The epidemiology of risk factors and short- and long-term outcome in the Swedish intensive care cohort

BJÖRN AHLSTRÖM
Abstract


The sepsis syndrome is present in ¼ to ⅓ of patients in intensive care units (ICUs) worldwide. The short-term prognosis is grim, with a 30-day mortality of 30–35%; however, the long-term outcomes are now being explored, as multi-professional follow-up after ICU care is increasingly being implemented. In 2020 the first and second waves of another severe infection, the Coronavirus disease 2019 (Covid-19) hit Sweden. The number of ICU beds were scaled up by several hundred percent while we simultaneously tried to understand the disease. Reports on risk factors for adverse outcomes in Covid-19 started to appear, but we needed to know more. Thus, we initiated this project aiming at assessing sepsis as an independent risk factor for later morbidity and mortality. Subsequently, with the onset of the pandemic, our focus shifted to identifying risk factors for adverse outcomes in Covid-19 and describing the functional recovery after severe Covid-19. We used the Swedish Intensive Care Registry and several governmental registries to this end.

In Cox regression, we compared one-year ICU sepsis survivors without previous dementia with ICU patients without sepsis, finding no increased risk of dementia during follow-up. In a similar cohort, we assessed the impact of sepsis on long-term mortality and causes of death in a series of Cox and multinomial models. We found a surprisingly small overall association between sepsis and mortality and a persistently increased risk of infectious causes of death in sepsis patients. We compared the prevalence of several common comorbidities and medications as risk factors for ICU admission and mortality in ICU patients with Covid-19 with that of age- and sex-matched population controls and in patients discharged alive with those that were deceased at discharge. We found associations between several comorbidities and medications with these adverse outcomes. To better understand the meaning of these comorbidities as risk factors for short-term mortality, we compared them in logistic regression models on patients with Covid-19, sepsis and acute respiratory distress syndrome (ARDS). We found very similar impacts from the comorbidities; however, greater age was more associated with mortality in Covid-19 than in either sepsis or ARDS. Finally, we investigated the long-term functional recovery in ICU patients with Covid-19 compared to hospital-admitted patients with Covid-19 and population controls matched to the ICU group. The ICU patients had a markedly impeded recovery that was not explained by demographics or comorbidities in statistical models.

Keywords: Intensive care, Intensive care unit, Sepsis, Covid-19, Epidemiology, Dementia, Mortality, Causes of death

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ISSN 1651-6206
URN urn:nbn:se:uu:diva-519461 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-519461)
To Eskil, Knut and Sara
List of Papers

This thesis is based on the following original papers, which are referred to in the text by their Roman numerals.


II Ahlström B, Larsson IM, Strandberg G, Lipcsey M. Association of sepsis with long-term mortality and causes of death in the Swedish intensive care cohort. Submitted manuscript (2023)


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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>ACE2</td>
<td>Angiotensin converting enzyme 2</td>
</tr>
<tr>
<td>ACEi</td>
<td>Angiotensin converting enzyme inhibitor</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>aPTT</td>
<td>Activated partial thromboplastin time</td>
</tr>
<tr>
<td>ARB</td>
<td>Angiotensin receptor blocker</td>
</tr>
<tr>
<td>ARDS</td>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>AT1</td>
<td>Alveolar type 1 cell</td>
</tr>
<tr>
<td>AT2</td>
<td>Alveolar type 2 cell</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomic Therapeutic Chemical Classification System</td>
</tr>
<tr>
<td>CCI</td>
<td>Charlson Comorbidity Index”</td>
</tr>
<tr>
<td>CDR</td>
<td>Causes of Death Registry</td>
</tr>
<tr>
<td>CFR</td>
<td>Case fatality rate</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CIM</td>
<td>Critical illness related myopathy</td>
</tr>
<tr>
<td>CIN</td>
<td>Critical illness related neuropathy</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Covid-19</td>
<td>Coronavirus disease 2019</td>
</tr>
<tr>
<td>CRRT</td>
<td>Continuous renal replacement therapy</td>
</tr>
<tr>
<td>DAD</td>
<td>Diffuse alveolar damage</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Statistical Classification of Diseases and Related Health Problems – 10th revision</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IFR</td>
<td>Infection fatality rate</td>
</tr>
<tr>
<td>IMV</td>
<td>Invasive mechanical ventilation</td>
</tr>
<tr>
<td>kPa</td>
<td>Kilopascal</td>
</tr>
<tr>
<td>LoS</td>
<td>Length of stay</td>
</tr>
<tr>
<td>MICE</td>
<td>Multivariable imputations by chained equations</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>mRR</td>
<td>Marginal risk ratio</td>
</tr>
<tr>
<td>NA</td>
<td>Not applicable</td>
</tr>
<tr>
<td>NIV</td>
<td>Non-invasive ventilation</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>NPR</td>
<td>National Patient Register</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>P/F ratio</td>
<td>Partial pressure of oxygen/fraction of inspired oxygen</td>
</tr>
<tr>
<td>PIN</td>
<td>Personal identification number</td>
</tr>
<tr>
<td>PRISMA</td>
<td>Preferred reporting items for systematic reviews and meta-analyses</td>
</tr>
<tr>
<td>PT-INR</td>
<td>Prothrombin – international normalized ratio</td>
</tr>
<tr>
<td>RAASi</td>
<td>Renin angiotensin aldosterone system inhibitors</td>
</tr>
<tr>
<td>RRT</td>
<td>Renal replacement therapy</td>
</tr>
<tr>
<td>SAPS 3</td>
<td>Simplified Acute Physiology Score 3</td>
</tr>
<tr>
<td>SARS-CoV</td>
<td>Severe acute respiratory syndrome coronavirus</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>Severe acute respiratory syndrome coronavirus-2</td>
</tr>
<tr>
<td>SIR</td>
<td>Swedish Intensive Care Registry</td>
</tr>
<tr>
<td>SIRI</td>
<td>Swedish Intensive Care Registry, influenza and viral infections</td>
</tr>
<tr>
<td>SIRS</td>
<td>Systemic inflammatory response syndrome</td>
</tr>
<tr>
<td>SOFA</td>
<td>Sequential Organ Failure Assessment Score</td>
</tr>
<tr>
<td>SPDR</td>
<td>Swedish Prescribed Drug Register</td>
</tr>
<tr>
<td>STROBE</td>
<td>Strengthening the reporting of observational studies in epidemiology</td>
</tr>
<tr>
<td>SveDem</td>
<td>Swedish Dementia Registry</td>
</tr>
<tr>
<td>T1DM</td>
<td>Type 1 diabetes mellitus</td>
</tr>
<tr>
<td>T2DM</td>
<td>Type 2 diabetes mellitus</td>
</tr>
<tr>
<td>TPR</td>
<td>Total Population Registry</td>
</tr>
<tr>
<td>VOC</td>
<td>Variant of Concern</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
1 Introduction

We initiated the scientific investigations supporting this thesis with the goal of providing an epidemiologic description of patients with sepsis in the ICU. In 2017, an estimated 50 million sepsis cases occurred globally, with an approximate mortality rate of 20% (1). Survivors of intensive care-treated sepsis face potential long-term consequences, such as persistent organ dysfunctions and a diminished health-related quality of life (HRQoL). While short-term effects, especially mortality, are well-documented, the understanding of long-term effects remains incomplete (2).

As the coronavirus disease 2019 (Covid-19) emerged and overwhelmed healthcare systems, hospitals and intensive care units (ICUs) worldwide, it became evident that there was a substantial lack of knowledge about various aspects of the disease. Simultaneously, a wealth of data was being generated, and reported into registries, providing an opportunity to extract valuable insights. Recognizing this, we redirected our efforts to investigate these data. Although epidemiologic features of Covid-19 were beginning to be described, many risk factors for transmission, severe disease, and mortality remained largely unknown (3). Finally, the long-term consequences for severe cases were inadequately described.


2 Background

2.1 Critical care

According to the Oxford English Dictionary, critical care is “specialized medical care for patients with acute, life-threatening conditions;...” (4). Critical care refers to specialized medical care provided to individuals with (potentially reversible) life-threatening illnesses or injuries, often in an ICU or a critical care setting within a hospital. The primary goal of critical care is to monitor and support the vital functions of the body, such as the respiratory, cardiovascular, and neurological systems, in order to prevent further deterioration and provide time and means for the patients to improve (5, 6). Swedish ICUs are mainly staffed with specially trained ICU nurses, assistant nurses, physiotherapists and physicians, in most cases anesthesiologists (i.e., specialists in anesthesia and intensive care), sometimes further sub-specialized in critical care.

2.2 Sepsis

The syndrome of sepsis has been defined in several, similar ways over the past decades. The definitions have in common the concept of sepsis being the result of the injurious effects of the host response to an infection. Sepsis is associated with poor outcomes (7) and in everyday work in our ICU, patients with septic shock are among the most demanding and rewarding to care for.

2.2.1 Definition of sepsis

Sepsis and its degrees of severity have been defined on three separate occasions at international consensus conferences in 1991, 2001 and 2016 (8-10).

2.2.1.1 Sepsis-1 and Sepsis-2

In our studies, patients enrolled with sepsis are defined by the Sepsis-2 definition based on the 2001 sepsis consensus conference (9) adopted by the Swedish Intensive Care Registry (SIR) (11). The Sepsis-2 definition, with no changes from the original sepsis conference definition (8), is divided into three degrees of severity in patients fulfilling the criteria of systemic inflammatory
response syndrome (SIRS) caused by a suspected or confirmed infection: sepsis, severe sepsis and septic shock (Table 1).

