportion of deaths of any cause among those admitted with sepsis during a specific year. Patients were followed from January 1, 2008, to December 31, 2021, and censored at their date of death and last death date was ascertained December 31, 2021.

Statistical analysis

Descriptive characteristics of the population are presented as frequencies with percentages, means with standard deviations, and medians as appropriate and shown for all sepsis patients, as well as stratified according to sepsis, and COVID-19-related sepsis. For each calendar year, we estimated 30-day, 90-day, 1-, 5-, and 10-year mortality by calculating the proportions of deaths from all causes, divided by the number of first sepsis admissions. The estimated mortality proportion was standardized according to age groups (18–29, 30–39, 40–49, 50–59, 60–69, ≥ 80 years) using the age distribution in 2009 as the base. Temporal trends in age-standardized mortality were estimated from least-squares linear regression across calendar years (2009–2021) and weighted by the inverse variance of the mortality proportion for all patients with a first sepsis epidose [32]. The year 2008 was excluded from trend analyses due to the increased likelihood of including recurrent and more severe sepsis episodes in the first year of observation. Similar analyses were conducted for subgroups of sepsis patients according to diagnosis, infections site, comorbidities. Analyses of patients receiving intensive care treatment or who were admitted to the ward was restricted to the period May 1, 2014, to December 31, 2021, since earlier information was not available.

The association between clinical characteristics (i.e., comorbidity, infection site, and acute organ dysfunction) and mortality were estimated by Cox regression with time to death as a dependent variable. First, we included each characteristic separately (crude). Thereafter we adjusted for sex age, the years 2009 to 2019 as a continuous covariate, and the years 2008, 2020 and 2021 as separate indicator variables to allow for deviations from a linear

association in the first year of observation and during the pandemic years. The patient characteristics were type of sepsis diagnosis (i.e., implicit, explicit, and COVID-19-related sepsis), type and number of comorbidities, infection site, number and type of acute organ dysfunction, and intensive care treatment. Comorbidities, infection sites, and acute organ dysfunctions were analyzed as categorical variables, using the most frequent category as a reference. The categories were mutually exclusive, and the analyses were therefore conducted on a restricted sample of patients with none or only one comorbidity, infection site, or acute organ dysfunction, respectively.

We report crude and adjusted hazard ratios (HRs) with 95% CIs. In the survival analyses the patients came at risk at the date of first admission and were censored at the death date or last day of follow-up (December 31, 2021). In the analysis assessing mortality in ICU patients compared to ward patients, both the ward and ICU patients entered the study after May 1, 2014, since earlier information was not available for the ICU patients. The proportional hazards assumption of the Cox model was examined by visual inspection of log–log plots.

Sensitivity analysis was conducted to account for the late entry of COVID-19-related sepsis patients. We used a similar Cox model as described above, but with follow-up time starting from February 27, 2020, for all patients with implicit, explicit, and COVID-19-related sepsis. The entry date corresponds with the first confirmed hospitalized COVID-19 case in Norway. Since many patients have more than one infection site, comorbidity and acute organ dysfunction, we also analyzed separate binary variables for each infection site, comorbidities and acute organ dysfunction (i.e., 0 = No, 1 = Yes).

All analyses were conducted using STATA version 16.1 (Stata Corp).

Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK) in Eastern Norway (2019/ 42,772) and the Data Access Committee in Nord-Trøndelag Hospital Trust (2021/184). In accordance with the approval from the REK and the Norwegian law on medical research, the project did not require written patient consent. This work was analyzed on TSD (Service for Sensitive Data) facilities owned by the University of Oslo, operated, and developed by the TSD service group at the University of Oslo, IT Department (USIT). TSD is designed for storing and post-processing sensitive data in compliance with the Norwegian "Personal Data Act" and "Health Research Act."

Results

Patient characteristics

The patient characteristics at first admission with sepsis and subgroups of sepsis are shown in Table 1. Among patients with first hospitalization for sepsis, the proportion of men was 54.1%, variating between 52.7% (implicit group), 55.6% (explicit group), and 65.5% (COVID-19-related sepsis group). Chronic heart and vascular disease was the most frequent comorbidity in 44.9% of all sepsis patients, with 48.2% in the implicit group, 41.0% in the explicit group, and 24.7% in the COVID-19-related sepsis group. Readmission within 30 days after the first hospitalization for all sepsis patients was 24.9% and occurred in 24.3% of the patients with implicit sepsis, in 25.9% of the patients with explicit sepsis, and in 16.7% of the patients with COVID-19-related sepsis. Overall the respiratory tract was the most common infection site with 36.8% and diagnosed in 50.2% of the implicit sepsis patients and in 91.1% of the COVID-19-related sepsis patients. Overall 8.5% of the sepsis patients were admitted to the ICU, and in the subgroups 8.7% of implicit sepsis patients, 7.9% of the explicit sepsis patients (data from 2014 to 2021), and 11.1% of those with COVID-19-related sepsis needed ICU treatment. (data from 2020 to 2021).

Temporal trends in mortality

The 30-day age-standardized mortality for patients admitted with a first sepsis episode declined 0.29% (95% CI − 0.39 to − 0.19) per year from 18.2% (95% CI 17.6 to 18.8) to 15.9% (95% CI 15.4 to 16.5), while the 90-day declined 0.43% (95% CI − 0.56 to − 0.29) per year from 26.0% (95% CI 25.3 to 26.7) to 22.3% (95% CI 21.6 to 23.0). The 1-year age-standardized mortality declined 0.61% (95% CI − 0.73 to − 0.49) per year from 36.8% (95% CI 36.1 to 37.6) to 31.8% (95% CI 31.1 to 32.5), while the 5-year declined 0.61% (95% CI − 0.73 to − 0.49) from 60.4% (95% CI 59.7 to 61.1) to 55.2% (95% CI 54.5 to 55.9) and the 10-year age-standardized mortality declined 1.23% per year (95% CI − 2.91 to 0.63) from 73.4% (95% CI 72.8 to 73.9) to 71.0% (95% CI 70.4 to 71.6) (Fig. 2 and Table 2). Subgroup analysis for patients reciving intensive care was stable from 2014 and througout the study period, shown in Supplementary Files, Supplementary Fig. 1.

Table 2 gives a detailed age-standardized percentage change per year in 30-day, 90-day, 1-, and 5-year mortality for implicit and explicit sepsis, sepsis patients admitted at ICU and wards, in addition to comorbidities and

Table 1 Characteristic of the study population with sepsis (2008–2021), including subgroups

	Sepsis[a]	Subgroups of sepsis		
		Implicit[b]	Explicit[c]	COVID-19-related[d]
Characteristics				
First admission, *n* (% of all)	222,832 (100)	127,059 (57.0)	92,928 (41.7)	2845 (1.3)
Male, *n* (%)	120,442 (54.1)	66,929 (52.7)	51,651 (55.6)	1862 (65.5)
Mean age, years (SD)	71.1 (16.6)	73.0 (15.7)	68.9 (17.5)	61.4 (16.1)
Comorbidities, *n* (%)				
Heart and vascular	100,062 (44.9)	61,251 (48.2)	38,109 (41.0)	702 (24.7)
Cancer	39,368 (17.7)	17,270 (13.6)	21,973 (23.6)	125 (4.4)
Lung	36,165 (16.2)	26,993 (21.2)	8866 (9.5)	306 (10.8)
Renal	8949 (4.0)	5830 (4.6)	3043 (3.3)	76 (2.7)
Diabetes	24,416 (10.9)	13,682 (10.8)	10,348 (11.1)	386 (13.6)
Dementia	8100 (3.6)	4561 (3.6)	3507 (3.8)	32 (1.1)
Immune	3140 (1.4)	1640 (1.3)	1451 (1 0.6)	49 (1.7)
Liver	994 (0.5)	564 (0.4)	427 (0.5)	≤5
Number of comorbidities, *n* (%)				
0	68,450 (30.7)	36,185 (28.5)	30,684 (33.0)	1581(55.6)
1	98,803 (44.3)	56,884 (44.7)	41,050 (44.2)	909 (32.0)
2	45,352 (20.4)	27,768 (21.9)	17,284 (18.6)	300 (10.5)
≥3	10,227 (4.6)	6262 (4.9)	3910 (4.2)	55 (1.9)
Site of infection, *n* (%)				
Respiratory	81,881 (36.8)	63,724 (50.2)	15,566 (16.8)	2591 (91.1)
Genitourinary	44,782 (20.1)	28,838 (22.7)	15,862(17.1)	82 (2.9)
Skin and soft tissue	8265 (3.7)	3578 (2.8)	4682 (5.0)	5 (0.2)
Gastrointestinal	10,810 (4.8)	8356 (6.6)	2424 (2.6)	30 (1.1)
Intra-abdominal	12,340 (5.5)	5401 (4.3)	6917 (7.4)	22 (0.8)
Infections following a procedure	8290 (3.7)	4042 (3.2)	4235 (4.6)	13 (0.5)
Endocarditis/myocarditis	2530 (1.1)	1008 (0.8)	1514 (1.6)	8 (0.3)
Other[e]	43,085 (19.3)	24,463 (19.3)	18,434 (19.8)	188 (6.6)
Organ system with acute dysfunction, *n* (%)				
Respiratory	61,864 (27.8)	51,453 (40.5)	8012 (8.6)	2399 (84.3)
Circulatory	14,892 (6.7)	10,647 (8.4)	4177 (4.5)	68 (2.4)
Renal	67,242 (30.2)	54,295 (42.7)	12,514 (13.5)	433 (15.2)
Hepatic	3209 (1.4)	2178 (1.7)	1014 (1.1)	17 (0.6)
Coagulation	6471(2.9)	3858 (3.1)	2570 (2.8)	43 (1.5)
Other[f]	22,173 (10.0)	20,095 (15.8)	1928 (2.1)	150 (5.3)
Number of acute organ dysfunctions, *n* (%)				
1	133,808 (87.7)	113,998 (89.7)	17,339 (76.0)	2471 (86.9)
2	15,262 (10.0)	11,038 (8.7)	3955 (17.3)	269 (9.5)
3	2864 (1.9)	1693 (1.3)	1144 (5.0)	27 (0.9)
≥4	699 (0.5)	330 (0.3)	264 (1.6)	≤5
Number of hospital admissions for sepsis[g], *n* (%)				
1	171,619 (77.0)	97,105 (76.4)	71,800 (77.3)	2714 (95.4)
2	33,221 (14.9)	19,339 (15.2)	13,757 (14.8)	125 (4.4)
3	10,129 (4.6)	5917 (4.7)	4208 (4.5)	≤5
4	4011 (1.8)	2363 (1.9)	1647 (1.8)	≤5
≥5	3852 (1.7)	2335 (1.8)	1516 (1.6)	≤5
Readmission[h], *n* (%)	55,441 (24.9)	30,895 (24.3)	24,072 (25.9)	474 (16.7)
ICU treatment[j], *n* (%)	10,602(8.5)	6946 (8.7)	3341 (7.9)	315 (11.1)
In-hospital death, *n* (%)	30,276 (13.6)	16,273 (12.8)	13,751 (14.8)	352 (12.4)

ICU intensive care unit

[a]Sepsis = All first sepsis admissions in the period 2008–2021, including implicit, explicit and COVID-

Table 1 (continued)

19-related sepsis (2020–2021)

[b]Implicit sepsis = ICD-10 code for infection in combination with a code for acute organ function, excluding those who had an explicit code at the same hospital admission

[c]Explicit sepsis = ICD-10 code for specific sepsis, including those who also had an implicit code at the same admission

[d]COVID-19-related sepsis = ICD-10 code for COVID-19 in combination with an acute organ dysfunction code and/or a specific sepsis code

[e]Other infections = Bone, obstetric, upper airway, central nervous system and unknown

[f]Other acute organ dysfunction = Acidosis, unspecific gangrene, central nervous system dysfunctions and Systemic Inflammatory Response Syndrome

[g]Number of hospital admissions = Calculated as new sepsis admission if admission with ICD-10 codes defining sepsis, regardless of time frame for the new sepsis admission

[h]Readmission = admission within 30 days after discharge regardless of cause

[j]Variable calculated from May 1, 2014

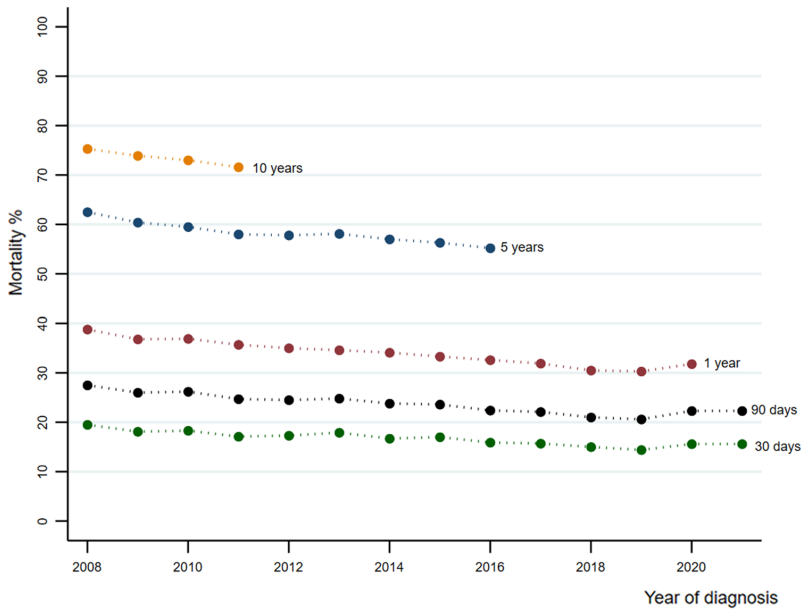

Fig. 2 Age-standardized mortality at 30-day, 90-day, 1-, 5- and 10-year according to admission year for all patients hospitalized with a first sepsis

infection sites. Over time, sepsis patients had a decline in mortality, and patients with implicit sepsis had a larger decline in mortality than explicit sepsis patients. Further, ward patients had a larger decline than patients admitted to ICU, but this reversed at 1-year. Lastly, from 1-year after admission, the age-standardized mortality among all infection sites declined year by year, with largest decline in respiratory tract infections.