**Table 1. Sepsis according to the Sepsis-2 criteria as adopted by the SIR, for adults.**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
</table>
| Systemic inflammatory response syndrome (SIRS) | At least two of four symptoms:  
- Body temperature outside the range of 36–38°C  
- Heart rate >90 beats per minute  
- Respiratory rate >20 /min or paCO₂ <4.3 kPa  
- White blood cell count outside the range 4–12 x 10⁹ cells/l or >10% immature forms |
| Sepsis | SIRS caused by a suspected or confirmed infection |
| Severe sepsis | Sepsis with at least one of three criteria:  
- Hypotension: systolic or mean blood pressure <90 or <70 mmHg, respectively  
- Hypoperfusion: blood lactate >3 mmol/l or >1 mmol/l above normal range; alternatively a base excess ≤-5  
- Organ failure:  
  - Oliguria, <0.5 ml/kg/h for ≥2 consecutive hours despite adequate fluid resuscitation  
  - Hypoxia, paO₂/fiO₂ <33 or, if lung is the focus of infection, <27 kPa  
  - Coagulopathy, blood platelets <100 x 10⁹/l, PT-INR >1.5 or aPTT >60 sec.  
  - Neurologic deterioration, e.g., confusion  
  - Hyperbilirubinemia, serum-bilirubin >45 µmol/l |
| Septic shock | Severe sepsis with hypotension not reversed by adequate fluid resuscitation |

**2.2.1.2 Sepsis-3**

The Sepsis-3 definitions are increasingly being used worldwide, and the definitions are also implemented in the SIR. Contrary to previous definitions, Sepsis-3 does not use the SIRS concept. Furthermore, there are only two degrees of sepsis: sepsis and septic shock. The key concept of an “injurious response to an infection” has been revised to a “dysregulated response”. Sepsis is now defined as “life-threatening organ dysfunction caused by a dysregulated host response to infection,” clinically defined as a worsening of the Sequential Organ Failure Assessment Score (SOFA) by ≥2 units as a consequence of the infection. This means that sepsis according to Sepsis-3 is substantially more similar to severe sepsis than sepsis according to Sepsis-2. Septic shock is defined as sepsis with circulatory compromise requiring vasopressors to retain a mean arterial pressure of ≥65 mmHg and a serum lactate >2 mmol/l despite
adequate fluid loading (12). SOFA is explained under the heading 2.7 Risk scores below.

2.2.2 Pathophysiology of sepsis

When bacteria, fungi or viruses bypass the outer barriers of the body (e.g., the skin and mucous membranes), the invading organism is detected through pattern recognition receptors (PRRs) by the local macrophage population and other cells of the innate immune system of the invaded tissue (13). The PRRs react to pathogen-associated molecular patterns expressed by the microorganisms and activate immune cells. Proteins and cellular components emanating from damaged tissues and damage-associated molecular patterns add to the activation. The activated macrophages secrete pro-inflammatory compounds to the surrounding tissues. Interleukin (IL)-1β, IL-6, IL-12 and tumor necrosis factor alpha, chemokine 2 and 5 are examples of such compounds (14). This secretion induces a local inflammatory reaction aiming at confining and killing the invading microorganisms. If this containment fails and parts of damaged tissues and microorganisms spread systemically, a widespread immune activation may ensue from the activation of PRRs on immune cells in distant tissues (15). If the immune activation is severe enough, it may cause organ dysfunction and reach the diagnostic level of sepsis or septic shock.

2.2.3 Epidemiology of sepsis

Reports on annual incidence of sepsis range from 131 cases per 100 000 residents in the United States to 1414 in the Faroe Islands (16-19). In Sweden the annual sepsis incidence has been reported between 149 and 780 per 100 000 residents. In 2015 the higher number was estimated in a small observational study (20). However, in 2020, Rudd et al. estimated the worldwide sepsis incidence from hospital records and death certificates (1). They found an age-standardized yearly incidence of 677 globally and 149 per 100 000 inhabitants in Sweden. A meta-analysis on claims and administrative data found an annual incidence of hospital-treated sepsis of 189 per 100 000, and the annual incidence of ICU-treated sepsis was 58 per 100 000 (21). The prevalence of sepsis in ICU admissions was reported at 30% in a worldwide survey including 10 069 patients (22). A similar prevalence was reported from England (23).

2.2.3.1 Sepsis mortality

In a 2020 meta-analysis, the hospital mortality in hospital-admitted patients with sepsis was 27% and in ICU patients 42% (21). From ICUs in England close to 200 000 cases of severe sepsis and just over 150 000 cases of septic shock (according to the Sepsis-2 definitions) were retrospectively identified between 2011 and 2015. Hospital mortality in severe sepsis decreased from 33% in 2011 to 30% in 2015, while hospital mortality in septic shock decreased from 37% to 33%; however, the temporal trend was not statistically
significant. When comparing Sepsis-2 severe sepsis and septic shock to Sepsis-3 sepsis and septic shock there was no difference between severe sepsis (Sepsis-2) and sepsis (Sepsis-3). However, according to the Sepsis-3 definitions, septic shock had a hospital mortality of 56%, significantly higher than the 35% for cases identified by Sepsis-2 definitions (23). In a Swedish cohort with ICU-treated sepsis patients (severe sepsis or septic shock according to the Sepsis-2 definitions) in 2016, the 30-day mortality was 32%, and one-year mortality was 45% (24).

2.3 Acute respiratory distress syndrome

In 1967 Ashbaugh et al. published a case study of 12 adults in respiratory distress resembling the respiratory distress syndrome seen in neonatal children (25). They described the syndrome strikingly: “The clinical pattern, which we will refer to as respiratory-distress syndrome, includes severe dyspnœa, tachypnœa, cyanosis that is refractory to oxygen therapy, loss of lung compliance, and diffuse alveolar infiltration seen on chest X-ray.” Since then the acute respiratory distress syndrome (ARDS) has received vast attention in the scientific literature.

2.3.1 Definition of ARDS

The first diagnostic criteria for ARDS were enunciated in 1992 by the American-European Consensus Conference (26) in an effort to facilitate research into the syndrome. The definition was based on hypoxic respiratory failure with acute onset and bilateral opacities on chest x-ray in absence of evidence of left ventricular failure. In 2012 the diagnostic criteria were updated (the Berlin definition) adding stages of severity to the diagnosis (27) and improving the prognostic properties of the diagnosis. ARDS is now defined as hypoxic respiratory failure within a week from a clinical insult, with bilateral opacities on chest x-ray (not fully explained by effusions, collapse or nodules). Furthermore, the respiratory failure should not be fully explained by left ventricular failure or volume overload. The grading of ARDS is based on the P/F ratio with <13.3, <26.6 and <40.0 kPa setting the limits for severe, intermediate and mild ARDS. For severe and intermediate ARDS, invasive mechanical ventilation (IMV) with positive end expiratory pressure ≥5 cmH₂O is mandatory, but for mild cases, non-invasive, continuous positive airway pressure ≥5 cmH₂O is sufficient.

2.3.2 Pathophysiology of ARDS

As ARDS is a syndrome and not a disease, the pathophysiology is diverse regarding the underlying condition causing the ARDS. Also, several diseases
(e.g., idiopathic pulmonary fibrosis, diffuse alveolar hemorrhage and Goodpasture’s syndrome) can, especially if there has been an insult within the past week, be mistaken for the process that was intended to be captured with the syndrome definition (28). The causes of ARDS are divided into intrinsic causes, such as thoracic trauma and viral or bacterial pneumonia, and extrinsic causes, such as non-pulmonary sepsis or trauma (29). The normal human lungs contain about 500 million alveoli, each around 0.2 mm in diameter, which are the sites for gas exchange between the atmosphere and the erythrocytes (30). Innermost is the air-filled cavity lined with an epithelium composed of alveolar type 1 (AT1) and type 2 (AT2) cells. The AT1 cells are large and very thin, allowing gas exchange, and the AT2 cells are more cuboid, secreting surfactant (a surface-tension lowering compound). These cells are connected with tight junctions, keeping the fluid in the underlying interstitial space from entering the cavity and also actively pumping electrolytes and fluid through the basal membrane into the interstitium. The interstitial fluid is drained into the lymph, and an array of capillaries traverse it, exposing the red blood cells to the alveolar gas (31). An inflammatory insult triggers the early phase of ARDS, which is characterized by interstitial and then alveolar edema, hyaline membrane formation, and an accumulation of immune cells, causing endothelial disruption and epithelial damage, leading to deaeration of parts of the lungs. The hyaline membranes are formed from fibrin and limit both fluid escape into the alveoli and gas exchange (Figure 1). This histological picture is called diffuse alveolar damage (DAD). In the later phase of ARDS, there is proliferation of AT2 cells and, if recovery ensues, transformation of AT2 into AT1 cells, recreating the normal histology of the alveolus. The repair process may be complicated by fibrosis, leading to a chronic impairment of lung function (29).
2.3.3 Epidemiology of ARDS

The global LUNG SAFE study reported an ARDS prevalence of 10% in roughly 29,000 included ICU patients. The incidence was highest in Oceania, followed by Europe and North America. From the study it was also evident that physicians are prone to overlooking the ARDS diagnosis, especially in the milder cases (32). From other ICU cohorts the prevalence is very diverse, being reported at between 3.7 and 19%. The temporal trends in incidence and mortality are unclear (33).

2.3.3.1 ARDS mortality

In the LUNG SAFE study, the hospital mortality was higher than the 28-day mortality and accounted for 35%, 40% and 46% in mild, intermediate and severe disease (32). Other cohort studies report very diverse hospital-, 30- or 90-day mortality at 27–56% (33).

2.4 Covid-19

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) resembles other beta coronaviruses such as SARS-CoV (34) and the Middle East respiratory syndrome CoV (35), having caused outbreaks in past decades (36). Since late 2019, the SARS-CoV-2 virus has spread globally, causing Covid-19. The first Swedish case was confirmed on 4 February 2020, and the first
ICU admission with the syndrome was on 6 March 2020 (37). During the initial wave of Covid-19, Swedish ICUs increased the number of beds by several hundred percent. Our ICU went from an eight-bed general ICU to a 23-bed unit over a few weeks. In parallel to this we tried to understand the disease and how to treat the affected patients. During the pandemic the virus has continuously mutated, causing new variants with evolving properties. The main types of the virus (variant of concern, VOC) with vast pandemic spread, are, so far, in temporal order: the wild type, Alpha, Beta, Gamma, Delta and Omicron. Each VOC has had an increased transmissibility from the prior VOC and, at least regarding Omicron, lessened virulence (38).