Crude and age-standarized mortality

The median follow-up time in the study was 3.3 years (range 0 to 14 years). 30- and 60-day, 1- and 5-year crude and age-standardized mortality for all sepsis patients, and subgroups of implicit, explicit, and COVID-19-related sepsis patients, and also divided in sepsis patients admitted at intensive care or wards are shown in Table 3. Overall, sepsis patients had a 30-day age-standardized mortality of 16.9% (95% CI 16.7 to 17.0). COVID-19-related sepsis had the highest age-standardized 30-day mortality (21.5%; 95% CI 19.4 to 23.6) versus 15.9% (95% CI 15.7 to 16.1) for implicit sepsis and 18.5% (95% CI 18.2 to 18.7) for explicit sepsis. ICU patients had higher mortality than ward patients until one years after first sepsis admission, whereas the 5-year mortality was largely similar in ICU and ward patients.

Characteristics associated with mortality

Compared to implicit sepsis patients, patients with explicit sepsis (HR 0.98; 95% CI 0.969 to 0.991) and

Table 2 Age-standardized percentage change per year in 30- and 90-day, 1- and 5-year mortality[a] in overall and within different subgroups (2008–2021)

	n	30-day	90-day	1-year	5-year
Group					
All first sepsis patients	222,832	− 0.29 (− 0.39, − 0.19)	− 0.43 (− 0.56, − 0.29)	− 0.61 (− 0.73, − 0.49)	− 0.66 (− 0.84, − 0.48)
Implicit	127,059	− 0.31 (− 0.43, − 0.19)	− 0.43 (− 0.60, − 0.25)	0.68 (− 0.87, − 0.49)	− 1.01 (− 1.19, − 0.83)
Explicit	92,928	− 0.19 (− 0.31, − 0.07)	− 0.32 (− 0.46, − 0.18)	− 0.40 (− 0.52, − 0.29)	− 0.39 (− 0.66, − 0.12)
ICU[b]	10,602	− 0.20 (− 0.62, 0.22)	− 0.39 (− 0.87, 0.89)	− 0.72 (− 1.37, − 0.08)	NA
Ward	212,230	− 0.39 (− 0.51, − 0.27)	− 0.53 (− 0.68, − 0.37)	− 0.70 (− 0.84, − 0.57)	− 0.73 (− 0.92, − 0.54)
Infection site[c]					
Respiratory	66,368	− 0.38 (− 0.57, − 0.19)	− 0.58 (− 0.82, − 0.34)	− 0.84 (− 1.04, − 0.65)	− 1.02 (− 1.25, − 0.79)
Genitourinary	28,938	− 0.13 (− 0.25, 0.004)	− 0.30 (− 0.47, − 0.13)	− 0.51 (− 0.71, − 0.30)	− 0.71 (− 1.00, − 0.43)
Skin and soft tissue	3583	− 0.06 (− 0.27, 0.16)	− 0.21 (− 0.43, 0.03)	− 0.49 (− 0.78, − 0.20)	− 0.98 (− 1.84, − 0.12)
Gastrointestinal	8394	− 0.13 (− 0.29, 0.02)	− 0.21 (− 0.44, 0.01)	− 0.42 (− 0.74, − 0.10)	− 0.40 (− 1.13, 0.33)
Intra− abdominal	5437	− 0.27 (− 0.46, − 0.07)	− 0.52 (− 0.74, − 0.31)	− 0.55 (− 0.74, − 0.57)	− 0.41 (− 1.07, 0.25)
Infections following a procedure	4070	− 0.06 (− 0.26, 0.14)	− 0.30 (− 0.58, − 0.02)	− 0.48 (− 0.83, − 0.14)	− 0.81 (− 1.76, 0.14)
Endocarditis/ Myocarditis	1020	− 0.29 (− 0.75, 0.17)	− 0.47 (− 0.90, − 0.04)	− 0.63 (− 1.12, − 0.13)	− 0.30 (− 1.54, 0.94)
Other[d]	24,687	− 0.05 (− 0.20, 0.10)	− 0.21 (− 0.41, 0.004)	− 0.27 (− 0.49, −0.05)	− 0.34 (− 0.58, − 0.11)
Comorbidities					
Heart and vascular	100,062	− 0.19 (− 0.32, − 0.05)	− 0.31 (− 0.47, − 0.16)	− 0.50 (− 0.62, − 0.37)	− 0.36 (− 0.53, − 0.20)
Cancer	39,368	0.14 (− 0.04, 0.31)	− 0.01 (− 0.20, 0.18)	− 0.18 (− 0.38, 0.01)	− 0.53 (− 0.84, − 0.23)
Lung	36,165	− 0.13 (− 0.30, 0.03)	− 0.12 (− 0.35, 0.10)	− 0.48 (− 0.76, − 0.20)	− 0.66 (− 1.12, − 0.20)
Renal	8949	− 0.01 (− 0.33, 0.32)	− 0.06 (− 0.45, 0.33)	− 0.47 (− 0.98, 0.04)	− 0.30 (− 1.46, 0.87)
Diabetes	24,416	− 0.36 (− 0.56, − 0.16)	− 0.49 (− 0.71, − 0.26)	− 0.84 (− 1.04, − 0.65)	− 0.89 (− 1.40, − 0.38)
Dementia	8100	− 0.37 (− 0.69, − 0.05)	− 0.50 (− 0.87, − 0.12)	− 0.46 (− 0.91, − 0.004)	0.32 (− 0.11, 0.74)
Immune	3140	− 0.22 (− 0.45, 0.02)	− 0.49 (− 0.972, − 0.003)	− 0.97 (− 1.71, − 0.21)	− 1.21 (− 2.21, − 0.21)
Liver	994	0.10 (− 0.79, 0.99)	− 0.46 (− 1.62, 0.69)	− 0.86 (− 2.15, 0.44)	− 1.79 (− 3.20, − 0.37)
All comorbidities[e]	154,382	− 0.19 (− 0.31, − 0.08)	− 0.30 (− 0.45, − 0.15)	− 0.46 (− 0.59, − 0.34)	− 0.47 (− 0.69, − 0.25)

NA not applicable, *ICU* intensive care unit

[a]Mortality adjusted according to the total age distribution in the total sample

[b]Period May 1, 2014, through December 31, 2021

[c]Infection side includes only those with implicit sepsis

[d]Other infections = Bone, obstetric, upper airway, central nervous system and unknown

[e]All comorbidities = ≥ 1 comorbidity

COVID-19-related sepsis (adjusted HR 0.916; 95% CI 0.836 to 1.003) had similar risk of mortality. In the sensitivity analysis restricted to entry dates from February 27, 2020, we found a HR of 1.09 (95% CI 1.04 to 1.14) in patients with explicit sepsis and an adjusted HR of 0.85 (95% CI 0.77 to 0.93) in COVID-19-related sepsis patients, compared to patients with implicit sepsis (Supplementary Files, Supplementary Table 1).

Sepsis patients with respiratory tract infections had higher risk of dying compared to sepsis patients with other infections. Sepsis patients with cancer (adjusted HR 2.48; 95% CI 2.42 to 2.53), chronic lung disease (adjusted HR 1.21; 95% CI 1.18 to 1.24), dementia (adjusted HR 1.58; 95% CI 1.52 to 1.65), and chronic liver disease (adjusted HR 3.44; 95% CI 3.09 to 3.83) had higher risk of dying compared to the reference group with chronic vascular disease. Compared to sepsis patients with none comorbidities, sepsis patients with one, two and, three or more comorbidities had increasing adjusted HRs of 1.71 (95% CI 1.69 to 1.71), 2.12 (95% CI 2.09 to 2.16), and 2.60 (95% CI 2.54 to 2.67). Compared to sepsis patients with acute respiratory organ dysfunction, the adjusted HRs of long-term mortality was 1.05 (95% CI 1.02 to 1.08) for sepsis patients with acute circulatory dysfunction, 1.33 (95% CI 1.27 to 1.38) for sepsis patients with acute coagulation dysfunction, and 1.95 (95% CI 1.82 to 2.07) for sepsis patients with acute hepatic acute dysfunction. Further, having ≥ 2 acute organ dysfunctions was associated with higher long-term mortality than ≤ 1 acute organ dysfunction, adjusted HR 1.46 (95% CI 1.43 to 1.49), adjusted HR 2.02 (95% CI 1.93 to 2.11), and adjusted HR

Table 3 Crude and age-standardized mortality[a] (%) at 30-day, 90-day, 1- and 5-year after first admission in different subgroups (2008–2021)

	Mortality							
	30-day (%)		90-day (%)		1-year (%)		5-year (%)	
	Crude	Adjusted[a] (95% CI)	Crude	Adjusted[a] (95% CI)	Crude	Adjusted (95% CI)	Crude	Adjusted[a] (95% CI)
All sepsis patients[b]	16.9	16.9 (16.7, 17.0)	23.9	23.9 (23.7, 24.1)	34.3	34.3 (34.1, 34.5)	58.5	58.5 (58.2, 58.7)
Subgroup								
Implicit	16.6	15.9 (15.7, 16.1)	23.8	22.8 (22.6, 23.1)	34.5	33.2 (32.9, 33.4)	62.1	59.4 (59.1, 59.7)
Explicit	17.3	18.5 (18.2, 18.7)	24.3	25.7 (25.4, 26.0)	34.2	36.0 (35.7, 36.3)	54.5	57.4 (57.1, 57.8)
COVID-19-related sepsis[c]	13.1	21.5 (19.4, 23.6)	14.6	25.1 (22.5, 27.7)	20.4	27.7 (24.1, 31.5)	NA	NA
ICU patients[d]	22.7	26.0 (25.1, 26.9)	28.5	32.2 (31.2, 33.2)	36.1	40.9 (39.8, 41.9)	54.2	61.1 (59.6, 62.6)
Ward patients	16.6	16.5 (16.3, 16.6)	23.7	23.5 (23.3, 23.7)	34.2	34.0 (33.8, 34.2)	58.6	58.4 (58.2, 58.6)

NA not applicable, *ICU* intensive care unit

[a]Mortality adjusted according to the total age distribution in the total sample

[b]Crude and adjusted proportions are similar since the total study sample is used as the reference population

[c]Period from February 27, 2020, through December 31, 2021

[d]Period May, 1 2014, through December, 31 2021

3.04 (95% CI 2.78 to 3.32) for 2, 3 and ≥ 4 acute organ dysfunctions, respectively (Table 4).

Patients treated in ICU had higher risk of death (adjusted HR 1.41; 95% CI 1.37 to 1.46) than those admitted to a general ward. Sensitivity analysis with binary categories is presented in Supplementary Files, Supplementary Table 2. In short, the sensitivity analysis showed that sepsis patients with respiratory infection had the highest risk of mortality (HR 1.38, 95% CI 1.27 to 1.30) compared to sepsis patients with other infection sites. Sepsis patients with cancer had the comorbidity with highest risk (HR 2.41, 95% CI 2.38 to 2.44) compared to sepsis patients with other comorbidities. Sepsis patients with acute hepatic organ dysfunction had the highest risk (HR 2.63 (95% CI 2.52 to 2.74) compared with sepsis patients with other organ dysfunctions.

(Supplementary Files, Supplementary results, Supplementary Table 3).

Discussion

Our nationwide study is the first to provide contemporary estimate of mortality among sepsis patients over a 14-year period, including the recent pandemic, and in one joint paper include sepsis patients admitted to the general wards as well as ICU. Our study shows improvements in 30-day, 90-day, 1- and 5-year mortality from 2008 through 2021, with the largest decline among patients with sepsis due to respiratory tract infections. Moreover, we observe that long-term mortality varies according to the various infection sites, comorbidities, and acute organ dysfunction in patients admitted with a first sepsis episode. Lastly, it seems that COVID-19-related sepsis patients have largely the same mortality as explicit and implicit sepsis patients.

Previously, Rhee et al. (2017) compared clinical and claims data from the USA and found an in-hospital decline in mortality for explicit sepsis codes from 2009 to 2014[33]. Our findings are consistent with their study, but direct comparison of mortality reduction is challenging due to the various coding practices of sepsis. Additionally, two well-conducted meta-analyses of mortality trends in severe sepsis and septic shock patients using clinical trial data found a decline in mortality rates over time [34, 35]. The meta-analysis by Stevenssons and colleagues (2014) found an annual decrease of 3.0% in 28-day mortality [34], while the meta-analysis by Luhr et al. (2019) found an annual decrease of 0.42% in 28-day mortality, which was more pronounced in studies with a mean age ≥ 65 years. Our approach of using administrative databases to calculate mortality trends in sepsis patients is common [2, 5, 6, 36, 37], but not without controversy [10, 38]. The decline in mortality rates are often attributed to the Will-Rogers phenomenon, which explains reduced mortality as a consequence of including a larger proportion of less severely ill sepsis patients due to increased sepsis awareness [39]. However, in a recent study, we report an overall incidence of 246 per 100 000 person years among patients with a first sepsis admission, and that the incidence was stable from 2008 to 2021 [7]. Stable sepsis incidence is less likely to be explained by increased coding of less severe sepsis and indicates that the reduced mortality is unlikely to be explained by the Will Rogers phenomenon. Although mortality estimates using administrative data are overestimated compared to clinical data [33], our results are in line with the two meta-analyses studying clinical trials [34, 35].

Table 4 Hazard ratio for death from Cox regression by sepsis characteristics during follow-up of sepsis patients

Variable	No. of patients	Person year at risk	Deaths	Mortality per 100 person year	Crude HR	Adjusted HR[a] (95% CI)
Sepsis subgroup						
Implicit	127,059	370,431	76,498	20.7	1.00	1.000 (Reference)
Explicit	92,928	356,820	54,738	15.3	0.86	0.980 (0.969–0.991)
COVID-19-related[b]	2845	1841	490	26.6	0.51	0.916 (0.836–1.003)
Site of infection[c]						
Respiratory	68,920	190,102	43,711	23.0	1.00	1.00 (Reference)
Genitourinary	27,311	87,844	16,416	18.7	0.83	0.68 (0.67–0.69)
Other infections[d]	24,450	85,671	12,610	14.7	0.70	0.84 (0.83–0.86)
Intra-abdominal	8857	27,536	5206	18.9	0.88	0.86 (0.84–0.89)
Gastrointestinal infections	8617	37,871	3844	10.2	0.52	0.58 (0.56–0.60)
Skin and soft tissue	5169	20,173	2395	11.9	0.58	0.65 (0.62–0.68)
Infections following a procedure	4111	18,082	1907	10.5	0.54	0.63 (0.61–0.66)
Endocarditis/myocarditis	1274	4186	731	17.5	0.83	1.01 (0.94–1.09)
Comorbidities[c]						
Heart and vascular	51,333	162,687	32,720	20.1	1.00	1.00(Reference)
Cancer	21,614	45,614	16,272	35.7	1.52	2.48 (2.43–2.53)
Lung	14,062	47,214	8426	17.8	0.88	1.21 (1.18–1.24)
Diabetes	5434	23,163	2288	9.9	0.53	0.77 (0.74–0.81)
Dementia	2955	4578	2537	55.4	1.97	1.58 (1.52–1.65)
Renal	1902	4522	1055	23.3	0.96	1.01 (0.95–1.07)
Immune	1040	5230	341	65.2	0.37	0.91 (0.81–1.01)
Liver	463	955	335	35.1	1.55	3.44 (3.09–3.83)
No. of comorbidities						
0	68,450	305,693	25,516	8.3	1.00	1.00 (Reference)
1	98,803	293,964	63,974	21.8	2.28	1.71 (1.69–1.74)
2	45,352	109,290	33,963	31.1	3.00	2.12 (2.09–2.16)
≥ 3	10,227	20,145	8273	41.1	3.56	2.60 (2.54–2.67)
Type of acute organ dysfunction[c]						
Respiratory	49,234	139,667	30,855	22.1	1.00	1.00 (Reference)
Renal	53,010	154,416	30,879	20.0	0.90	0.68 (0.67–0.70)
Other acute organ dysfunctions[e]	17,954	67,926	9642	14.2	0.69	0.52 (0.51–0.53)
Circulatory	7425	18,784	4520	24.1	1.09	1.05 (1.02–1.08)
Coagulation	4820	14,881	2784	18.7	0.87	1.33 (1.27–1.38)
Hepatic	1365	2857	988	34.6	1.46	1.95 (1.82–2.07)
No. of acute organ dysfunctions						
1	133,808	398,531	79,668	20.0	1.00	1.00 (Reference)
2	15,262	36,114	9928	27.5	1.32	1.46 (1.43–1.49)
3	2864	6205	1881	30.3	1.48	2.02 (1.93–2.11)
≥ 4	699	1215	494	40.6	1.88	3.04 (2.78–3.32)
ICU treatment[f]						
No	114,423	261,062	56,398	21.6	1.00	1.00 (Reference)
Yes	10,602	23,034	5021	21.8	1.02	1.41 (1.37–1.46)

HR hazard ratio, *CI* confidence interval, *ICU* intensive care unit

[a]Cox regression with time to death as dependent variable, the listed variable as covariate (one at the time), adjusted for per year 2009–2019 as continuous covariate, indicator covariates for the years 2008, 2020 and 2021, and sex and age

[b]Enter date = February 27, 2020

[c]Categorical variable where one ICD-10 code excludes other ICD-10 codes in the same diagnosis group

[d]Other infections = Bone, obstetric, upper airway, central nervous system and unknown

[e]Other acute organ dysfunctions = Acidosis, unspecific gangrene, central nervous system dysfunctions and Systemic Inflammatory Response Syndrome.

[f]Enter date = May 1, 2014

Three recent observational studies by Vesteinsdottir (2021), Stranberg (2020) and Buchman (2021 found stable mortality trends [8, 9, 40]. In comparison, we observed decreasing short- and long-term mortality trends in mortality among ward patients, whereas for ICU patients the trend in 1-year mortality was stable. However, since Buchman et al. included patients with explicit sepsis ≥ 65 years and persons with disabilities and end-stage renal disease, it is likely that the diverging result is due to a more severe ill sample with a worse prognosis. The discrepancy in the results compared to Vesteinsdottir (2021) and Stranberg (2020) may be due to underestimation of the number of sepsis patients. Vesteinsdottir et al. (2021) excluded patients who developed severe sepsis or septic shock while admitted to the ICU for another admission diagnosis [8], while Stranberg et al. (2020) used the Swedish Intensive Care Registry [9], which is reported to underestimate the incidence of sepsis [41]. Our study, in contrast, utilized a large and diverse population-based sample of all sepsis admissions in Norway, including patients developing sepsis while admitted, during a 14-year study period. As the majority of sepsis patients are treated in wards, comparing our study with previous studies limited to selected ICU cohorts is challenging; however, our study's contribution to understanding sepsis mortality among all sepsis patients is important for health care resource planning.

Stressing the importance of identifying the site of infection in sepsis management could have increased awareness and therefore improved the efforts to determine the site of infection. Our study found that the short-term mortality among patients admitted with known infection site (implicit sepsis) was lower than those admitted with unknown infection site (explicit sepsis), but that this reversed with longer observation time. One possible explanation can be that more patients in the explicit group had zero comorbidities and thus supposedly better long-term outcomes than those with comorbidities [22]. Further, one previous study evaluated in-hospital mortality trends stratified by site of infection in sepsis patients. They found that mortality from all infection sites had decreased significantly, with the largest decrease in skin/skin structure, primary bacteremia, and catheter-related bloodstream infections [18]. The annual decrease was much higher than in the current study, and for comparison, we had a higher number of respiratory tract infections and a lower number of skin infections, in addition to a longer follow-up time. Further, the decline in mortality trends among patients with respiratory tract infections in our study can in some extent be explained by pneumococcus vaccinations [42] and the relatively low bacterial resistance in Norway [43].

The literature on the association between infection sites and mortality also provides conflicting results. A Danish study (2016) found that urinary tract infection was an independent predictor of mortality [44], while a long-term follow-up of ICU patients in England (2019) found that all infection sites had a lower adjusted hazard ratio compared to respiratory tract infections [4]. The latter study is consistent with our results. Another study by Nygård et al. (2013) identified endocarditis/myocarditis and intra-abdominal infections as independent predictors of poor outcomes [19]. These differences in results may be due to variations in follow-up, study design, and selection of cohorts.

Our study found a strong association between liver dysfunction and long-term mortality, which is in line with previous findings [25, 26]. Similarly, a study with three year of follow-up found acute liver dysfunction to be strongly associated with long-term mortality, together with acute coagulation and acute neurologic dysfunction in sepsis survivors [25]. However, the effect size of acute liver dysfunction in these studies was smaller than in ours, which can be explained by differences in study population (sepsis patients at ICU or sepsis patients who went through the emergency department versus all hospital departments), data sources to identify sepsis patients (SOFA-scores versus discharge codes) and inclusion criteria (sepsis patients surviving hospital stay versus all patients admitted with sepsis for the first time). Including only sepsis patients that survive discharge can cause an underestimation of the severity of sepsis, thus affecting the association between clinical characteristics and mortality. In the planning of our study, an expert panel found acute neurologic dysfunction codes to come with great uncertainty, especially among sepsis patients at high age. Therefore, acute neurological dysfunctions were not categorized as a single dysfunction, thus making comparisons for the number of organ dysfunctions and mortality risk challenging. Furthermore, we did not have the possibility to exclude end-stage comorbidity diseases, possibly contributing to a stronger association between acute organ dysfunctions and mortality.

To our knowledge, no previous study has investigated the long-term mortality of implicit, explicit, and COVID-19-related sepsis in one joint study. Interestingly, in light of all the media coverage directed toward the COVID-19-patients' risk of death, the mortality in patients with COVID-19-related sepsis was similar to patients with implicit and explicit sepsis. In sensitivity analysis restricted to the pandemic years 2020 and 2021 the risk of death was slightly lower for COVID-19-related sepsis patients. We also found that the frequencies of underlying comorbid diseases among patients admitted with implicit, explicit and COVID-19-related sepsis in our study were higher compared to the previously reported prevalence of comorbidity in the general population in Norway [45]. These results emphasize the need to discuss the recourses used after discharge including all sepsis patients, not focused to COVID-19 patients. Further, we found that implicit sepsis patients had the same risk as explicit sepsis patients. This is in contrast to a nationwide study based on ICD-10 codes, and a study investigating

mortality trends comparing clinical versus claims data, and found that explicit sepsis had a higher in-hospital mortality [33, 37]. For comparison, some of the diverging results can be explained by ICD-10 code selection and search strategies, where they included other combinations of ICD-10 codes to identify implicit sepsis and searched in a lower number of secondary diagnoses to combine infection and organ dysfunction. The latter can contribute to a underestimation of sepsis, especially implicit sepsis, and therefore recommended approach is to search in minimum 15 diagnosis fields to capture sepsis [46].

Surprisingly, only 8.5% of the sepsis patients received ICU treatment. In comparison, a recent French nationwide study found that over 50% of sepsis patients received ICU treatment [37]. Possible explanation of this diverging result can be that the ICU capacity in Norway is found to be in the lower range [47]. In addition, some of the less severe ill sepsis patients can be admitted at intermittent wards (not defined as ICUs) that manage acute organ dysfunctions, including non-invasive ventilation and medical treatment for low blood pressure..

Strengths and limitations

This study has several strengths. We included 222,832 patients with a first hospitalization of sepsis from 2008 to the end of 2021 in all Norwegian hospitals, which enabled us to conduct reliable subgroup analysis and examine recent survival trends. NPR and The Norwegian Cause of Death Registry are both widely used in research and have minimal missing data [31, 48]. Reporting to all three registries used are mandatory and followed by yearly quality controls, which limits participation bias due to completeness. Using the Norwegian Patient Registry also allows us to avoid survivor bias, as we have the date of admission to hospital for all patients, not only those who survive hospital. Further, using the Norwegian cause of death registry enables us complete follow-up to death date, thus avoiding attrition bias. Further, also the variable ICU-admission (yes/no) is expected to be complete since weekly reporting to ensure sufficient health care planning was mandatory the first two pandemic years. This amplifies the correctness of the ICD-10 codes in our study period. Another strength is that we, in one study, report the overall age-standardized long-term mortality for implicit, explicit, and COVID-19-related sepsis. To the best of our knowledge, this is the first study that provides nationwide trends in long-term mortality in patients admitted with sepsis over 14 years with separate analyses for patients admitted at ICU and ward patients and includes COVID-19-related sepsis.

There are also several limitations to our study. First, the use of registry-based study design is dependent on ICD-code abstraction [38], and different extractions of ICD-codes have been investigated to find the most fitted design, with diverging results [49–52]. In global counting of sepsis, Rudd et al. (2020) has been criticized for code-selecting strategies, that one strategy do not fit all countries, and most probable cause an overestimation of sepsis [53]. Fleishmann-Struzek (2018) compared the validity of different ICD coding for sepsis in Germany and found that explicit sepsis coding had a positive predictive value (PPV) of 59.6% and a threefold risk of underestimating sepsis incidence, while implicit sepsis had a PPV of 22.1%, and a 2.7-fold risk overestimating sepsis incidence [54]. The systematic review by Jolley et al. (2015) concludes that sepsis is largely undercoded in administrative data using ICD-9 and ICD-10 codes [55]. Our approach, using both explicit and implicit sepsis codes, may be in line with the under- and overestimation of explicit and implicit sepsis coding strategies described in these above studies. The strategy was designed to capture ICD-10 codes used to identify sepsis in Norway and included search for both explicit and implicit codes in 20 secondary diagnosis fields, which is in line with recommandations [46]. The ICD-10 codes are not static, and new codes for SIRS and septic shock were implemented in 2010 [56]. We used the Sepsis-3 definition during the entire study period, albeit the new definition first came in 2016 [1]. Second, retrieving organ dysfunction codes to identify implicit sepsis can generate false-positive outcomes since not all organ dysfunctions are caused by a specific infection. On the other hand, false-negative results can occur if the sepsis episode is inadequately documented. Third, although we did separate analysis for patients receiving intensive care treatment, we cannot rule out the possibility that illness severity could have influenced the risk differences observed between subgroups of patients. Fourth, presenting results adjusting for age and sex could mask possible age or sex specific associations with mortality. Finally, the level of SARS-CoV-2 incidence in Norway has been relatively low, and therefore, it can be speculated that mortality after COVID-19-related sepsis would have been different if the capacity in hospitals and ICUs was exceeded, as reported from other countries [57, 58].

Our results have implications for health policymakers, clinicians, and researchers. Although the case fatality is decreasing, sepsis survivors have high mortality in months and years after discharge. Long-term mortality in sepsis survivors requires further attention as more sepsis survivors put more pressure on skilled nursing facilities and in-home care.

Conclusion

This is the first study including sepsis patients admitted at wards and ICU that during fourteen years (2008–2021) demonstrates decreasing long-term mortality. Decrease was observed for all sepsis patients and all infections sites but was largest among patients with respiratory tract infections. Lastly, it seems that COVID-19-related sepsis patients have the same mortality risk as explicit and implicit sepsis patients.

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Data availability No additional data available.

Declarations

Conflict of interest None of the authors have any conflicts of interest to declare.