2.4.1 Pathophysiology of Covid-19

Like other CoV, SARS-CoV-2 surface spike glycoproteins bind to the cellular surface receptor angiotensin-converting enzyme 2 (ACE2) (36) (Figure 2). ACE2 is densely distributed in airway multiciliate epithelial cells, AT2 cells and enterocytes of the small intestine. The distribution correlates with end-organ affection during clinical disease. Moreover, ACE2 is abundant in smooth muscle and endothelial cells of arteries and veins (39).
Figure 2. SARS-COV-2 virus cellular entry.
The figure was produced in Biorender.com.
The physiological role of ACE2 is to degrade angiotensin II to angiotensin, which means its effect is the opposite of that of ACE (40). Viral entry into human cells is mainly facilitated by the protease TMPRSS2, which activates the fusion of the virus with the cell once the spike protein has bound to the ACE2 receptor. Other, less efficient, modes of viral entry use endosomes (41).

The infection, following viral entry into the host cells of the nasopharyngeal mucosa, spreads to the lower airways via aspiration of mucus or through inhalation of virus particles. However, in the Omicron variants, which have higher affinity for ACE2 compared with older SARS-CoV-2 variants, the TMPRSS2 is less efficient. This mainly affects the viral entry into AT2 cells, possibly explaining the milder course of Omicron pneumonia (42). The virus also spreads throughout the body via the circulatory system, both as free virus and in macrophages that have phagocytosed it. The spread of the infection leads to varying degrees of inflammatory response responsible for the nature and degree of organ injury and dysfunction in Covid-19 (43). Severe Covid-19 and Covid-19 mortality is mainly caused by Covid-19-associated ARDS with DAD ensuing from destruction of AT2 cells and subsequent inflammatory reactions. Imbalance between thrombosis and fibrinolysis in the lung microvasculature is also a prominent feature of DAD in Covid-19 (41).

2.4.2 Clinical picture of Covid-19

The most common presenting symptoms of Covid-19 infection are fever, respiratory complaints, fatigue and neurological and gastrointestinal symptoms (Table 2) (44).

**Table 2. Common onset symptoms of Covid-19 (44)**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Relative frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>58%</td>
</tr>
<tr>
<td>Cough</td>
<td>54%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>31%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>28%</td>
</tr>
<tr>
<td>Malaise</td>
<td>27%</td>
</tr>
<tr>
<td>Respiratory secretions</td>
<td>25%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>25%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>22%</td>
</tr>
<tr>
<td>Neurological symptoms</td>
<td>20%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>16%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>15%</td>
</tr>
<tr>
<td>Sore throat</td>
<td>14%</td>
</tr>
<tr>
<td>Sneezing</td>
<td>13%</td>
</tr>
<tr>
<td>Headache</td>
<td>12%</td>
</tr>
<tr>
<td>Goosebumps</td>
<td>11%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10%</td>
</tr>
</tbody>
</table>
The major cause of ICU admission is respiratory failure due to pneumonitis and ARDS. However, severe disease may also be caused by venous thromboembolism, cardiac injury and acute kidney injury (45). The main cause of ICU mortality in admitted Covid-19 patients is refractory respiratory failure, followed by shock with multi-organ failure, and cardiac death (pulmonary embolism or unexpected cardiac arrest) (46).

2.4.3 Epidemiology of Covid-19

The estimated worldwide case fatality rate (CFR) based on national data was, at the beginning of the pandemic, 2–3% (47). In the Stockholm region the 30-day infection fatality rate (IFR) was estimated at 0.58% (95% CI 0.37–1.05), with higher IFR with greater age. The corresponding CFR for the same period (i.e., spring 2020) and population was 25.9%. Both IFR and CRF in these studies are subject to a risk of bias because of restricted testing policies and asymptomatic infections. IFR differs from CFR in that it is an estimate of infected individuals rather than confirmed cases, the latter of which were highly affected by the limited testing capacity at that time (48). Later in the pandemic the IFR of the Omicron variant was estimated at 6.2 (CI: 5.1–7.5) per 100 000 infections in Danish blood donors (49).

In the beginning of the pandemic several risk factors for severe Covid-19 disease and mortality were suggested. In different models and ICU populations greater age was the most important risk factor for hospital admission (50), ICU admission (51) and ICU mortality (52, 53). Other proposed risk factors for ICU admission and mortality were male sex or gender (51, 53, 54), chronic pulmonary disease (53), diabetes (53, 55), heart failure (51), ischemic heart disease (56), obesity (51), hypertension (55, 57) and also social factors (47). It has been suggested that several chronic medications might affect the risk of severe Covid-19 and death. Much interest has been shown in renin-angiotensin-aldosterone system inhibitors (RAASi) due to the central role of the ACE2 receptor in cellular virus entry (36). However, an excess risk of clinical, severe or terminal disease from RAASi was not found (53, 58, 59). Statins have been suggested as potential protective agents against severe disease and Covid-19 mortality due to their anti-inflammatory and antithrombotic properties (60); however, there was conflicting evidence regarding the clinical effect on outcome (61-63).

2.4.4 Long-Covid

Early during the pandemic, it was already obvious that apart from differing acute disease severity, the persistence of disease symptoms of Covid-19 was also widely different in patients. It has been uncertain whether these longer-term symptoms were related to the acute disease severity (64). However, long-
Covid symptoms are more frequent in hospitalized than non-hospitalized patients (65).

2.4.5 Return to work after Covid-19

Return to work is a proxy for functional recovery (66, 67), and previous small cohort studies report a wide range of proportions of return to work during different time frames after hospital or ICU admission with Covid-19 disease (41–98%) (68-75). However, return to work or persisting sick leave has not been evaluated in statistical models using relevant control groups. In Sweden, paid sick leave is a privilege available to all employed individuals and individuals in the working-age population who are registered as actively searching for employment. After an initial week of self-reported sickness, a medical certificate from a physician is necessary to benefit from continued sick leave. From this it can be understood that, beyond the first week, being on sick leave or not is a decision made after a medical assessment. The medical assessment is aimed at the functional reserve of the patient and can, as such, be used as a proxy for functional recovery.

2.5 Dementia

In the International Statistical Classification of Diseases and Related Health Problems – 10th revision (ICD-10) – of the WHO, dementia is defined: “Dementia (F00-F03) is a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement.” (76). The definition also states that consciousness should not be affected, nor should a temporary delirium be present. Finally, there is usually an impact on motivation, social behavior or emotional control. From this, it follows that the symptoms of dementia impair daily functioning and may severely affect HRQoL (77). Dementia also has an extensive impact on the life of the affected individual’s family (78).

2.5.1 Pathophysiology of dementia

In the research into, and clinical management of, dementia and its underlying diseases, it is increasingly important to differentiate between the cognitive consequence (i.e., dementia) and the underlying disease (e.g., Alzheimer’s disease, AD), as specific therapies against the underlying diseases are evolving (79, 80). The evolvement of the underlying disease to clinical dementia is usually slow and gradual, as in the case of AD (81) or vascular dementia (82).
2.5.1.1 Pathophysiology of Alzheimer’s disease

At autopsy, amyloid plaques, partly consisting of polymerized amyloid beta, and infiltration of blood vessel walls with amyloid beta and intracellular neurofibrillary tangles of hyperphosphorylated tau filaments are found. The changes are most densely concentrated in the temporal lobes and the nucleus basalis of Meynert (79, 83). Amyloid beta consists of small, lipid-soluble peptides normally found in small amounts. In AD, however, there is an imbalance in the production and metabolism of amyloid beta, causing the formation of toxic amyloid or neuritic plaques with inflammatory properties, most prominent in the early-onset form of AD. Several models have been proposed to explain the pathophysiologic causes of late-onset AD. Research indicates that disease severity correlates poorly with the amount of amyloid plaque but greatly with neurofibrillary tangles and amyloid beta oligomers outside the plaques (84). Increased levels of phosphorylated tau protein in tau fibrils are also suspected elements of the pathophysiology (85). In recent years two monoclonal antibodies against amyloid beta, aducanumab and lecanemab, have been approved for treatment of mild cognitive impairment and mild dementia in the setting of Alzheimer’s disease in the USA. However, the antibodies’ merits are disputed (86).

2.5.1.1.1 The cholinergic hypothesis

Cholinergic signaling is important in memory function. In this context the anticholinergic drug scopolamine has been shown to impair short-term memory in normally functioning adults (87). Moreover, chronic use of anticholinergic drugs is associated with reduced cortical volume on magnetic resonance imaging and worse memory and executive function (88). Additionally, the nucleus basalis of Meynert, which is found to begin a gradual loss of volume in preclinical AD (89, 90), is the origin of cholinergic neurons projecting into the cortex. The degenerative changes found here are thought to be of importance in symptomatic AD (91). Finally, besides the antibodies against amyloid beta, the only drugs proven to alleviate symptoms in AD, the cholinesterase inhibitors, target this system.

2.5.1.1.2 Underlying causes of cell death

Brain macrophage (microglial) activation, and activation of other immune cells, and an increase of inflammatory proteins in the affected areas, have been reported in AD (92, 93).

2.5.2 Epidemiology of dementia

The prevalence of dementia increases rapidly with age. In a Swedish cohort of 298 individuals ≥75 years of age, it was approximately 18% (94). In another Swedish cohort of 70- and 75-year-olds, the prevalence was 2–2.2 and 5–6%, respectively. There are conflicting views on the secular trend in dementia
prevalence by age in Western Europe, but it may be slightly decreasing (95). However, worldwide, the incidence of dementia is rapidly increasing, possibly due to aging populations (85). AD is the most common cause of dementia (estimated at 50–70%) (85, 96). Lewy body and vascular dementias are the second and third most prevalent causes of the dementia syndrome, followed by frontotemporal dementia and several less common neurologic diseases (79, 97, 98). In AD, except for the early onset variant, age is the most important risk factor. Sex, hypertension, cerebrovascular diseases, diabetes mellitus (DM), obesity, smoking, certain nutritional insufficiencies and head trauma are other risk factors of varying importance. There are also genetic predispositions that make up important risk factors, such as the existence of the apolipoprotein E ε4 allele. As opposed to late-onset AD, early-onset AD is predominantly caused by mutations in a precursor protein to the amyloid beta peptide (83).