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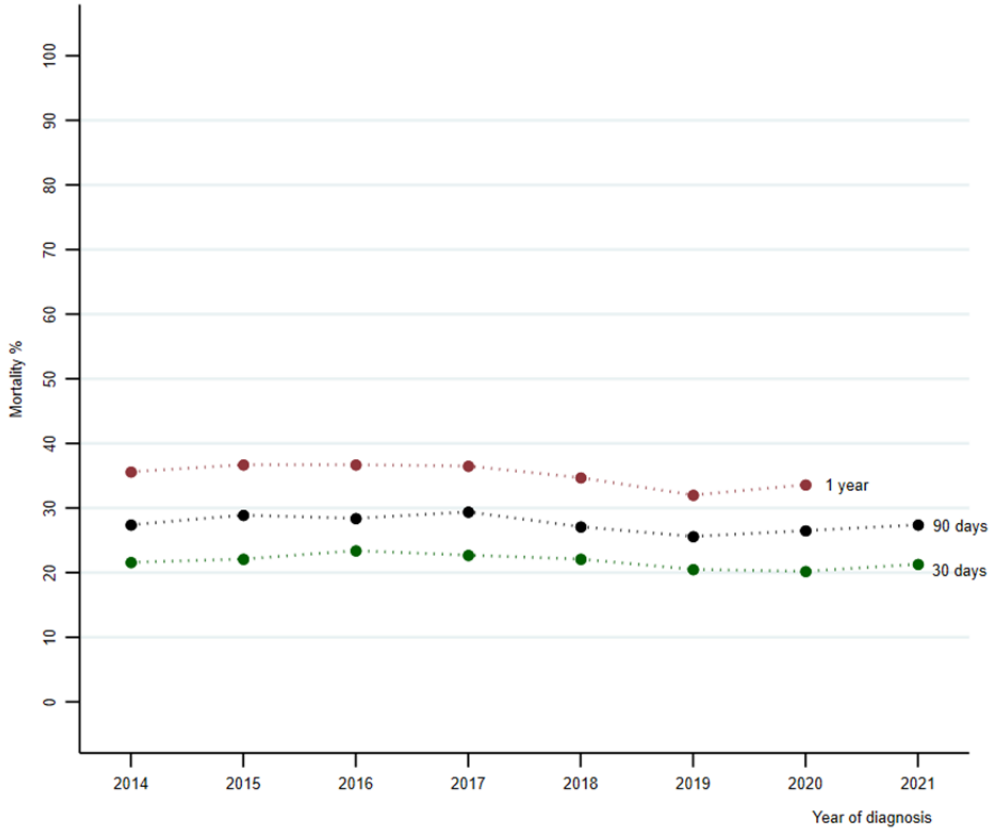
Supplementary File Paper II



Supplementary Fig. 1 Age-standardized mortality at 30- and 90-day and 1-year for patients with sepsis receiving intensive care treatment.

Supplementary Table 1 Hazard ratio for death from Cox regression by sepsis characteristics during follow-up of sepsis patients.

Variable	No. of patients	Person year at risk	Deaths	Mortality per 100 person year	Crude HR	Adjusted HR[a] (95% CI)
Sepsis subgroup[b]						
Implicit	17 315	11 079	5 598	50.5	1.00	1.00 (Reference)
Explicit	8 258	5 526	2 660	48.1	0.99	1.09 (1.04–1.14)
COVID-19-related	2 845	1 841	490	26.6	0.53	0.85 (0.77–0.93)

Abbrevation: HR=Hazard Ratio, CI= Confidence Interval.

[a] Cox regression with time to death as dependent variable, the listed variable as covariate, adjusted for indicator covariate for the year 2020, sex and age.

[b] All patients entered after 27th February 2020

Supplementary Table 2 Hazard ratio for death from Cox regression by sepsis characteristics during follow-up of sepsis patients.

Variable	No. of patients	Person year at risk	Deaths	Mortality per 100 person year	Crude HR	Adjusted HR[a] (95% CI)
Infection site						
Respiratory[b]	81 881	225 907	51 954	23.0	1.31	1.28 (1.27–1.30)
Genitourinary[b]	44 782	128 256	25 781	18.6	0.95	0.76 (0.75–0.77)
Intra-abdominal[b]	12 340	39 111	6 995	17.9	0.99	0.99 (0.97–1.02)
Gastrointestinal infections[b]	10 810	44 706	5 126	11.5	0.67	0.72 (0.70–0.74)
Skin and soft tissue[b]	8 265	20 173	2 395	11.9	0.69	0.80 (0.78–0.82)
Infections following a procedure[b]	8 290	33 392	3 674	11.0	0.64	0.74 (0.72–0.77)
Endocarditis/myocarditis[b]	2 530	8 033	1 371	17.1	0.94	1.09 (1.03–1.15)
Other infections[b,c]	43 085	141 556	21 391	15.1	0.75	0.86 (0.85–0.87)
Comorbidities						
Heart and vascular[d]	100 062	277 421	69 884	25.2	1.66	1.14 (1.13–1.16)
Cancer[d]	39 368	75 212	30 876	41.1	2.10	2.41 (2.38–2.44)
Lung[d]	36 165	100 190	25 675	25.6	1.37	1.32 (1.31–1.43)
Diabetes[d]	24 416	78 015	15 519	19.9	1.08	1.03 (1.01–1.05)
Dementia[d]	8 100	11 800	7 187	60.9	2.39	1.47 (1.43–1.51)
Renal[d]	8 949	17 553	6 140	35.0	1.50	1.24 (1.21–1.27)
Immune[d]	3 140	12 369	1 535	12.4	0.72	1.21(1.16–1.28)
Liver[d]	994	1 902	746	39.2	1.83	3.01 (2.81–3.25)
Type of acute organ dysfunction						
Respiratory[e]	61 864	169 225	39 335	23.2	1.29	1.47 (1.45–1.48)
Renal[e]	67 242	186 433	40 216	21.6	1.15	0.95 (0.94–0.96)
Circulatory[e]	14 982	35 239	9 278	26.3	1.38	1.55 (1.52–1.59)
Coagulation[e]	6 471	18 820	3 831	20.4	1.08	1.72 (1.67–1.78)
Hepatic[e]	3 209	6 232	2 337	37.5	1.84	2.63 (2.52–2.74)
Other acute organ dysfunctions[e,f]	22 173	78 441	12 249	15.6	0.85	0.72 (0.70–0.73)

Abbrevation: HR=Hazard Ratio, CI= Confidence Interval.

[a] Cox regression with time to death as dependent variable, the listed variable as covariate (one at the time), adjusted for per year 2009-2019 as continuous covariate, indicator covariates for the years 2008, 2020 and 2021, and sex and age.

[b] Reference group= All other infection sites

[c] Other infections= Bone, obstetric, upper airway, central nervous system and unknown

[d] Reference group= All other comorbidities

[e] Reference group= All other acute organ dysfunctions

[f] Other acute organ dysfunctions= Acidosis, unspecific gangrene, central nervous system dysfunctions and Systemic Inflammatory Response Syndrome.

Supplementary Table 3. Hazard ratio for death from Cox regression by admission year 2008-2021 of sepsis patients.

	Crude HR	Adjusted[a] HR (95% CI)
2008	1.059	1.058 (1.037-1.080)
2009	1	1
2010	0.984	0.975 (0.973–0.976)
2011	0.969	0.950 (0.946–0.953)
2012	0.954	0.930 (0.920–0.931)
2013	0.934	0.902 (0.895–0.909)
2014	0.925	0.879 (0.870–0.888)
2015	0.910	0.857 (0.846–0.867)
2016	0.896	0.835 (0.823–0.846)
2017	0.882	0.813 (0.801–0.826)
2018	0.869	0.793 (0.779–0.807)
2019	0.855	0.773 (0.757–0.788)
2020	0.884	0.794 (0.772–0.817)
2021	0.904	0.829 (0.803–0.856)

[a] Cox regression with time to death by year as dependent variable, unadjusted (crude), and adjusted for age and sex. The year 2009 is reference.

PAPER III

Return to work after hospitalization for sepsis; a nationwide, registry-based cohort study.

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Abstract

Background: Survivors of sepsis hospitalization commonly experience functional impairment, which may limit return to work. We aimed to investigate return to work (RTW) of patients with sepsis and the associations between patient and clinical characteristics with RTW. Methods: Working-age patients (18 to 60 years) admitted to a Norwegian hospital with sepsis between 2010 and end of 2021 were identified using the Norwegian Patient Registry and linked to sick-leave data from the Norwegian National Social Security System Registry. The outcomes were time to RTW, trends in age-standardized proportions of RTW and probability of sustainable RTW (31 days of consecutive work). The trends were calculated for each admission year, reported as annual percentage change with 95% CI. Cox regression analysis, including crude and adjusted hazard risk (HRs), was used to explore the association between sustainable RTW and patient and clinical characteristics (e.g., COVID-19 vs non-COVID-19 sepsis, ward vs intensive care admission) with RTW. Results Among 35.839 hospitalizations for sepsis among patients aged 18 to 60 years during the study period, 12.260 (34.2%) were working prior to hospitalization and included in this study. The mean age was 43.7 years. At 6 months, 1 year, and 2 years post-discharge, 58.6%, 67.5%, and 63.4%, respectively, were working. The overall annual age-standardized RTW proportion at 6 months and 1 year remained stable throughout the study period, while the 2-year age-standardized RTW declined by 1.51% (95% CI, -2.22 to -0.79) per year, from 70.01% (95% CI, 67.21 to 74.80) in 2010 to 57.04% (95% CI, 53.81to 60.28) in 2019. Characteristics associated with sustainable RTW were younger age, fewer comorbidities, and fewer organ dysfunctions. The probability of sustainable RTW was higher in patients with COVID-19-related sepsis (HR 1.31; 95% CI 1.15 to 1.49) than in sepsis patients and lower in ICU-patients (HR 0.56; 95% CI 0.52 to 0.61) compared to ward-patients. Conclusion The decrease in RTW from 1 to 2 years and the temporal trend of declining RTW at 2 years needs attention, and further work facilitation efforts are required, especially in vulnerable groups that may need other interventions than today to achieve sustained RTW.

Introduction

Sepsis is caused by a dysregulated host immune response to infection, resulting in acute organ dysfunction(1), and is a major cause of worldwide morbidity and mortality, with an estimated 50 million cases and 11 million sepsis-related deaths in 2017(2). Sepsis survivors often experience poor long-term outcomes with new or worsened cognitive and functional impairments(3, 4), making normal activities hard to resume. However, the impact of these problems on sepsis survivors' ability to return to work (RTW) is less clear.

RTW is a recommended measure of the long-term functional level after disease, including trauma (5), acute respiratory distress syndrome (ARDS), and conditions requiring intensive care and organ support(6-10). A previous Danish study (2018) investigating a general Intensive Care Unit (ICU) cohort found that among survivors receiving organ support therapy 60% had returned to work at 1 year and 68% at 2 years after discharge(9). Prior studies suggest that sepsis survivors have worse overall functional outcomes than other intensive care survivors(11, 12). This is supported by a recent administrative based German

study (2023) investigating RTW using the Sepsis-1 and Sepsis-2 definition, which found that only 55% and 65 % of ICU treated sepsis patients returned to work 6 months and 1 year after discharge(13). This suggests delayed RTW up to 1 year, thus negatively health impact can persist over years(10), which warrants RTW estimates beyond 1 year based on latest Sepsis-3 definition to monitor prognosis and trends to plan appropriate interventions for sepsis survivors working prior to the admission.

In light of the recent pandemic, the research on reduced functioning after infection with COVID-19 is evolving, suggesting that 30% of survivors are affected(14-17). RTW estimates at 6 months after a COVID-19 admission varies between 57% to 89%(18-21). Currently, limited research is available on RTW for patients with COVID-19-related sepsis, but one study of 120 COVID-19 patients found no differences in self-reported RTW after 110 days between ward and ICU patients(22).

In sum, knowledge about more long-term outcomes is warranted to understand and facilitate the RTW process for sepsis patients and COVID-19-related sepsis(23). The aim of this nationwide registry study was therefore to investigate the proportion and temporal trends for RTW in patients admitted with sepsis, including COVID-19 sepsis, at 6 months, 1 year, and 2 years in the period from 2010 through 2021. In addition, we examined characteristics associated with sustainable RTW, defined as working at least 31 consecutive days after a hospital discharge with an index sepsis episode.

Methods

Design and setting

In this Norwegian nationwide registry-based study, we identified hospitalizations for sepsis using ICD-10 codes in the Norwegian Patient Registry (NPR)(24). We included patients from all Norwegian hospitals in the period from 2010 through 2021 with an index admission for sepsis, defined by an ICD-10 code for infection in combination with an ICD-10 code for acute organ dysfunction (implicit) and/or an ICD-10 code for specific sepsis (explicit) (see Supplemental file, Supplementary Table 1)(2, 25). We used this strategy in the primary and up to 20 secondary co-existing ICD-10 discharge codes. To focus on index sepsis hospitalizations, we examined data from 2008 and excluded patients who had previously been hospitalized with sepsis between 2008 and 2010.

Patients with sepsis were linked to individual data from the Registry of the Norwegian National Social Security System. We limited the study cohort to patients of working age (18 to 60 years), which is 2 years before the earliest retirement possibility in Norway. The rationale for the upper age limit was to identify patients who stopped working due to sepsis, as opposed to patients who retired unrelated to sepsis. We also excluded patients with any disability pension prior to the sepsis hospitalization and patients who did not survive hospital discharge.

Details on the Norwegian National Insurance Scheme

In Norway, all workers have a compulsory membership in The Norwegian National Insurance Scheme(26). Individuals who have been working for at least four weeks before illness, with an income higher than ½ of the 'basic amount' (NOK 118 620, or USD 11 798 in 2023), and who have lost work income as a result of a medically-certified illness are entitled to sickness benefits of up to 52 weeks. Sickness benefits begin on the day the employer is notified of the illness. Self-employed individuals and freelance workers are also entitled to benefits but must cover the first 16 days of absence themselves. After 52 weeks, it is possible to apply for more long-term medical benefits, work assessment allowance and permanent disability pension. To qualify for a disability pension, individuals must have at least a 50% reduction in workability documented by a doctor`s certificate. A membership of The Norwegian National Insurance Scheme qualifies for a medical benefit application, even though the patient is without sickness benefits rights. All individuals with benefits in Norway are registered by their social security number in the Norwegian National Social Security System Registry, run by The Norwegian Labour and Welfare Administration(27).

Definition of variables in the study

Working was defined by two criteria, and both had to be met. First, patients had to be registered with no sickness benefit or long-term medical benefit (work assessment allowance and permanent disability pension) for at least 90 of 121 days in the 6-2 months prior to sepsis admission in order to exclude those patients on sickness or medical benefits for other medical conditions than to sepsis as a cause of not being able to RTW. Second, patients had to be registered with a sickness benefit 31 days before the hospital admission date or 31 days after the hospital discharge date in order to identify those patients working before to the sepsis admission.

ICD-10 discharge codes for selected comorbidities were based on diagnostic groups(28), the details regarding comorbidities are provided in a previous publication(29). COVID-19-related sepsis was included based on the presence of a discharge code for COVID-19 (U07.1, U07.2) and ≥one organ dysfunction code and/or explicit code. We categorized infection and acute organ dysfunctions by ICD-10 discharge codes, while ICU stay were retrieved from The Norwegian Intensive Registry(30). A readmission after hospitalization with sepsis was defined as an admission within 30 days after discharge, regardless of cause.

Outcome measures

We subsequently evaluated work status at 6 months, 1 year, and 2 years after discharge from index sepsis hospitalization. We categorized work status at each time point as RTW, ever RTW, never RTW, and dead. Patients without any sickness or medical benefit at the measurement point were categorized as RTW. Patients on sickness or medical benefit at all the measurement points were categorized as never RTW. Lastly, patients who had returned to work at an earlier time point but were back on sickness or medical benefits were categorized as ever RTW. We also investigated sustainable RTW, defined as the absence of any sickness or medical benefit for at least 31 consecutive days after discharge from sepsis hospitalization.

Death and death date was retrieved from the Norwegian Cause of Death Registry(31).

Statistical analysis

Descriptive results are presented as frequencies with percent, means with standard deviation, and medians as appropriate.

Clinical characteristics of interest included sex, age group (18-29, 30-39, 40-49, 50-60 years), number and type of comorbidities, site of infection, number and type of acute organ dysfunctions, ICU treatment, COVID-19-infection status, length of stay (LOS) and readmission within 30 days. These descriptive analyses were also repeated in the group of patients that did not work prior to sepsis admission.

The Norwegian National Social Security System Registry contains information about all members` entry and exit dates and degrees of sickness and medical benefits. To calculate the proportion of patients returning to work, we counted sepsis survivors from discharge date that had status as RTW, never RTW or dead at 6 months, and as RTW, never RTW, ever RTW or dead at 1 year, and 2 years, and divided by all patients working prior to admission, subtracting those who died between each measure point. We also completed analyses stratified by treatment in the ICU vs ward only and by COVID-19-related vs non-COVID-19-related sepsis.

To examine temporal trends in RTW, we calculated 6-month, 1-year, and 2-year RTW by calendar year. This was calculated as the proportions with RTW divided by the number of survivors after the index sepsis admission each year. To avoid potential bias of sepsis hospitalizations over time due to changing age distribution, the RTW proportion was standardized according to 10-year age groups (18-29, 30-39, 40-49, 50-60 years) using the age distribution in 2011 as the base for patients admitted to wards, and the age distribution in 2015 as the base for patients admitted to ICU. Temporal trends in age-standardized RTW were estimated from least-squares linear regression across calendar years and weighted by the inverse variance of the RTW proportion(32).

Clinical characteristics potentially associated with the probability of sustainable RTW were investigated using Cox regression to estimate crude and adjusted hazard ratios (HRs) with 95% confidence intervals (CI). Association with age and sex where mutually adjusted, whereas all other associations were adjusted for both sex (male, female) and age (years). Comorbidities, site of infection, and acute organ dysfunctions were analyzed as categorical variables, using the most common category as the reference. The categories were mutually exclusive, and the analyses were conducted on a restricted sample of patients with none or only one infection site, comorbidity, or acute organ dysfunction, respectively. In all Cox regression models, the patients were followed for 2 years after the date of discharge with an index sepsis admission to make sure the follow-up time covered the time-span of possible sick leave and was within the first possible retirement age. The discharge date was restricted to after 1 July, 2010, to validate the sick-leave data and ensure the participants were in the workforce. In the analysis assessing sustainable RTW in ICU patients compared to ward patients, both the ward and ICU patients entered the

study after 1 May, 2014, since earlier information for the ICU patients was unavailable(30). A similar analysis was conducted to compare sepsis and COVID-19-related sepsis patients, but with an entry date of 28 February, 2020, corresponding to the first confirmed hospitalized COVID-19 case in Norway. Patients were censored at the date of sustainable RTW, death date, or the last day of follow-up (31 December, 2021). The last date for inclusion was 1 October, 2021, to allow for a valid assessment of sustainable RTW. As many individuals go on and off sickness benefits, we conducted a sensitivity analysis where sustainable RTW was defined as at least 92 consecutive days without any sickness benefit. The proportional hazards assumption of the Cox model was examined by visual inspection of log-log plots.

All analyses were conducted using STATA version 16.1 (Stata Corp).

Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK) in Eastern Norway (2019/42772) and the Data Access Committee in Nord-Trøndelag Hospital Trust (2021/184). In accordance with the approval from the REK and the Norwegian law on medical research, the project did not require a written patient consent. This work was analyzed on TSD (Service for Sensitive Data) facilities, owned by the University of Oslo, operated, and developed by the TSD service group at the University of Oslo, IT Department (USIT).

Results

Among 35.839 patients aged 18–60 years who were discharged alive from an index sepsis hospitalization during the study period, 12.260 (34.2%) were confirmed to be working prior to sepsis hospitalization and included in this study. 10.533 (29.3%) patients were excluded for disability pension prior to sepsis hospitalization, 4.735 (13.2%) patients were excluded for > 30 days of sickness or long-term medical benefits in the months prior to sepsis hospitalization indicating other illnesses than sepsis affecting RTW, and 8.311 (23.1%) patients were excluded for lack of employment prior to sepsis hospitalization, as inferred by no sickness or medical benefit surrounding sepsis hospitalization. A flow chart of the exclusion and inclusion process is displayed in Fig. 1.

Figure 1 *Flowchart of the selection process*

Patient characteristics

Characteristics of the study cohort are shown in Table 1. The mean age was 43.7 years, and 59.9% were male. The most common comorbidity was heart or vascular disease, present in 19.5%. The most common sites of infection were respiratory (30.2%) and genitourinary (13.1%). The mean length of hospitalization was 13.9 days. 7.8% were admitted to an intensive care unit, and 29.9% were re-hospitalized within 30 days.

Table 1
Characteristics of the 12.260 patients working prior to sepsis hospitalization

Characteristics	N (%) or mean (SD)
Male, n (%)	7 341 (59.9)
Age, years, mean (SD)	43.7 (11.8)
Age-group, n (%)	
18–29	2 077 (16.9)
30–39	2 314 (18.9)
40–49	3 121 (25.4)
50–60	4 748 (38.7)
Comorbidities, n (%)	
Heart and vascular	2 394 (19.5)
Cancer	1 941 (15.8)
Lung	681 (5.6)
Diabetes	666 (5.4)
Immune	269 (2.2)
Renal	145 (1.2)
Liver	44 (0.4)
Number of comorbidities, n (%)	
0	7 290 (58.5)
1	3 933 (32.1)
2	911 (7.4)
≥3	126 (1.0)
Site of infection, n (%)	
Respiratory	3 692 (30.2)
Genitourinary	1 602 (13.1)
Skin and soft tissue	558 (4.4)
Gastrointestinal	827 (6.8)
Intra-abdominal	755 (6.2)
Infections following a procedure	625 (5.1)

Characteristics	N (%) or mean (SD)
Endocarditis/myocarditis	190 (1.6)
Other[a]	2 056 (16.8)
COVID-19-related sepsis[b]	384 (3.1)
Organ system with acute dysfunction, n (%)	
Respiratory	3 063 (25.0)
Circulatory	878 (7.2)
Renal	2 627 (21.4)
Hepatic	194 (1.6)
Coagulation	757 (6.2)
Other[c]	2 543 (20.7)
Number of acute organ dysfunctions, n (%)	
1	6 422 (87.2)
2	736 (10.0)
3	164 (2.2)
≥4	42 (0.6)
ICU treatment[f], n (%)	951 (7.8)
LOS, days, mean (SD)	
Ward patients	12.9 (22.2)
ICU patients[g]	25.4 (35.4)
30-day Readmission[e] n (%)	3 664 (29.9)

Characteristics	N (%) or mean (SD)
Abbreviation: NA = Not Applicable. ICU = Intensive Care Unit, LOS = Length of stay	
[a] Other infections = Bone, obstetric, upper airway, central nervous system and unknown	
[b] Variable calculated from 28th February 2020	
[c] Other acute organ dysfunction = Acidosis, unspecific gangrene, central nervous system dysfunctions and Systemic Inflammatory Response Syndrome.	
[d] Number of hospital admissions = Calculated as new sepsis admission if admission with ICD-10 codes defining sepsis, regardless of time frame for the new sepsis admission.	
[e] Readmission = admission within 30 days after discharge regardless of cause	
[f] Variable calculated from May 1, 2014	

Table 1 *Characteristics of the 12.260 patients working prior to sepsis hospitalization*

Supplementary Table 2 shows characteristics of the 8.311 individuals inferred to be not working prior to sepsis based on lack of sickness or medical benefit. Compared to patients working before sepsis hospitalization, non-working patients were younger (mean age 40.5 (SD = 13.2) vs 43.7 years, SD = 11.8) and consisted of more women (46.2% vs 40.1%).

Return to work

In the total cohort, the proportion with RTW was 58.6% at 6 months, 67.5% at 1 year, and 63.4% at 2 years. Among patients admitted to wards, the RTW proportion was 60.3% at 6 months, 68.6% at 1 year, and 64.2% at 2 years after discharge. Among patients admitted to ICU, the RTW proportion was 38.5% at 6 months, 53.6% at 1 year, and 52.2% at 2 years after discharge. In 2020 and 2021, for patients admitted with COVID-19-related sepsis, the RTW proportion was 66.9% and 77.8% at 6 months and 1 year after hospital discharge (Table 2).

Table 2
The proportion of RTW, never RTW and ever RTW and dead at 6 months, 1 year and 2 years in the period 2010 through 2021.

Patient group and measurement point	n[a]	RTW[b] (%)	Never RTW[c] (%)	Ever RTW [d] (%)	Dead (%)
All sepsis patients					
6 months	12 260	58.6	37.9	NA	3.4
1 year	11 751	67.5	21.6	5.6	5.4
2 year	10 845	63.4	15.3	13.7	7.7
Ward patients					
6 months	11 309	60.3	36.2	NA	3.4
1 year	10 856	68.6	20.4	5.6	5.4
2 year	10 085	64.2	14.4	13.7	7.6
ICU patients					
6 months	951	38.5	58.0	NA	3.5
1 year	895	53.6	36.2	4.8	5.4
2 year	760	52.2	26.7	13.0	8.0
COVID-19-related sepsis[e,f]					
6 months	384	66.9	32.6	NA	0.5
1 year	135	77.8	15.6	5.2	1.5

Patient group and measurement point	n[a]	RTW[b] (%)	Never RTW[c] (%)	Ever RTW [d] (%)	Dead (%)

Abbrevation: RTW = return to work, NA = Not Applicable

[a] Includes all sepsis patients who survived an admission,

[b] Without medical benefit or disability pension at measurement point

[c] Patients at medical benefit or disability pension since discharge.

[d] Patients without a medical benefit in a period after discharge, but back on medical benefit at measurement point

[e] Includes the years 2020 and 2021

[f] Includes those who were admitted at wards and ICU

Table 2 *The proportion of RTW, never RTW and ever RTW and dead at 6 months, 1 year and 2 years in the period 2010 through 2021.*

Temporal trends in RTW

Overall, the annual age-standardized RTW proportion at 6 months was stable with a change of 0.14% (95% CI, -0.20 to 0.47), from 57.57% (95% CI, 53.58 to 61.56) in 2010 to 63.10% (95% CI, 58.23 to 67.87) in 2021. The annual age-standardized RTW proportion at 1 year also remained stable throughout the study period with a change of -0.45% (95% CI, -0.94 to 0.53), from 69.52% (95% CI, 65.71 to 73.33) in 2010 to 64.89% (95% CI, 61.56 to 68.22) in 2020. However, the 2-year age-standardized RTW declined by 1.51% (95% CI, -2.22 to -0.79) per year over the study period, from 70.01% (95% CI, 67.21 to 74.80) in 2010 to 57.04% (95% CI, 53.81to 60.28) in 2019.

For patients admitted to the wards, the annual age-standardized RTW proportion at 6 months and 1 year after discharge remained stable throughout the study period. However, the 2-year age-standardized RTW declined by 1.32% (95% CI, -2.14 to -0.49) per year over the study period, from 70.01% (95% CI, 67.21 to 74.80) in 2010 to 56.96% (95% CI, 53.54 to 60.38) in 2019. This decline was driven mainly by the years after 2016. For patients admitted to the ICU, the annual age-standardized RTW proportion at 6 months, 1 year, and 2 years after discharge remained stable from 2014 through 2021, as shown in Fig. 2A and 2B.

Figure 2 *Age-standardized proportions RTW by discharge year for sepsis patients admitted A. wards (2010–2021) and B. ICU (2014–2021).*

Characteristics associated with sustainable RTW

The median follow-up time for sustainable RTW was 0.2 years (range 0 to 2 years) and ended when a person started working. The results displayed in Table 3 show that patients and clinical characteristics were associated with sustainable RTW. In short, younger age, fewer comorbidities, and fewer organ

failures were associated with sustainable RTW. In addition, patients with genitourinary, gastrointestinal, and skin and soft tissue sites of infection had higher rates of sustainable RTW than the other infections sites, and COVID-19-related sepsis had a 1.31 (95% CI; 1.15 to 1.49) higher chance of sustainable RTW compared to all sepsis patients.