2.5.3 Sepsis and dementia

Inflammation is a vital pathophysiologic factor in AD (84) and atherosclerosis in vascular dementia (99, 100). These pathophysiologic factors are the mechanistic explanation for the theoretic link between sepsis and dementia (101). In rodents exposed to experimental sepsis, histologic and cognitive disturbances compatible with dementia have been demonstrated (102, 103). These consequences of sepsis are reflected in humans showing persistent cognitive disturbances associated with septic encephalopathy (104-106). Moreover, dementia has been linked to hospital- and ICU-treated sepsis of varying severity in cohort and case-control studies (107-109).

2.6 Registries

In Sweden there are >100 quality registries, of which most are related to an organ or a diagnosis, such as the SWEDHEART for heart disease or Nationella prostatacancerregistret for prostate cancer. Other registries are targeted toward a process, e.g., Svenska perioperativregistret, which targets the perioperative process, or a level of care, such as the SIR, targeting intensive care unit admissions. Moreover, the quality registries are divided into four certifying levels, where level 1 is the highest and level 4, or K, is a candidate level. At level 1 the demand for data validation and proportion of included patients is high (110). There are also several governmental registries used for research despite their purpose being to deliver data to the government. The data collection for these registries is governed by statutory and common law, and as such, they have (almost) complete coverage relating to their purpose.
2.6.1 The Swedish Intensive Care Registry

The SIR is a quality registry certified at level 1. The proportion of actively reporting general ICUs has increased from 62% in 2006 to 100% in 2017 (111, 112). Administrative data, intensive care diagnoses, interventions and complications for virtually all patients admitted to general ICUs in Sweden are registered in the SIR (113). It receives data on vital status from the Population Statistics, with some delay. The SIR was used to identify the full population in Papers I, II and IV. Moreover, the critical care populations for Paper III and V were collected from the registry. The SIR also provided data on some demographics and data on the ICU admission for Paper I through V. Finally, the registry provided data on ICU mortality for paper III.

2.6.1.1 The Swedish Intensive Care Registry for influenza and viral infections

The SIR’s sub-registry, the Swedish Intensive Care Registry for influenza and viral infections (SIRI), contains limited data on all admissions with epidemic viral infections: originally only influenza was listed, but from February 2020, Covid-19 (114) was added. To register a care episode in SIRI a positive polymerase chain reaction to influenza or SARS-CoV-2 is required. During the Covid-19 pandemic, swift reporting of all eligible patients was of high priority. The SIRI has also been used to validate Covid-19 admissions in the SIR. The sub-registry provided the cohort for Paper III.

2.6.2 The National Patient Register

All specialized care in Sweden is reported to the National Patient Register (NPR), with its two sub-registries, the inpatient and outpatient registries. The NPR was established by the Swedish Board of Health and Welfare as a statistics and research tool. Reporting of demographic and administrative data, diagnoses and interventions is mandatory (115). The inpatient section has more than 99% coverage, and the validity of the diagnostic coding is estimated at 85–95% (116). The NPR provided data on comorbidity for Paper I through V and on an exclusion criterion and the outcome in Paper I.

2.6.3 The Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register (SPDR) is a nationwide database with complete coverage of all dispensed prescription drugs in Sweden (117). Like the NPR, the SPDR was established by the Swedish Board of Health and Welfare as a statistics and research tool. The dispensing pharmacies, report anatomic therapeutic chemical classification system (ATC), drug name, generic name, concentration or strength and amount is governed by law.
2.6.4 The Causes of Death Registry
The Causes of Death Registry (CDR), established, again, by the Swedish Board of Health and Welfare, contains information on all deaths in Sweden since 1952 and is widely used in research, statistics, planning and quality assurance. All deaths in Sweden are reported to the registry by the ascertaining physician. At the same or a later time point, the underlying and direct causes of death are reported by a physician (118). The Registry provided data on vital status for Paper I, II and III through V.

2.6.5 The Swedish Dementia Registry
All Swedish specialized memory units and, increasingly, primary care units report patients with newly diagnosed dementia to the Swedish Dementia Registry (SveDem) (119). The SveDem is an instrument to improve the quality of diagnostics, treatment and care of patients with dementia. It contains demographic information, test scores and diagnoses. The SveDem is certified at level 2 and provided data on an exclusion criterion and the outcome in Paper I.

2.6.6 The Total Population Registry
Microdata on the Swedish population is gathered and stored in the Total Population Registry (TPR) by the government agency Statistics Sweden (120). The TPR provided the population control populations and data on demographics for Paper III and V.

2.6.7 The Swedish Social Security Agency Registry
The Swedish Social Security Agency keeps a registry on all sick leave and sickness (disability) pension that they administer. The first two weeks of a sick leave period, in employed individuals, is paid for by the employer and is not added to the registry. Sick leave and sickness pension can be approved at 25, 50, 75 and 100% and can also be combined in such a way that an individual, temporarily, has more than 100% combined sick leave and sickness pension. The Swedish Social Security Agency provided us with data on sick leave and sickness pension for Paper V.

2.7 Risk scores
There is keen interest in predicting outcomes in hospitalized and ICU-admitted patients. The most important use of risk scores is benchmarking between care providers and between patient groups. However, risk scores are also used
in statistical modeling (24, 121). The scores are validated on populations and must not be used to predict outcomes in individual patients.

2.7.1 Charlson Comorbidity Index

The Charlson Comorbidity Index (CCI), comprises 17 comorbid diseases and predicts one-year mortality after hospital admission (122). The index was updated with the ICD-10 codes and validated against several cohorts by Quan et al. in 2005 and 2011 (123, 124). In the update, the predictive comorbidities were reduced to 12 and given new weights (Table 3). The CCI is frequently used as a compound measure of comorbid status in research populations and we used the score as such in Papers I, II and V.

Table 3. The Updated Charlson Comorbidity Index (124)

<table>
<thead>
<tr>
<th>Comorbid condition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>2</td>
</tr>
<tr>
<td>Dementia</td>
<td>2</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>1</td>
</tr>
<tr>
<td>Rheumatic disease</td>
<td>1</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>2</td>
</tr>
<tr>
<td>Moderate or severe liver disease</td>
<td>4</td>
</tr>
<tr>
<td>Diabetes mellitus with chronic complications</td>
<td>1</td>
</tr>
<tr>
<td>Hemiplegia or paraplegia</td>
<td>2</td>
</tr>
<tr>
<td>Renal disease</td>
<td>1</td>
</tr>
<tr>
<td>Any malignancy, including leukemia and lymphoma</td>
<td>2</td>
</tr>
<tr>
<td>Metastatic solid tumor</td>
<td>6</td>
</tr>
<tr>
<td>AIDS/HIV</td>
<td>4</td>
</tr>
</tbody>
</table>

Mild and moderate liver disease, as well as any malignancy and metastatic solid tumor, are mutually exclusive.

2.7.2 Acute Physiology and Chronic Health Evaluation II

The Acute Physiology and Chronic Health Evaluation (APACHE) II score is an older severity score mainly used to benchmark ICUs. APACHE II consists of an acute physiologic section, an age section and a comorbidity section (125). A major criticism of APACHE II is that the acute physiologic parameters are measured during the first 24 hours of ICU care, which might favor ICUs who allow their patients to deteriorate during the first day (126). The SIR began phasing out APACHE II in 2008, and 2011 was the last year of its use (127). In Papers I, II and IV, the APACHE II score was used in imputations.
### 2.7.3 Simplified Acute Physiology Score 3

The Simplified Acute Physiology Score 3 (SAPS 3) is a severity score and mortality estimation tool predicting hospital mortality in ICU-admitted patients. However, the SAPS 3 is currently also validated for prediction of 28-, 30-, 60- and 90-day mortality. The score consists of three “boxes”: box I represents what is known about the patient before admission; box II constitutes the circumstances of the admission; and box III corresponds to the physiological derangement at ICU admission (Table 4). By equation, the SAPS 3 can be transformed into a risk of death, an estimated mortality ratio (128, 129). Several such equations are in use and are validated for different healthcare systems and populations (130-132). The SIR began using SAPS 3 in 2008, mainly due to its superior calibration compared with APACHE II (127). The SAPS 3 with modifications was used as a predictor in statistical models in Paper I through IV.

#### Table 4. SAPS 3, boxes I, II, and III (129)

<table>
<thead>
<tr>
<th>Variables as assessed at ICU admission ±1 h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Box I</strong></td>
</tr>
<tr>
<td>Before admission</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Comorbidities</td>
</tr>
<tr>
<td>Hospital LoS before ICU admission</td>
</tr>
<tr>
<td>Hospital location before ICU admission</td>
</tr>
<tr>
<td>Use of vasoactive drugs before ICU admission</td>
</tr>
<tr>
<td><strong>Box II</strong></td>
</tr>
<tr>
<td>The admission</td>
</tr>
<tr>
<td>Planned or unplanned ICU admission</td>
</tr>
<tr>
<td>Surgical status at ICU admission</td>
</tr>
<tr>
<td>Anatomical site of surgery</td>
</tr>
<tr>
<td>Acute infection at ICU admission</td>
</tr>
<tr>
<td><strong>Box III</strong></td>
</tr>
<tr>
<td>The physiological disturbance</td>
</tr>
<tr>
<td>Glasgow Coma Scale (lowest)</td>
</tr>
<tr>
<td>Total bilirubin (highest)</td>
</tr>
<tr>
<td>Body temperature (highest)</td>
</tr>
<tr>
<td>Creatinine (highest)</td>
</tr>
<tr>
<td>Heart rate (highest)</td>
</tr>
<tr>
<td>Leukocytes (highest)</td>
</tr>
<tr>
<td>Hydrogen ion concentration (pH, lowest)</td>
</tr>
<tr>
<td>Platelets (lowest)</td>
</tr>
<tr>
<td>Systolic blood pressure (lowest)</td>
</tr>
<tr>
<td>Oxygenation, P/F ratio* (lowest)</td>
</tr>
</tbody>
</table>

* The P/F ratio is the partial pressure of oxygen in arterial blood divided by the fraction of inspired oxygen
2.7.4 Sequential Organ Failure Assessment Score
The SOFA is a risk score based on laboratory and physiological variables used to follow patients’ disease severity during an ICU admission. The score ranges from 0 to 24 and is based on the P/F ratio, platelet count, s-bilirubin, mean arterial pressure or vasoactive support, level of consciousness and renal function (133).