Table 3
Associations of patient and clinical characteristics with sustained RTW

Variable	Person year (py) at risk	Events	Rate per py	Crude HR	Adjusted[a] HR (95% C)
Age-group					
18–29	720	1 779	2.47	1.00	1.00 (Reference)
30–39	824	1 966	2.38	0.90	0.90 (0.84–0.96)
40–49	1 080	2 552	2.36	0.80	0.78 (0.75–0.85)
50–60	1 595	3 592	2.25	0.69	0.69 (0.65–0.73)
Sex					
Male	2 579	5 939	2.30	1.00	1.00 (Reference)
Female	1 639	3 950	2.41	1.03	1.01 (0.97–1.05)
Sepsis subgroup[b]					
Sepsis	362	989	2.73	1.00	1.00 (Reference)
COVID-19-related	95	324	3.41	1.25	1.31 (1.15–1.49)
Site of infection[c]					
Respiratory	988	2 462	2.49	1.00	1.00 (Reference)
Genitourinary	260	785	3.01	1.40	1.38 (1.27–1.50)
Intra-abdominal	162	391	2.41	1.03	1.03 (0.92–1.14)
Gastrointestinal infections	169	637	3.80	1.69	1.64 (1.51–1.79)
Skin and soft tissue	105	276	2.64	1.26	1.27 (1.12–1.44)
Infections following a procedure	136	244	1.80	0.83	0.84 (0.73–0.96)
Endocarditis/myocarditis	46	74	1.60	0.70	0.70 (0.56–0.88)
Other infections[d]	793	1 800	2.27	1.00	0.96 (0.91–1.02)
Comorbidities[c]					
Heart and vascular	652	1 175	1.80	1.00	1.00 (Reference)
Cancer	749	736	0.98	0.52	0.52 (0.48–0.58)
Lung	139	367	2.65	1.57	1.60 (1.42–1.80)

Variable	Person year (py) at risk	Events	Rate per py	Crude HR	Adjusted[a] HR (95% C)
Diabetes	97	269	2.80	1.58	1.58 (1.39–1.81)
Renal	17	25	1.48	0.99	0.98 (0.66–1.46)
Immune	29	99	3.42	2.07	2.06 (1.67–2.53)
Liver	5	10	2.03	0.60	0.62 (0.33–1.15)
No. of comorbidities					
0	2 113	6 598	3.12	1.00	1.00 (Reference)
1	1 687	2 681	1.59	0.45	0.46 (0.44–0.48)
2	377	547	1.45	0.38	0.39 (0.36–0.42)
≥3	41	63	1.55	0.30	0.32 (0.25–0.41)
Type of acute organ dysfunction[c]					
Respiratory	819	1 858	2.27	1.00	1.00 (Reference)
Renal	563	1 761	3.12	1.45	1.48 (1.39–1.58)
Circulatory	187	353	1.89	0.89	0.91 (0.82–1.03)
Coagulation	332	407	1.23	0.62	0.64 (0.58–0.71)
Hepatic	37	66	1.79	0.83	0.82 (0.64–1.04)
Other acute organ dysfunctions[e]	275	735	2.67	1.33	1.30 (1.19–1.41)
No. of acute organ dysfunctions					
1	2 214	5 180	2.34	1.00	1.00 (Reference)
2	337	492	1.46	0.60	0.60 (0.55–0.66)
3	82	109	1.33	0.57	0.56 (0.46–0.68)
≥4	18	25	1.42	0.49	0.49 (0.33–0.72)
ICU treatment[f]					
No	2 335	5 974	2.56	1.00	1.00 (Reference)
Yes	396	660	1.67	0.57	0.56 (0.52–0.61)

Variable	Person year (py) at risk	Events	Rate per py	Crude HR	Adjusted[a] HR (95% C)

Abbrevation: HR = Hazard Ratio, CI = Confidence Interval, ICU = Intensive Care Unit, LOS = Length of hospital stay in days

[a] Cox regression with time to death as dependent variable, the listed variable as covariate (one at the time), and sex and age.

[b] Enter date = February 27, 2020

[c] Categorical variable where one ICD-10 code excludes other ICD-10 codes in the same diagnosis group

[d] Other infections = Bone, obstetric, upper airway, central nervous system and unknown

[e] Other acute organ dysfunctions = Acidosis, unspecific gangrene, central nervous system dysfunctions and Systemic Inflammatory Response Syndrome.

[f] Enter date= May 1, 2014

Table 3*Associations of patient and clinical characteristics with sustained RTW.*

Sensitivity analysis

In sensitivity analysis changing the definition of sustainable RTW to working at least 92 consecutive days after discharge date with an index sepsis episode, the adjusted hazard ratio from Cox regression did not differ from the results in Table 3, see Supplemental File, Supplementary Table 3.

Discussion

Our study is the first to use complete nationwide registries to estimate RTW in sepsis patients, and we demonstrate that RTW is a challenge for many patients, even 2 years after discharge. Our estimates show that a higher proportion of patients with sepsis returned to work at 1 year compared to 6 months and 2 years after discharge. The trends in RTW were stable throughout the study period, except for the RTW at 2 years where we observed a yearly decrease. Further, we found that decreasing age, fewer comorbidities, and fewer acute organ dysfunctions were associated with sustainable RTW in sepsis survivors and that COVID-19-related sepsis patients had a higher probability of achieving sustainable RTW than other sepsis patients.

One previous study have used administrative data covering 30% of the German population to estimate RTW in sepsis patients with a follow-up to 12 months after discharge(13). They found that 69% returned to work at 6 months and 76% returned to work at 12 months. This is a much higher RTW rate in our study. While they extracted explicit sepsis ICD-10 codes, we extracted both implicit and explicit ICD-10 sepsis

codes. Notably, an explicit approach is previous found to underestimate sepsis estimates and may be a possible explanation of the diverging results(33).

Previous studies on RTW in sepsis patients have used critical illness populations, where sepsis patients were a small proportion of the cohorts, and RTW was not reported separately(9, 10, 34–36). Thus, direct comparisons of our results with previous studies are not feasible. A systematic review of ICU studies suggests increasing rates of RTW over time(37), but the included studies have a high degree of RTW variability(9, 35, 37–41). While we use a national mandatory registry to calculate RTW, 51 of the 52 included studies in this systematic review used self-reported answers to questions in face-to-face or telephone interviews or mailed questionnaires to collect data. The majority of the included studies had more than 10% lost to follow-up since ICU/hospital discharge(37), while our complete national registries including weekly updates on RTW enabled us to follow-up everybody until death date and thus no loss to follow-up. In previous studies, the self-reported RTW at 1 year varied between 55–78%(37). The only registry study found that 60% of the ICU patients, regardless of diagnosis, returned to work at 1 year(9). For comparison, we found that 53.6% of the ICU patients with sepsis had returned to work at 1 year. Previous studies have found worse overall functioning outcomes in sepsis survivors compared to other intensive care survivors(11, 12), and since we only included sepsis patients, our result in the lower range is expected.

A Danish study of RTW in COVID-19 patients found that 6.6% of the patients hospitalized with COVID-19 did not work at 3 months(42). In contrast, we found that 33.1% of patients with COVID-19-related sepsis were not working at 6 months. Both our and the Danish study (2022) were based on registry data. However, while the Danish study included all hospitalized patients with a positive SARS-CoV-2 polymerase chain reaction (PCR) test, regardless of organ dysfunction, our study focused solely on COVID-19-related sepsis patients with one or more acute organ dysfunctions. This difference in patient selection with more severely sick patients in our study may explain the diverging results.

The literature regarding new episodes of sick leave after initial RTW is limited for sepsis patients(9, 37, 38). Investigating ICU patients, organ support therapy and RTW, Riddersholm et al. (2018) found that 29% were back on medical benefits within 1 year. For comparison, this is higher than our result (4.8%) at one year among sepsis patients admitted to ICU. If we compare the RTW proportion at 2 years, Riddersholm et al. found that 68% of the patients returned to work, which is higher than our age-standardized proportion at 2 years (58.4%). As previously argued, sepsis patients are expected to have worse outcomes than other critically ill patients, thus the dividing result. In addition, there are differences in social infrastructure with earlier transfer to long-term medical benefit in Denmark than in Norway(27, 43). Thus, potential differences may not all be health-related but may also be influenced by social infrastructure.

Interestingly, we found a decreasing trend of 2-year RTW for sepsis patients admitted to the wards from 2010 through 2021. To our knowledge, these trends in RTW in sepsis patients are not previously described. Based on our previous works, we observed decreasing case fatality rates and decreasing 1- and 2-year mortality in ward patients in this population(29, 44), pointing to a higher proportion of very ill

ward sepsis patients being discharged. We therefore hypothesize that the decreasing trend in RTW can be explained by this increased survival. The fact that the ICU patients' proportion of RTW was stable can be explained by stable mortality in patients receiving ICU treatment over time in the cohort(29, 44), i.e., the same proportion of ill ICU sepsis patients survive and are potential candidates for RTW.

Associations between patients and clinical characteristics in sepsis patients are limited. A recent registry-based Danish study (2018) of ICU patients and the need for organ support therapy found mechanical ventilation to be associated with a decreased chance of RTW(9). Another study investigating different severity stages of acute kidney injury (AKI, stages I-III) in ICU patients surviving acute respiratory failure and/or sepsis found that 50% of those with AKI I and 22% of those with AKI II-III returned to work at 3 months follow-up(45). Our study found that acute renal dysfunctions had a higher probability of sustainable RTW compared to acute respiratory dysfunction. However, we did not have the availability of AKI stages to differentiate and compare directly to Riddersholm et al. Another study by Poulsen and colleagues (2009) investigating patients with septic shock found that 43% of patients returned to work at 1 year(46). This is lower than in our study, where approximately 58% of the ICU patients RTW at 1 year. The diverging result may be explained by differences in the severity of sepsis since our study included all patients with sepsis receiving ICU treatment and not only septic shock. To our knowledge, no previous study has investigated characteristics associated with the probability of sustainable RTW in a patient group consisting of only patients admitted with sepsis, including sepsis patients admitted at the wards. Our findings support results from previous studies reporting that increasing age and pre-existing chronic comorbidities are associated with work status(38, 39). However, compared to our study, these studies were small and based on self-reports, thus direct comparisons are difficult.

There are some limitations to our study. First, the sepsis cohort is extracted from NPR using ICD-10 codes. We used the Sepsis-3 definition throughout the study period when extracting ICD-10 codes, albeit the definition first came in 2016(1). Second, implicit sepsis codes are found to overestimate sepsis while explicit sepsis codes often underestimate sepsis, and by using both approaches, we assume to align the chances for over- and underestimation(33). Moreover, we cannot be sure that all acute organ dysfunction codes are associated with the infection, and thus this could generate an overestimation of sepsis. Third, we observed that 40% of the sepsis patients were without sickness benefits in the period around hospitalization, and as these could not be verified to be working, we had to exclude these patients. The excluded patients were younger and likely consisted of more students, i.e., the RTW might have been higher if these had been included. In addition, we did not differentiate between employed and self-employed individuals. The possibility of not being on sick leave is higher for self-employed since they are only entitled to sickness benefits after the 17th day of absence compared to the first day of absence for employees, which may have caused an underestimation of RTW. Fourth, we did not investigate whether patients received graded sickness or medical benefits, meaning that some could have partly returned to work. Notably, the incidence rate and case fatality are in the lower range compared to estimates from a recent meta-analysis from 2020 and the global burden of disease study from 2017(2, 29, 47). The return to work estimates may also be influenced by social infrastructure, and therefore, the interpretation of the analysis is primarily relevant to countries with the same burden and comparable social welfare systems,

One major strength is that our study is based on complete national administrative data(48), thus the selection bias is minimized. We have complete follow-up data, which is generally not possible in other cohorts based on patients' self-report, where over 10% lost to follow-up since discharge is common(37). We studied characteristics associated with sustainable RTW, while previous studies report only RTW at fixed time points after receiving ICU treatment. Our group of patients is without any form of benefits and has sustained work for at least 31 consecutive days, thus our results account for the fact that they have probably resumed work after the index sepsis episode. This is a strength because estimates of only fixed time points are snapshots of RTW and lack sustainable RTW. Furthermore, another strength is that we studied RTW over 11 years, thus making it possible to detect RTW trends and report RTW results beyond 1 year.

CONCLUSION

Two thirds of the patients working prior to the sepsis admission returned to work at 1 year, which was higher compared to 6 months and 2 years. While the trends in RTW at 6 months and 1 year were stable, the trend at 2 years RTW after discharge decreased throughout the study period. Vulnerable groups for not achieving sustainable RTW were patients at higher ages, patients with an increasing number of comorbidities and an increasing number of acute organ dysfunctions, which warrants targeted interventions to improve long-term outcomes.

Declarations

Ethical Approval and consent to participate

Regional Committee for Medical and Health Research Ethics (REK) in Eastern Norway (2019/42772). Data Access Committee in Nord-Trøndelag Hospital Trust (2021/184).In accordance with the approval from the REK and the Norwegian law on medical research, the project did not require a written patient consent.

Consent for publication

Not applicable

Competing interests

None of the authors have any conflicts of interest to declare

Contributorship statement

Study concept and design: N.V.S., K.M., T.I.L.N., L.A., J.K.D., L.T.G.

Acquisition of data: N.V.S., L.T.G.

Analysis and interpretation of data: N.V.S., K.M., T.I.L.N., L.T.G.

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Drafting of the manuscript: N.V.S

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Study supervision: T.I.L.N., J.K.D., L.T.G.

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Role of the Funder:

The funding body had no role in the designs of the study, data collection, analysis, interpretation of data, or in writing the manuscript.