2.8 Registry research
Compared with research on uncommon diseases, in large hospital settings, national cohorts, such as the Swedish intensive care cohort, have the advantage of high statistical power. Research that would otherwise be extremely expensive can be performed when these large cohorts are combined with the Swedish governmental registries, thereby allowing unrestricted access to mortality, comorbidity and demographic data using the Swedish personal identification number (PIN). The PIN system allows linkage at the individual level to Swedish national registries and other data sources (134). There is considerable controversy about whether the data collected from quality registries are collected prospectively or retrospectively. The study’s design may be retrospective, but data collection for the registries has been made prospectively, before the outcome has occurred (135).

2.8.1 Bias
As with all research, epidemiological studies based on registry data are susceptible to systematic errors or biases. Bias can be divided into selection bias, information bias and confounding bias (136). Registry studies, in particular, require special considerations related to the classification of exposure, outcome, availability of information regarding confounders, and the selection of research subjects (134).

2.8.2 Information bias
Information bias is linked to misclassification, which occurs when the exposure or outcome of interest is erroneously classified. Misclassification can be categorized into two different types, not mutually exclusive: differential or nondifferential and dependent or nondependent. Differential means that the misclassification of the exposure is related to the true level of the outcome, or vice versa. Dependent means that a measurement error of the exposure (or the outcome) affects the risk for measurement error of the outcome (or the exposure) (137). Regarding exposure, recall bias is a common form of information bias in studies where the exposure is not prospectively recorded, which may
or may not be the case in registry studies. Recall bias is usually differential in the sense that recall is related to the outcome. The risk for dependent misclassification is greater if the exposure and the outcome is measured with the same method or instrument. The impact of nondifferential and independent misclassification in a dichotomous variable usually results in a dilution of the effect. However, for exposures with more than two levels, the effect may remain unchanged, diluted, or increased (134, 136, 138). Depending on the proportion of individuals with differential or dependent misclassification, the potential effect of the exposure on the outcome is over or underestimated.

2.8.3 Selection bias

Selection bias is associated with how the participants were chosen for the study. Any imbalance in the relation between the exposure and outcome in the selected population compared to the underlying population, to which the results are extrapolated, causes bias (136). However, under some circumstances, if the researcher has access to a variable that explains the difference between the selected population and the underlying population selection bias can be dealt with statistically (139). By including the entire population, selection bias is eliminated. However, caution is needed when extrapolating inferences to other, neighboring populations. In a case-control study matching cases to controls may introduce bias if the matched variable is related to the outcome, but this can be amended by controlling for the matching factors (140). Nevertheless, efficiency may be increased (139).

2.8.4 Confounding

Confounding literally means “confusion of effects” (136), i.e. an apparent effect caused (in part or fully) by another effect. The confounding factor must influence both the exposure and the outcome.

2.8.5 Directed acyclic graphs

Unlike selection bias (not caused by missing values) and most information bias, confounding can be dealt with statistically by stratification or statistical modeling. To correctly choose the model variables, the paths between variables have to be correctly identified as confounding pathways, mediating pathways or colliding pathways. If a factor is caused or prevented by the exposure and affect the outcome it is an intermediate factor, a mediator, in the casual pathway (134, 136). A collider is a variable which is affected by both the exposure and the outcome. Adjusting for a mediator will dampen the effect of the exposure on the outcome (i.e. remove the direct effect of the mediator), and adjusting for a collider will introduce confounding. A directed acyclic
A directed acyclic graph (DAG) is a tool to facilitate this classification. Figure 3 is a small example of a DAG.

Figure 3. Directed acyclic graph example

Sepsis is evaluated as a risk factor for incident renal failure. Hypotension is a mediator, as it is caused by sepsis and causes renal failure. Chemotherapy is a confounder, as it is a cause of both sepsis and renal failure. Finally, anemia is a collider, as it is caused by both sepsis and renal failure. The figure was produced on the dagitty.net web page.
3 Aims

This project aimed to assess risk factors, and short- and long-term outcomes in critical care; more specifically, to evaluate sepsis as an independent risk factor for later morbidity and mortality and also to identify risk factors for critical Covid-19, short-term mortality and longer-term functional recovery associated with Covid-19. The specific aims of the studies were to:

Paper I Evaluate severe sepsis and septic shock as a risk factor for later dementia development.

Paper II Evaluate severe sepsis and septic shock as a risk factors for mortality and describe the pattern of causes of death over long-term follow-up.


Paper IV Investigate the relative importance of specific risk factors for short-term mortality in Covid-19, sepsis and ARDS.

Paper V Investigate the degree of sick leave as a surrogate measure of functional recovery in ICU-admitted patients with Covid-19 compared with hospitalized patients with Covid-19 and population control individuals.
4 Materials and methods

Paper I is a cohort study on the risk of incident dementia among all adult patients in the SIR admitted to the ICU from 2005 to 2015.

Paper II is a cohort study on long-term mortality and causes of death in patients in the SIR admitted to the ICU from 2005 to 2016.

Paper III is a case-control and cohort study on risk factors for ICU admission and mortality in Swedish Covid-19 patients.

Paper IV is a cohort study on the relative importance of risk factors for 60-day mortality after ICU admission with Covid-19, sepsis or ARDS.

Paper V is a cohort study on the long-term burden of sick leave after ICU admission with Covid-19, compared to non-ICU hospital admission with Covid-19 and population controls.

4.1 Registration

All studies were prospectively registered with primary clinical trials registries: Papers I and II were registered with the Australian and New Zealand Clinical Trials Registry (registration no: ACTRN12618000533291 and ACTRN12619001281189); Papers III, IV and V were registered with ClinicalTrials.gov (registration no: NCT04390074; NCT04542538; and NCT05054608). The reporting of our cohort and case-control studies follow the STROBE (Strengthening the reporting of observational studies in epidemiology) statement (143).
4.2 Definitions

In this section core terms are defined.

4.2.1 Sepsis definition

In the present studies we have focused on severe sepsis and septic shock as a common cold might reach the diagnostic threshold of sepsis according to Sepsis-2. Until 2011, severe sepsis and septic shock were reported with the ICD-10 diagnosis code A49.1. From 2011 until the present, severe sepsis (or sepsis according to Sepsis-3) is reported with the ICD-10 code R65.1 and septic shock with the code R57.2 (144). In the SIR, sepsis is one of a few prioritized diagnoses that have to be confirmed or negated at reporting. In the following methods, results and discussion sections, Sepsis is used to report severe sepsis or septic shock when referring to groups and patients in our cohorts.

4.2.2 Dementia definition

For Paper I we defined dementia using the updated CCI dementia definition (124)(Table 5).

<table>
<thead>
<tr>
<th>Updated CCI</th>
<th>F00.x–F03.x, F05.1, G30.x, G31.x</th>
</tr>
</thead>
</table>

4.2.3 Covid-19 definition

The WHO defines suspected, probable and confirmed Covid-19 cases by the degree of certainty of SARS-CoV-2 infection (145). However, to the SIR and SIRI only confirmed cases, i.e., those with a positive polymerase chain reaction to SARS-CoV-2 ribonucleic acid, are reported. Reporting to the SIR is validated to the ICD-10 code U07.1 in the SIR (and vice versa), where the same criteria as for the SIRI apply. For Paper III we defined a Covid-19 patient by a registration with Covid-19 in the SIRI, as reporting to SIRI was done at admission. In Papers IV and V, we defined a Covid-19 patient by a Covid-19 ICD-10 code in the SIR.

4.2.4 ARDS definition

ARDS is, like Sepsis, a prioritized diagnosis by the SIR and is defined by the ICD-10 code J80.9x. The SIR used the American-European consensus conference on the ARDS (26) definition until 2015. From 2016 the Berlin definition (27) was used (144).
4.3 Data collection and cohorts

Data were requested from the registries after we were granted ethical approval.

4.3.1 Data collection and cohort – Paper I

The SIR identified all adult patients with a PIN admitted to Swedish ICUs from 2005 to 2016 and sent their PINs to the Swedish Board of Health and Welfare. The board coordinated data delivery and created a pseudonymization key. The Board also extracted data on diagnoses and delivered care and demographics from all inpatient visits in the NPR from five years before ICU admission until 2016. The SIR delivered data on vital status, diagnoses, interventions and demographics from the ICU admissions. From the SveDem, we received data on dementia diagnoses and CDR provided data on vital status until 2016. As the outcome was incident dementia more than one year after ICU admission, we excluded patients admitted in 2016 in order to have at least one day of follow-up in all individuals. Also, patients who died or received a diagnosis of dementia within one year of ICU admission were excluded. The patients were divided into two groups: patients with a sepsis diagnostic code during ICU care were allocated to the Sepsis group and patients without a sepsis diagnostic code, to the Non-sepsis group.

4.3.2 Data collection and cohort – Paper II

The cohort for Paper II was similar to that for Paper I. However, from patients admitted to ICUs in 2005 to 2016 we excluded children and individuals (admissions) lacking a PIN. We used the same NPR data, but data on vital status and cause of death was extended until June 2020. The patients were divided into two groups: patients with and without a sepsis diagnostic code during ICU care, the Sepsis and Non-sepsis groups.

4.3.3 Data collection and cohort – Paper III

The SIR identified all patients registered in the SIRI with Covid-19 until 27 May 2020 and sent PINs and patient data, including vital status at discharge, to Statistics Sweden. Patients (admissions) without a PIN were excluded. Statistics Sweden created a pseudonymization key and identified population controls, matched for age and sex, four per patient, from the TPR. The key file was sent to the Swedish Board of Health and Welfare, who coordinated data delivery from the NPR, the in- and outpatient sub-registries and the Prescribed Drug Register.
4.3.4 Data collection and cohort – Paper IV
Patients admitted to an ICU on 6 February, 2020 to 16 June, 2021 and coded with Covid-19 (ICD-10 code U07.1) were identified by the SIR, giving the Covid-19 group. These patients’ outcomes were compared with the outcomes of patients admitted to an ICU between 2011 and 2016 and coded with Sepsis (R65.1 or R57.2), the Sepsis group, or coded with ARDS (J80.9x), the ARDS group. The patients in the Sepsis and ARDS groups were identified in the data collection for Papers I and II. Likewise, the patients in the Covid-19 group were identified in the data collection for Paper V. Data on comorbidity were procured from the NPR inpatient section and data on ICU care, demographics and vital status were acquired from the SIR. Finally, vital status was obtained from the CDR.

4.3.5 Data collection and cohort – Paper V
The ICU-admitted Covid-19 patients were identified in the SIR by the ICD-10 code U07.1, the ICU group. The hospital-admitted Covid-19 patients were identified in the NPR inpatient section by the ICD-10 code U07.1, the hospital group. In the TPR, four population controls per ICU patient were identified on the date of admission for the corresponding ICU patient, the population control group. Matching for sex, age and county was performed. Population controls were excluded if they had a history of admission with Covid-19 during the study period. Statistics Sweden coordinated the PIN listings for the three groups, created a pseudonymization key and provided data on demographics, country of birth, work, income and education. Data on ICU care was obtained from the SIR, data on comorbidity was procured from the NPR in- and outpatient parts, data on sick leave was received from the Swedish Social Security Agency, and finally, vital status was obtained from the CDR.

4.4 Statistics
In this section, certain statistical methods are elaborated upon. Moreover, specific methods are outlined for each paper; however, for methodological details the original publications and manuscripts of Paper I to V have to be consulted. Statistical significance was set at p<0.05 (two-sided).

4.4.1 Missing data and imputation
Several of the variables had missing data. In all papers we used multivariate imputation by chained equations (MICE) in an attempt to control the bias from the missing data. MICE is typically used when data is missing at random, i.e., the missingness is linked to some other, measured, variables (i.e. missingness random conditionally on some variable). Several authors state that unless the
missingness is, beyond any doubt, completely at random, the bias from the imputation process will be smaller than the bias from excluding all cases with a missing value (146, 147). In Paper IV imputations were performed in a sensitivity analysis and the main analysis was performed on complete cases only, as requested in the review process. We used the MICE algorithm on all of the predictor variables, on some other variables deemed predictive of the missing variable, and on the outcome variables (147). Imputations were performed to obtain five to 50 datasets, and the outputs from the regression models were pooled according to Rubin’s rule (148).

4.4.2 Continuous variables and restricted cubic splines

Continuous variables are seldom linearly (straight) connected to an outcome; e.g., when predicting mortality using age, there is an exponential relationship where a one-year increase in age from 25 to 26 years is not the same as the increase from zero to one days or 98 to 99 years. To deal with this we applied restricted cubic splines with three to five knots placed at software default loci to neutralize the non-linear nature of the continuous variables in the Cox proportional hazards and logistic regression models of Papers I to V. An exception to this was the conditional logistic regression models in Paper III, where penalized splines were used. The spline allows the line to bend, usually at three to five pre-specified locations (149). That is, RCS can be conceptualized as a piecewise model where each piece is allowed to take a cubic relationship with the outcome, except for the tails where the relationship is assumed to be linear (149). See this illustrative explanation by Gauthier et al., (150) and Figure 4 for a visualization. Cubic or penalized splines are preferred over the transformation of a continuous variable into a categorical variable by grouping of values because there is less information loss. The disadvantage is a more complicated interpretation of the effect of the variables on the outcome and of the statistical significance.
The figure illustrates HRs for incident dementia according to SAPS 3 Score box 2+3 in a Cox model adjusted for some of the variables used in Paper I. Three knots were added at software default loci, at the 10th, 50th, 90th percentiles (reference is the 50th percentile). The curved line indicates HRs, and shadowed areas indicate 95% CIs.

4.4.3 Descriptive statistics

For all studies, we presented descriptive statistics using counts with percentages and medians with interquartile range (IQR), as appropriate. Only a few of the continuous variables had a Gaussian distribution. Crude differences were tested using the Mann-Whitney U test for continuous variables and the Fisher’s exact test or the Chi-square test were used for frequencies.

4.4.4 Logistic regression

Logistic regression is a set of regression methods allowing modeling of two or several levels of an outcome, while adjusting for confounding factors, disregarding the time of observation in each case. The model yields odds ratios for the predictor variables; e.g., the predictor sex:
Odds ratio = \frac{\text{Odds for females}}{\text{Odds for males}}

The difference between odds and risk is in the denominator (151), \textit{i.e.}:

\text{Odds} = \frac{\text{something happens}}{\text{something does NOT happen}}

\text{Risk} = \frac{\text{something happens}}{\text{something COULD happen}}

From this it can be deducted that an odds and a risk are very similar if the outcome happens at a low frequency.

\textbf{4.4.4.1 Binary logistic regression}

Binary logistic regression is used when the outcome has two levels. The method was used in Papers III, IV and V.

\textbf{4.4.4.2 Ordinal logistic regression}

Ordinal logistic regression can be used when investigating case-control study designs with causal effect estimation in the setting of several, ordered outcomes. Also, ordinal logistic regression can be used in place of linear regression in situations where the assumption of a normal distribution of the error term does not hold (152). Ordinal logistic regression was used in Paper V.

\textbf{4.4.4.3 Multinomial logistic regression}

Multinomial logistic regression is used when the outcome has several, unordered, levels. It is commonly used in econometrics with survey data. Its use precludes the need to collapse unordered outcomes to only two categories (153) but at the cost of substantially more degrees of freedom used. Multinomial logistic regression was used in Paper II.

\textbf{4.4.4.4 Conditional regression}

Conditional regression can be employed to address confounding arising from matching cases to controls in case-control studies. The term “conditional” indicates that each stratum of cases and controls is analyzed separately in the regression model (139). In matched cohort studies this approach is not needed (154).

\textbf{4.4.5 Survival analysis}

Survival analysis methods can be crude or model based with adjustment for confounding.
4.4.5.1 Kaplan-Meier estimator

Kaplan-Meier survival curves are a means to visualize survival, *i.e.*, absence of an event such as death, a myocardial infarction or any other event that has a distinct time. Each individual in a Kaplan-Meier analysis provides event-free time from inclusion until end of follow-up. Follow-up may end at the end of study, if the individual has another event that makes the studied event impossible, *e.g.*, death, or if the individual experiences the event. The former two outcomes are examples of censoring. The survival times and events are stored in a life table and then plotted, according to certain rules, in a Kaplan-Meier graph. To make inferences from the graph, the log rank test is most often used (155, 156). Kaplan-Meier plots were used in Papers I and II.

4.4.5.2 Cox proportional hazards regression

Cox proportional hazards regression is a multivariable regression method used on survival data to adjust for confounding. The Cox model yields hazard ratios for the predictors. *E.g.*, given the predictor sex, the hazard ratio for having the outcome of interest during any given time of the observation period can be calculated:

\[
\text{Hazard ratio} = \frac{\text{Hazard for females}}{\text{Hazard for males}}
\]

The Cox proportional hazards model allows the hazards to take any form. However, an important assumption of Cox proportional hazards models is that the hazard ratios are the same over different time spans of the study period (*i.e.*, the hazard form is assumed to be the same for both groups) (157, 158). By splitting the follow up time at one, or several, time points, the model can yield several hazard ratios, one for each time period assuming proportional hazard ratios within each time frame. Cox models were used in Papers I, II and III.

4.4.6 Software packages

Data management and descriptive statistics were performed in SPSS for Windows, version 24, 27 and 28 (Microsoft Inc., IL, USA). Descriptive statistics, imputations, statistical modeling, and figure production were performed in R software version 3.5.3, 4.0.3 and 4.2.3 (The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org). The R software is a basic statistical application allowing extensive programming in R language. However, much functionality is distributed as add-on packages. The R packages used are listed in Table 6.
Table 6. R packages used.

<table>
<thead>
<tr>
<th>Package</th>
<th>Description</th>
<th>Version</th>
<th>URL</th>
</tr>
</thead>
</table>

4.4.7 Statistics – Paper I

We included all patients alive and without a diagnosis of dementia one year after ICU admission in a crude assessment of dementia incidence in patients with or without Sepsis using a Kaplan-Meier graph. Statistical significance of the difference between groups was determined with the log rank test. The primary outcome HR for the risk of dementia, was calculated in a multivariable Cox proportional hazards regression model censoring mortality and at end of follow-up.
4.4.7.1 **Predictive variables – Paper I**

After a literature review and DAG application, we used: age at ICU admission, updated CCI, sex and Sepsis in the Cox model. Because our intention was to separate the causal effect of sepsis from the severity of acute illness, several variables reflecting this approach were added to the model: ICU and hospital LoS, SAPS 3 (box II and III), renal replacement therapy (RRT) and IMV in the ICU.

4.4.8 **Statistics – Paper II**

For the primary outcome, HR of Sepsis for mortality we performed a multivariable Cox proportional hazards regression, censoring at emigration and end of study, both for the full follow-up, 15.5 years, and for eight pre-specified assessment periods during that time. We modeled the secondary outcome, cause of death, with multivariable multinomial logistic regression in the same manner as for the primary outcome. Based on the resulting ORs, we calculated marginal risk ratios (mRR)s for causes of death between Sepsis and Non-sepsis patients.