Availability of data and materials

No additional data available. We do not have ethical approval to deposit our datasets in publicly available repositories. Researchers need approval by the Regional Ethical Committee for handling of NPR, NIR and NAV data files. The NPR has precise information on all data exported to different projects and there are no restrictions regarding data export given REK approval.

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Not applicable

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Figures

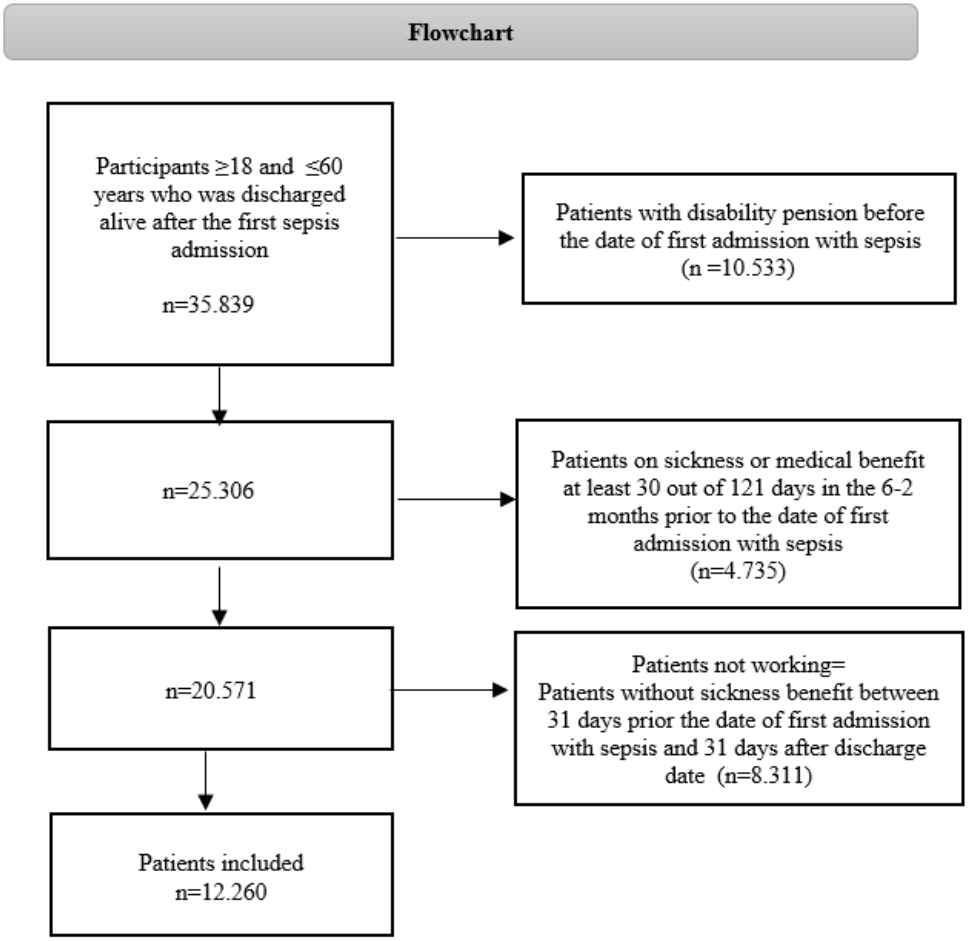

Figure 1

Flowchart of the selection process

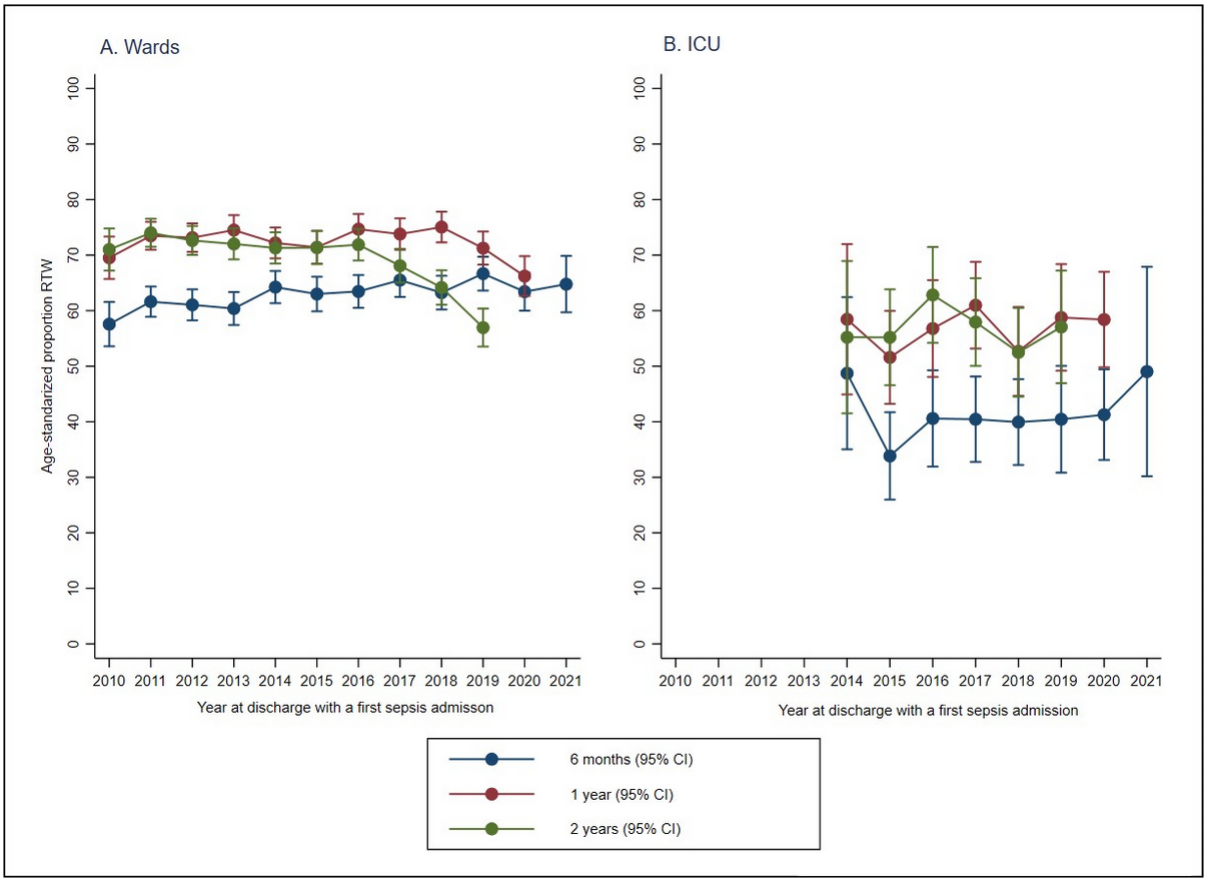

Figure 2

Age-standardized proportions RTW by discharge year for sepsis patients admitted A. wards (2010-2021) and B. ICU (2014-2021).

Supplementary File Paper III

Supplementary Table 1 Characteristics of patients working and not working prior to the first sepsis admission and discharged alive

Characteristics	Working	Not working
Male, n (%)	7 341 (59.9)	4 475 (53.8)
Age, years, mean(SD)	43.7 (11.8)	40.5 (13.2)
Age-group, n (%)		
18-29	2 077 (16.9)	2 240 (27.0)
30-39	2 314 (18.9)	1 605 (19.3)
40-49	3 121 (25.4)	1 837 (22.1)
50-59	4 748 (38.7)	2 629 (31.6)
Comorbidities, n (%)		
Heart and vascular	2 394 (19.5)	1 249 (15.0)
Cancer	1 941 (15.8)	711 (8.6)
Lung	681 (5.6)	476 (5.7)
Diabetes	666 (5.4)	547 (6.6)
Immune	269 (2.2)	165 (2.0)
Renal	145 (1.2)	122 (1.5)
Liver	44 (0.4)	36 (0.4)
Number of comorbidities, n (%)		
0	7 290 (58.5)	5 601 (67.4)
1	3 933 (32.1)	2 193 (26.4)
2	911 (7.4)	442 (5.3)
≥3	126 (1.0)	75 (0.9)
Site of infection, n (%)		
Respiratory	3 692 (30.2)	2 694 (32.4)
Genitourinary	1 602 (13.1)	1 185 (14.3)
Skin and soft tissue	558 (4.4)	576 (6.9)
Gastrointestinal	827 (6.8)	485 (6.0)
Intra-abdominal	755 (6.2)	391(4.7)
Infections following a procedure	625 (5.1)	374 (4.5)
Endocarditis/myocarditis	190 (1.6)	125 (1.5)
Other[a]	2 056 (16.8)	1 507 (18.2)
COVID-19-related sepsis[b]	384 (3.1)	713 (8.6)
Organ system with acute dysfunction, n (%)		
Respiratory	3 063 (25.0)	2 204 (26.5)
Circulatory	878 (7.2)	471 (5.7)
Renal	2 627 (21.4)	1 697 (20.4)
Hepatic	194 (1.6)	106 (1.3)
Coagulation	757 (6.2)	346 (4.2)
Other[c]	2 543 (20.7)	1 847 (22.2)
Number of acute organ dysfunctions, n (%)		
1	6 422 (87.2)	4 564 (90.2)
2	736 (10.0)	398 (7.9)
3	164 (2.2)	80 (1.6)
≥4	42 (0.6)	18 (0.4)
ICU treatment[f] , n (%)	951 (7.8)	590 (7.1)
LOS, days, mean (SD)		
Ward patients	12.9 (22.2)	9.2 (13.7)
ICU patients[g]	25.4 (35.4)	18.6 (19.8)
30-day Readmission[e] n (%)	3 664 (29.9)	1 854 (22.3)

Abbreviation: NA=Not Applicable. ICU= Intensive Care Unit, LOS=Length of stay

[a] Other infections= Bone, obstetric, upper airway, central nervous system and unknown

[b] Variable calculated from 28th February 2020

[c] Other acute organ dysfunction= Acidosis, unspecific gangrene, central nervous system dysfunctions and Systemic Inflammatory Response Syndrome.

[d] Number of hospital admissions= Calculated as new sepsis admission if admission with ICD-10 codes defining sepsis, regardless of time frame for the new sepsis admission.

[e] Readmission= admission within 30 days after discharge regardless of cause

[f] Variable calculated from May 1, 2014

Supplementary Table 2 Adjusted hazard ratio from Cox regression by characteristics of patients working in at least 92 consecutive days without sickness benefit after index sepsis admission.

Variable	Person year (py) at risk	Events	Rate per py	Crude HR	Adjusted[a] HR (95% C)
Age-group					
18-29	1 065	1 686	1.58	1.00	1.00 (Reference)
30-39	1 218	1 854	1.52	0.91	0.91 (0.85 – 0.97)
40-49	1 548	1 548	1.53	0.82	0.82 (0.77 – 0.87)
50-60	2 157	2 157	1.52	0.71	0.71 (0.67 – 0.75)
Sex					
Male	3 605	5 493	1.52	1.00	1.00 (Reference)
Female	2 382	3 710	1.56	1.04	1.01 (0.97 – 1.06)
Sepsis subgroup [b]					
Sepsis	280	561	2.00	1.00	1.00 (Reference)
COVID-19-related	137	298	2.18	1.31	1.35 (1.17 – 1.56)
Site of infection[c]					
Respiratory	1 410	2 288	1.51	1.00	1.00 (Reference)
Genitourinary	411	743	1.81	1.36	1.34 (1.23 – 1.45)
Intra-abdominal	255	364	1.61	1.05	1.05 (0.94 – 1.17)
Gastrointestinal infections	309	610	1.97	1.59	1.55 (1.42 – 1.69)
Skin and soft tissue	145	263	1.82	1.27	1.29 (1.13 – 1.47)
Infections following a procedure	181	227	1.25	0.82	0.83 (0.72 – 0.95)
Endocarditis/myocarditis	58	64	1.11	0.66	0.66 (0.51 – 0.84)
Other infections[d]	1 115	1 685	1.51	1.01	0.97 (0.91 – 1.04)
Comorbidities[c]					
Heart and vascular	807	1 044	1.29	1.00	1.00 (Reference)
Cancer	822	603	0.73	0.50	0.51 (0.46 – 0.56)
Lung	204	343	1.67	1.62	1.61 (1.43 – 1.83)
Diabetes	156	250	1.60	1.54	1.55 (1.35 – 1.78)
Renal	19	20	1.03	0.91	0.90 (0.58 – 1.40)
Immune	50	95	1.89	2.01	2.02 (1.64 – 2.50)
Liver	8	8	1.00	0.53	0.54 (0.27 – 1.08)
No. of comorbidities					
0	3 410	6 314	1.85	1.00	1.00 (Reference)
1	2 067	2 363	1.14	0.44	0.45 (0.43 – 0.47)
2	460	471	1.02	0.37	0.38 (0.34 – 0.42)
≥3	50	55	1.09	0.31	0.32 (0.25 –0.42)
Type of acute organ dysfunction[c]					
Respiratory	1 113	1 722	1.54	1.00	1.00 (Reference)
Renal	905	1 676	1.85	1.42	1.43 (1.34 – 1.53)
Circulatory	240	325	1.36	0.89	0.92 (0.82 – 1.03)
Coagulation	398	356	0.89	0.60	0.59 (0.52 – 0.66)
Hepatic	48	57	1.20	0.78	0.77 (0.588 – 0.997)
Other acute organ dysfunctions[e]	411	679	1.65	1.25	1.22 (1.12 – 1.34)
No. of acute organ dysfunctions					
1	3 114	4 815	1.54	1.00	1.00 (Reference)
2	387	409	1.05	0.55	0.56 (0.51 – 0.62)
3	98	91	0.93	0.52	0.51 (0.42 – 0.63)
≥4	17	22	1.25	0.50	0.50 (0.33 – 0.76)
ICU treatment[f]					
No	3 437	5 785	1.68	1.00	1.00 (Reference)
Yes	476	568	1.19	0.54	0.53 (0.49 – 0.58)

Abbrevation: HR=Hazard Ratio, CI= Confidence Interval. ICU= Intensive Care Unit

[a] Cox regression with time to death as dependent variable, the listed variable as covariate (one at the time), and sex and age.