4.4.8.1 **Predictive variables – Paper II**

We used DAGs to identify variables to be included in the models. The Cox models were adjusted for age, sex, CCI and modified SAPS 3 (without points for age and comorbidity), and the multinomial models were adjusted for age, sex and CCI.

4.4.9 **Statistics – Paper III**

As little was known about Covid-19, we performed a series of exploratory, univariate analyses. To address the primary outcomes, risk factors for ICU-admission and risk factors for mortality in ICU patients, we performed two sets of statistical models: three multivariable conditional logistic regression models on the risk of ICU admission, and three multivariable Cox proportional hazards regression models on the risk for ICU mortality. The first logistic and Cox models evaluated comorbidities, the second logistic and Cox models evaluated medications and the third models evaluated comorbidities and medications together.

4.4.9.1 **Predictive variables – Paper III**

After the literature review, we included 12 comorbidities and nine chronic medications in the models. The comorbidity “immunosuppressed” was replaced with “systemic inflammatory disease” and “solid organ transplant recipient” in the combined models because immunosuppressant use was a part of the definition of “immunosuppressed.” Age, SAPS 3 (without points for age and comorbidity) and sex were added to the Cox models.
4.4.10 Statistics – Paper IV

The p-values for crude outcomes were treated with Bonferroni correction due to repeated measures. The primary outcome was assessed in two multivariable binary logistic regression models, one on the Sepsis and Covid-19 groups and one on the ARDS and Covid-19 groups. We added an interaction term between groups (Sepsis or Covid-19 and ARDS or Covid-19) and all other variables in the model. A significant p-value for the interaction indicates that that variable has a differential effect depending on the group affiliation.

4.4.10.1 Predictive variables – Paper IV

In addition to the comorbidities, SAPS 3 box III, age and sex were added to the models. During the review process, hospital type was also added to the model due to an imbalance in that sense over the groups.

4.4.11 Statistics – Paper V

As the data did not fit the assumptions of linear regression, the primary outcome was assessed in two sets of multivariable ordinal logistic regressions on OR for one additional sick-leave-free day alive between the ICU group and the hospital group and between the ICU group and the population control group. The secondary outcome OR for being on sick leave, on the day, one year after inclusion was assessed accordingly with multivariable binary logistic regression.

4.4.11.1 Predictive variables – Paper V

The confounding variables (listed in Figure 16) were limited to those available from registries and chosen based on a DAG.
5 Results

The results are described in detail in Paper I through V and the main findings are outlined here.

5.1 Results – Sepsis morbidity and mortality

5.1.1 Dementia

After exclusions, 210 334 patients, of which 16 115 (8%) had Sepsis during ICU care, were included in the analysis for Paper I. The Sepsis patients were older, had more comorbidities, were sicker at admission and subsequently had a longer LoS in the ICU and hospital (Table 7). The median follow-up time was 3.9 (1.7–6.6) years, and imputations were performed in 91 920 (44%) patients due to missing SAPS 3. We found a higher risk of a new diagnosis of dementia in the Sepsis than in the Non-sepsis group, as indicated by the Kaplan-Meier plot depicted in Figure 5. However, in the Cox model Sepsis was not a significant risk factor of dementia >1 year after ICU admission (HR 1.01, 95% CI 0.91–1.11, P=0.87, Figure 6). In our cohort of ICU survivors, the prevalence of dementia and incident mortality was higher in the older age groups.

5.1.1.1 Sensitivity analyses

The result was stable over several sensitivity analyses.
Table 7. Characteristics of adult patients treated in Swedish ICUs from 2005 to 2015 alive without a dementia diagnosis one year after ICU admission.

<table>
<thead>
<tr>
<th></th>
<th>Sepsis patients</th>
<th>Non-sepsis patients</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>16 115</td>
<td>194 219</td>
<td>210 334</td>
</tr>
<tr>
<td>Female sex</td>
<td>6 954 (43.2)</td>
<td>79 803 (41.1)</td>
<td>86 757 (41.2)</td>
</tr>
<tr>
<td>Age at ICU admission (years)</td>
<td>66 (54–74)</td>
<td>61 (42–72)</td>
<td>61 (43–72)</td>
</tr>
<tr>
<td>SAPS 3</td>
<td>61 (53–70)</td>
<td>45 (37–55)</td>
<td>47 (38–57)</td>
</tr>
<tr>
<td>CCI score</td>
<td>1 (0–2)</td>
<td>0 (0–2)</td>
<td>0 (0–2)</td>
</tr>
<tr>
<td>Hospital LoS (days)</td>
<td>20 (11–41)</td>
<td>11 (5–21)</td>
<td>11 (5–22)</td>
</tr>
<tr>
<td>ICU LoS (days)</td>
<td>2.94 (1.27–7.70)</td>
<td>0.91 (0.55–1.89)</td>
<td>0.94 (0.58–2.06)</td>
</tr>
<tr>
<td>RRT</td>
<td>1 492 (9.3)</td>
<td>2019 (1.0)</td>
<td>3 511 (1.7)</td>
</tr>
<tr>
<td>IMV</td>
<td>4 897 (30.4)</td>
<td>40 221 (20.7)</td>
<td>45 118 (21.5)</td>
</tr>
</tbody>
</table>

Data are presented as numbers with percentages or medians with interquartile range, as appropriate. The table was originally used in Paper I and is adapted and reprinted under a Creative Commons Attribution 4.0 International License.
Figure 5. Kaplan-Meier curves (95% CI) for dementia showing Non-sepsis patients (No-Sepsis) and Sepsis patients (Sepsis) initially having survived without dementia, one year after ICU admission. Log-Rank P<0.001. The figure was originally used in Paper I and is reprinted under a Creative Commons Attribution 4.0 International License.

Figure 6. Forest-plot of the Cox-regression model for dementia >1 year after ICU admission for patients ≥18 years of age treated in Swedish ICUs from 2005 to 2015. The figure was originally used in Paper I and is adapted and reprinted under a Creative Commons Attribution 4.0 International License.
5.1.2 Mortality

For paper II we included 33,994 Sepsis patients and 280,635 Non-Sepsis patients admitted to Swedish ICUs between 2005 and 2016. The Sepsis patients were numerically sicker at admission, had a higher burden of comorbidities and were older than the Non-sepsis patients (Table 8). The patients were followed for 3071 (median, IQR 2137–7136) days. Crude short- and long-term mortality was higher in the Sepsis group than in the Non-sepsis group (Table 9).

Table 8. Baseline and intensive care characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sepsis patients</th>
<th>Non-Sepsis patients</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>33,994</td>
<td>280,635</td>
<td>314,629</td>
</tr>
<tr>
<td>Sex, Female</td>
<td>14,463 (42.5%)</td>
<td>116,255 (41.5%)</td>
<td>130,988 (41.6%)</td>
</tr>
<tr>
<td>Age</td>
<td>69 (60–78)</td>
<td>65 (49–75)</td>
<td>65 (50–76)</td>
</tr>
<tr>
<td>CCI</td>
<td>2 (0–3)</td>
<td>0 (0–2)</td>
<td>0 (0–2)</td>
</tr>
<tr>
<td>SAPS 3</td>
<td>66 (57–76)</td>
<td>50 (40–62)</td>
<td>53 (42–65)</td>
</tr>
</tbody>
</table>

Patients admitted to the ICU in Sweden between 2005 and 2016 grouped by whether they had a sepsis diagnosis or not during care. The table is adapted from the manuscript of Paper I.

Table 9. Mortality rates for ICU-admitted patients with and without sepsis and numbers at risk

<table>
<thead>
<tr>
<th></th>
<th>Sepsis</th>
<th>Non-sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital mortality (n=314,624)</td>
<td>10,362 (30.5%)</td>
<td>38,677 (13.8%)</td>
</tr>
<tr>
<td>30-day mortality (n=314,619)</td>
<td>10,420 (30.7%)</td>
<td>41,962 (15.0%)</td>
</tr>
<tr>
<td>90-day mortality (n=314,597)</td>
<td>12,627 (37.1%)</td>
<td>50,960 (18.2%)</td>
</tr>
<tr>
<td>1-year mortality (n=314,550)</td>
<td>15,353 (45.2%)</td>
<td>65,595 (23.4%)</td>
</tr>
<tr>
<td>3-year mortality (n=314,540)</td>
<td>18,747 (52.2%)</td>
<td>88,599 (31.6%)</td>
</tr>
<tr>
<td>5-year mortality (n=273,129)</td>
<td>17,679 (62.6%)</td>
<td>92,645 (37.8%)</td>
</tr>
<tr>
<td>10-year mortality (n=130,218)</td>
<td>78,55 (74.2%)</td>
<td>60,292 (50.4%)</td>
</tr>
</tbody>
</table>

The table is adapted from the manuscript of Paper II.

In the multivariable Cox proportional hazards model on mortality during the full follow-up, the HR of Sepsis was 1.02 (95% CI 1.00–1.04, p=0.32). Sepsis appeared protective in the first 30 days and was associated with mortality during the following assessment periods until five years from admission (Figure
In the multivariable multinomial logistic regression, the causes of death differed between the Sepsis and Non-sepsis groups on several accounts. Sepsis was a risk factor for infectious causes of death (mRR 3.82, 3.63–4.02, p<0.001) during the full follow-up. The highest mRR was seen for the first assessment period, but the effect was significant during all later assessment periods (Figure 8).

### 5.1.2.1 Sensitivity analyses

None of the performed sensitivity analyses altered our conclusions, although a complete case analysis gave a different outcome regarding the adjusted risk for mortality.
Figure 7. Visual presentation of the variation of HRs for the variables in the Cox regressions for the eight assessment periods.

The shaded areas represent the 95% CIs, not adjusted for repeated measures. The figure is used in the manuscript of Paper II.
Figure 8. Visual presentation of mRRs from multinomial logistic regression models for 10 causes of death over eight assessment periods.