[b] Enter date=February 27, 2020

[c] Categorical variable where one ICD-10 code excludes other ICD-10 codes in the same diagnosis group

[d] Other infections= Bone, obstetric, upper airway, central nervous system and unknown

[e] Other acute organ dysfunctions= Acidosis, unspecific gangrene, central nervous system dysfunctions and Systemic Inflammatory Response Syndrome.

[f] Enter date= May 1, 2014

4. ICD-10 codes description

Supplementary File

ICD-10 codes: Explicit sepsis

ICD-10	Description
A02.1	Salmonellasepsis
A20.7	Sepsispest
A21.7	Generalisert tularemi
A22.7	Miltbrannsepsis
A24.1	Akutt eller fulminant melioidose
A26.7	Sepsis som skyldes Erysipelothrix
A28.2	Ekstraintestinal yersiniose
A32.7	Listeriasepsis
A 39.2	Akutt meningokokkemi
A39.4	Uspesifisert meningokokkemi
A40	Streptokokksepsis
A41	Annen sepsis
A42.7	Aktinomykotisk sepsis
B00.7	Disseminert herpesvirussykdom
B37.7	Candidasepsis

ICD-10 codes: Infection

ICD-10	Description
A00	Kolera (cholera)
A01	Tyfoidfeber og paratyfoidfeber
A02	Andre salmonellainfeksjoner
A03	Shigellose
A04	Andre bakterielle tarminfeksjoner
A05	Andre bakterielle matforgiftninger, ikke klassifisert annet sted
A06	Amøbeinfeksjon
A07	Andre protozosykdommer i tarmkanalen
A08	Virusinfeksjoner og andre spesifiserte infeksjoner i mage-tarmkanalen
A09	Annen gastroenteritt og kolitt av infeksiøs og uspesifisert årsak
A19	Miliærtuberkulose
A20	Pest (pestis)
A21	Tularemi
A22	Miltbrann (anthrax)
A23	Brucellose
A24	Snive og melioidose
A25	Rottebittfeber
A26	Erysipeloid
A27	Leptospirose
A28	Andre bakterielle zoonoser, ikke klassifisert annet sted
A30	Lepra
A31	Infeksjon som skyldes andre mykobakterier
A32	Listeriose
A36	Difteri
A37	Kikhoste

A38	Skarlagensfeber
A39	Meningokokkinfeksjon
A42	Aktinomykose
A43	Nokardiose
A44	Bartonellose
A46	Erysipelas
A48	Andre bakteriesykdommer, ikke klassifisert annet sted
A49	Bakterieinfeksjon med uspesifisert lokalisasjon
A54	Gonokokkinfeksjon
A59	Trikomonasinfeksjon
A69.0	Nekrotiserende ulcerøs stomatitt
A69.1	Annen Vincent-infeksjon
A69.9	Uspesifisert spiroketinfeksjon
A70	Chlamydia psittaci-infeksjon
A74	Andre sykdommer forårsaket av klamydia
A75	Flekktyfus overført ved lus, lopper og midd
A77	Flekkfeber
A78	Q-feber
A79	Andre rickettsioser
A80	Akutt poliomyelitt
A81	Atypiske virusinfeksjoner i sentralnervesystemet
A83	Virusencefalitt overført ved mygg
A84	Virusencefalitt overført ved flått
A85	Annen virusencefalitt, ikke klassifisert annet sted
A86	Uspesifisert virusencefalitt
A87	Virusmeningitt
A88	Andre virusinfeksjoner i sentralnervesystemet, ikke klassifisert annet sted
A89	Uspesifisert virusinfeksjon i sentralnervesystemet
A92	Andre virussykdommer overført ved mygg
A93	Andre virussykdommer overført ved artropoder , ikke klassifisert annet sted
A94	Uspesifisert virussykdom overført ved artropode
A95	Gulfeber (febris flava)
A96	Hemoragisk arenavirussykdom (febris haemorrhagica arenaviralis)
A97	Dengue
A98	Annen hemoragisk virussykdom, ikke klassifisert annet sted
A99	Uspesifisert hemoragisk virussykdom
B00	Herpesvirusinfeksjoner
B01	Varicella
B02	Herpes zoster
B03	Kopper
B04	Apekopper
B05	Meslinger
B06	Rubella
B08	Andre virusinfeksjoner kjennetegnet ved hud- og slimhinnelesjoner, ikke klassifisert annet sted
B09	Uspesifisert virusinfeksjon kjennetegnet ved hud- eller slimhinnelesjon
B25	Cytomegalovirussykdom
B26	Kusma (parotitis epidemica)
B27	Mononukleose (mononucleosis infectiosa)

B33	Andre virussykdommer, ikke klassifisert annet sted
B34	Virusinfeksjon med uspesifisert lokalisasjon
B37	Candidainfeksjon
B38	Koksidioidomykose (coccidioidomycosis)
B39	Histoplasmose (histoplasmosis)
B40	Blastomykose (blastomycosis)
B41	Paracoccidioidomycosis
B42	Sporotrikose (sporotrichosis)
B43	Kromomykose (chromomycosis) og feomykotisk abscess
B44	Aspergillose (aspergillosis)
B45	Kryptokokkose (cryptococcosis)
B46	Zygomykose (zygomycosis)
B48	Andre soppsykdommer , ikke klassifisert annet sted
B49	Uspesifisert soppsykdom
B50	Malaria som skyldes Plasmodium falciparum
B54	Uspesifisert malaria
B55	Leishmaniasis
B57	Chagas sykdom (trypanosomiasis americana)
B58	Toksoplasmose
B60	Andre protozosykdommer, ikke klassifisert annet sted
B64	Uspesifisert protozosykdom
B67	Ekinokokkose (echinococcosis)
B95	Streptokokker og stafylokokker som årsak til sykdommer klassifisert i andre kapitler
B96	Andre spesifiserte bakterier som årsak til sykdommer klassifisert i andre kapitler
B97	Virus som årsak til sykdommer klassifisert i andre kapitler
B99	Annen eller uspesifisert infeksjonssykdom
G00	Bakteriell meningitt , ikke klassifisert annet sted
G01	Meningitt ved bakteriesykdom klassifisert annet sted
G02	Meningitt ved andre infeksjons- og parasittsykdommer klassifisert annet sted
G03	Meningitt som har andre og uspesifiserte årsaker
G04	Encefalitt , myelitt og encefalomyelitt
G05	Encefalitt , myelitt og encefalomyelitt ved sykdommer klassifisert annet sted
G06	Intrakraniell og intraspinal abscess og granulom
G07	Intrakraniell eller intraspinal abscess eller granulom ved sykdom klassifisert annet sted
G08	Intrakraniell eller intraspinal flebitt eller tromboflebitt
H05.0	Akutt betennelse i øyehule
H60.2	Ondartet betennelse i ytre øre
H70.0	Akutt mastoiditt
I00	Giktfeber uten opplysning om hjertesykdom
I33	Akutt og subakutt ikke-reumatisk endokarditt (endocarditis acuta et subacuta)
I38	Endokarditt i uspesifisert klaff
I39	Endokarditt og hjerteklaffefeil ved sykdommer klassifisert annet sted
I40.0	Infeksiøs myokarditt
J01	Akutt sinusitt
J02	Akutt faryngitt (pharyngitis acuta)
J03	Akutt tonsillitt (tonsillitis acuta)
J04	Akutt laryngitt (laryngitis acuta) og trakeitt (tracheitis acuta)
J05	Akutt obstruktiv laryngitt og epiglottitt

J06	Akutte infeksjoner i de øvre luftveiene, med flere og uspesifiserte lokalisasjoner
J09	Influensa som skyldes identifisert zoonotisk eller pandemisk influensavirus
J10	Influensa som skyldes identifisert sesongvariabelt influensavirus
J11	Influensa, uidentifisert virus
J12	Viruspneumoni , ikke klassifisert annet sted
J13	Pneumoni som skyldes Streptococcus pneumoniae
J14	Pneumoni som skyldes Haemophilus influenzae
J15	Bakteriell pneumoni , ikke klassifisert annet sted
J16	Pneumoni som skyldes andre mikroorganismer, ikke klassifisert annet sted
J17	Pneumoni ved sykdommer klassifisert annet sted
J18	Pneumoni , uspesifisert mikroorganisme
J20	Akutt bronkitt
J21	Akutt bronkiolitt
J22	Uspesifisert akutt infeksjon i nedre luftveier
J36	Peritonsillær abscess
J39.0	Retrofaryngeal eller parafaryngeal abscess
J39.1	Annen abscess eller cellulitt i svelg
J85	Abscess i lunge (pulmo) og mediastinum
J86	Pyotoraks (empyema pleurae)
K35	Akutt appendisitt (appendicitis acuta)
K36	Annen spesifisert appendisitt
K37	Uspesifisert appendisitt
K57	Divertikkelsykdom i tarm
K61	Abscess i anal- og rektalområdet
K63.0	Tarmabscess
K63.1	Perforasjon av tarm
K65	Peritonitt (peritonitis)
K75.0	Leverabscess
K81.0	Akutt galleblærebetennelse
K83.0	Kolangitt
L02	Kutan abscess, furunkel og karbunkel
L03	Cellulitt
L04	Akutt lymfadenitt
L08	Andre lokale infeksjoner i hud og underhud
M00	Pyogen artritt (arthritis pyogenes)
M01	Direkte leddinfeksjon ved infeksjonssykdommer og parasittsykdommer klassifisert annet sted
M72.6	Nekrotiserende faceitt
M86	Osteomyelitt (osteomyelitis)
N10	Akutt tubulointerstitiell nefritt
N15.1	Renal eller perinefrisk abscess
N30	Cystitt
N39.0	Urinveisinfeksjon med uspesifisert lokalisasjon
N41.0	Akutt prostatitt
N41.2	Abscess i blærehalskjertel
N41.3	Prostatocystitt
N45	Orkitt og epididymitt
N49	Forniers gangren
N70	Salpingitt og ooforitt

N71	Inflammatorisk sykdom i livmor (uterus), unntatt livmorhals (cervix uteri)
N72	Inflammatorisk sykdom i livmorhals
N73	Andre inflammatoriske sykdommer i kvinnelige bekkenorganer
N74	Infeksjonssykdommer og andre betennelsestilstander i kvinnelige bekkenorganer ved sykdommer klassifisert annet sted
N98.0	Infeksjon i forbindelse med kunstig befruktning
O03.0	Spontan inkomplett abort komplisert med infeksjon i kjønnsorganer eller bekken
O03.5	Spontan komplett eller uspesifisert abort komplisert med infeksjon i kjønnsorganer eller bekken
O04.5	Legal komplett eller uspesifisert abort, komplisert med infeksjon i kjønnsorganer eller bekken
O08.0	Infeksjon i kjønnsorganer eller bekken etter abort, svangerskap utenfor livemoren eller blæremola
O23	Infeksjoner i urinveier og kjønnsorganer under svangerskap
O75.3	Annen infeksjon under fødsel
O85	Barselfeber
O86	Andre barseltidsinfeksjoner
O88.3	Obstetrisk pyemi eller septisk emboli
O91	Infeksjoner i bryst (mamma) i forbindelse med fødsel
O98	Infeksjonssykdommer/ parasittsykdommer hos mor, klassifiseres annet sted, men som kompliserer svangerskap , fødsel og barseltid
R02	Gangren, ikke klassifisert annet sted
T80.2	Infeksjon etter infusjon, transfusjon eller terapeutisk injeksjon
T81.4	Infeksjon etter kirurgiske eller medisinske prosedyrer ikke klassifisert annet sted
T82.6	Infeksjon eller betennelsesreaksjon som skyldes hjerteklaffprotese
T82.7	Infeksjon eller betennelsesreaksjon som skyldes andre innretning, implantat eller transplantat i hjerte eller blodkar
T83.5	Infeksjon eller betennelsesreaksjon som skyldes protese, implantat eller transplantat i urinveier
T83.6	Infeksjon eller betennelsesreaksjon som skyldes protese, implantat eller transplantat i kjønnsorganer
T84.5	Infeksjon eller betennelsesreaksjon som skyldes innvendig leddprotese
T84.6	Infeksjon eller betennelsesreaksjon som skyldes innvendig fiksasjonsanordning
T84.7	Infeksjon eller betennelsesreaksjon som skyldes annen innvendig ortopedisk protese, implantat eller transplantat
T85.7	Infeksjon eller betennelsesreaksjon som skyldes annen innvendig protese, implantat eller transplantat
T88.0	Infeksjon etter vaksinasjon
U04	Alvorlig, akutt luftveissyndrom (sars)
U07.1	Covid-19 med påvist virus
U07.2	Covid-19 uten påvist virus

ICD-10 codes: Acute organ dysfunction

ICD-10	**Description**
D65	Disseminert intravaskulær koagulasjon
D69.5	Sekundær trombocytopeni
E87.2	Acidose
G93.4	Uspesifisert encefalopati
I46	Hjertestans
I95.9	Uspesifisert hypotensjon
J80	Respiratorisk distressyndrom hos voksne
J95.2	Akutt lungeinsuffisiens etter ikke-torakal kirurgi
J96	Respirasjonssvikt, ikke klassifisert annet sted
K72.0	Akutt eller subakutt leversvikt
K72.9	Uspesifisert leversvikt
N00	Akutt nefrittisk syndrom
N17	Akutt nyresvikt

R09.0	Asfyksi
R09.2	Respirasjonsstans
R40.0	Somnolens
R40.1	Stupor
R40.2	Uspesifisert koma
R41	Andre symptomer og tegn med tilknytning til kognitive funksjoner og bevissthet
R55	Synkope eller kollaps
R57	Sjokk, ikke klassifisert annet sted
R57.2	Septisk sjokk
R65.1	Systemisk inflammatorisk responssyndrom av infeksiøs årsak med organsvikt

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