The shaded areas represent the 95% CIs, not adjusted for repeated measures. The figure is adapted from the manuscript of Paper II.
5.2 Results – admission and mortality in Covid-19, ARDS and Sepsis

5.2.1 Risk factors for ICU admission and mortality in Covid-19

In Paper III we identified 1981 adult patients with Covid-19 (after exclusion of patients without a Swedish PIN) in the SIRI. The Statistics Sweden matched 7924 controls for age and sex (Figure 9). Missing SAPS 3 data were imputed for 256 patients and time at risk was imputed for 36. The patients with Covid-19 treated in the ICU had, in crude numbers, more comorbidities and chronic medications than controls. Some baseline characteristics are found in Table 10. However, patients dying in the ICU had a higher proportion of males, a greater age, a worse SAPS 3 score and a higher number of procedures in the ICU compared to the survivors (Table 11).

Figure 9. Patient selection.

The figure is adapted from Paper III and is reprinted under a Creative Commons Attribution 4.0 International License.
Table 10. Baseline characteristics of patients ≥18 years old who were admitted to Swedish ICUs with Covid-19 6 March 2020 to 27 May 2020 and their age and sex-matched population controls.

<table>
<thead>
<tr>
<th></th>
<th>Covid-19 admitted to ICU</th>
<th>Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1981</td>
<td>7924</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>516 (26)</td>
<td>2064 (26)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Age at ICU admission</td>
<td>61 (52–69)</td>
<td>61 (52–69)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>SAPS 3</td>
<td>53 (46–69)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CCI</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as numbers with percentages or medians with the interquartile range, as appropriate. The table was originally used in Paper II and is adapted and reprinted under a Creative Commons Attribution 4.0 International License.

Table 11. Baseline characteristics of patients ≥18 years old who were discharged from Swedish ICUs with Covid-19 between 6 March 2020 and 27 May 2020, stratified on their vital status.

<table>
<thead>
<tr>
<th></th>
<th>Discharged alive</th>
<th>Discharged dead</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1198</td>
<td>346</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>345 (28.7)</td>
<td>74 (21.4)</td>
<td>0.006</td>
</tr>
<tr>
<td>Age at ICU admission</td>
<td>58 (50–67)</td>
<td>67 (59–74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SAPS 3</td>
<td>51.5 (45–57)</td>
<td>58 (52–65.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CCI</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>0.189</td>
</tr>
<tr>
<td>IMV</td>
<td>772 (64.3)</td>
<td>300 (86.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NIV</td>
<td>227 (19.8)</td>
<td>54 (15.8)</td>
<td>0.056</td>
</tr>
<tr>
<td>Prone positioning</td>
<td>374 (32)</td>
<td>182 (54.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as numbers with percentages or medians with the interquartile range. The table was originally used in Paper II and is adapted and reprinted under a Creative Commons Attribution 4.0 International License.

5.2.1.1 Risk of ICU admission in Covid-19
A conditional logistic regression analysis was performed on the risk of ICU admission. Hypertension, type 2 DM (T2DM), chronic renal failure, asthma, obesity, solid organ transplants and ongoing medication with immunosuppressants were associated with an increased risk for admission in the model. Ongoing treatment with anticoagulants was associated with a lower risk for admission (Figure 10).

5.2.1.2 Risk of ICU mortality in Covid-19
A multivariable Cox proportional hazards analysis was performed on the risk of ICU mortality. Risk factors in the model were a higher vs. lower SAPS 3 and age, stroke, chronic obstructive pulmonary disease (COPD), asthma and
RAASi treatment. Ongoing treatment with statins was associated with a lower risk for mortality (Figure 11).

5.2.1.3 Sensitivity analyses
None of the sensitivity analyses altered our conclusions.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease</td>
<td>1.01</td>
<td>0.78 - 1.32</td>
<td>0.92</td>
</tr>
<tr>
<td>Non-ischemic heart disease</td>
<td>1.18</td>
<td>0.92 - 1.50</td>
<td>0.19</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.41</td>
<td>1.26 - 1.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>0.91</td>
<td>0.69 - 1.23</td>
<td>0.68</td>
</tr>
<tr>
<td>Type 2 diabetic mellitus</td>
<td>2.17</td>
<td>2.12 - 2.87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>1.04</td>
<td>0.75 - 1.44</td>
<td>0.36</td>
</tr>
<tr>
<td>Cholestrol, treated failure</td>
<td>2.09</td>
<td>1.44 - 3.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD</td>
<td>1.32</td>
<td>0.96 - 1.82</td>
<td>0.091</td>
</tr>
<tr>
<td>Asthma</td>
<td>1.50</td>
<td>2.06 - 4.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity</td>
<td>2.37</td>
<td>1.81 - 3.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systemic inflammatory disease</td>
<td>1.28</td>
<td>0.98 - 1.68</td>
<td>0.066</td>
</tr>
<tr>
<td>Solid organ transplant recipients</td>
<td>2.30</td>
<td>1.03 - 5.14</td>
<td>0.043</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.98</td>
<td>0.76 - 1.26</td>
<td>0.88</td>
</tr>
<tr>
<td>RAASI</td>
<td>0.92</td>
<td>0.78 - 1.08</td>
<td>0.31</td>
</tr>
<tr>
<td>Alpha-blocker</td>
<td>0.61</td>
<td>0.43 - 1.50</td>
<td>0.49</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>0.94</td>
<td>0.80 - 1.11</td>
<td>0.47</td>
</tr>
<tr>
<td>Statins</td>
<td>0.95</td>
<td>0.81 - 1.12</td>
<td>0.53</td>
</tr>
<tr>
<td>Immunosuppressant and glucocorticoids</td>
<td>1.73</td>
<td>1.40 - 2.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>0.75</td>
<td>0.57 - 0.98</td>
<td>0.032</td>
</tr>
<tr>
<td>Platelet aggregation inhibitors</td>
<td>1.05</td>
<td>0.86 - 1.29</td>
<td>0.65</td>
</tr>
<tr>
<td>Lokalnavir/Ritonavir</td>
<td>1.27</td>
<td>0.10 - 15.90</td>
<td>0.86</td>
</tr>
<tr>
<td>Anti hepatitis C</td>
<td>0.51</td>
<td>0.06 - 4.21</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Figure 10. Forest plot of the conditional binary logistic regression models for the risk of ICU admission, comorbidity and medications combined.

The figure was originally used in Paper III and is reprinted under a Creative Commons Attribution 4.0 International License.
Figure 11. Forest plot of the Cox proportional hazards regression model for the risk of ICU mortality, comorbidity and medications combined.

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5.2.2 Differential risk factors for mortality from Covid-19, sepsis and ARDS

After exclusion of children and patients (admissions) lacking a PIN, we included 7382 ICU patients with Covid-19, 22,354 patients with Sepsis and 2776 patients with ARDS (Figure 12) for Paper IV. Numerically the groups differed, with a lower proportion of females and a lower median age, SAPS 3 and CCI in the Covid-19 group than in the Sepsis and ARDS groups. Also, the distribution of patients over hospital types differed between groups (Table 12). Crude 60-day mortality was lower in the Covid-19 group (27.5%) than in the Sepsis group (31.1%) and in the ARDS group (45.0%). The Sepsis patients had a higher prevalence of all studied comorbidities than the Covid-19 patients. The same pattern was true for ARDS compared with Covid-19 patients;
however, no difference was found for T2DM, chronic renal failure, asthma or obesity.

In the logistic model on 60-day mortality including Covid-19 and Sepsis patients, the interaction with group was significant for sex, age and asthma. This is compatible with a stronger association with mortality for males, greater age and asthma in Covid-19 than in Sepsis. Moreover, the OR for 60-day mortality was 2.03 (1.83–2.26) in Covid-19 compared with Sepsis. (Figure 13). In the model on Covid-19 and ARDS, the interaction with group was significant for SAPS 3 box 3, age and chronic renal failure, meaning that greater age and SAPS 3 box 3 were more strongly associated with mortality in the Covid-19 patients than the ARDS patients. However, chronic renal failure was associated with a more favorable outcome in ARDS patients than in Covid-19 patients. Finally, the OR for 60-day mortality was 0.74 (0.62–0.88) in Covid-19 compared with ARDS patients (Figure 14).

Figure 12. Flowchart of the patient selection procedure for Paper IV.

The figure was originally used in Paper IV and is slightly adapted and reprinted under a Creative Commons Attribution 4.0 International License.
5.2.2.1 Sensitivity analyses

None of the sensitivity analyses altered our conclusions.

Table 12. Baseline characteristics of patients included in the Covid-19, sepsis and ARDS cohorts.

<table>
<thead>
<tr>
<th></th>
<th>Sepsis patients</th>
<th>Covid-19 patients</th>
<th>ARDS patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>22 354</td>
<td>7 382</td>
<td>2 776</td>
</tr>
<tr>
<td>With Covid-19</td>
<td>0 (0)</td>
<td>7 382 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>With sepsis</td>
<td>22 354</td>
<td>1389 (18.8)</td>
<td>1 100 (39.6)</td>
</tr>
<tr>
<td>With ARDS</td>
<td>1 100 (4.9)</td>
<td>5491 (74.0)</td>
<td>2 776</td>
</tr>
<tr>
<td>Female sex</td>
<td>9 500 (42.5)</td>
<td>2 191 (29.7)</td>
<td>1 033 (37.2)</td>
</tr>
<tr>
<td>Age at ICU-admission</td>
<td>70 (60–78)</td>
<td>63 (53–72)</td>
<td>65 (53–74)</td>
</tr>
<tr>
<td>SAPS 3</td>
<td>66 (57–76)</td>
<td>54 (48–61)</td>
<td>66 (57–76)</td>
</tr>
<tr>
<td>CCI</td>
<td>1 (0–3)</td>
<td>0 (0–1)</td>
<td>1 (0–2)</td>
</tr>
<tr>
<td>Hospital type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>5 676 (25.4)</td>
<td>2 566 (34.8)</td>
<td>1 167 (42.0)</td>
</tr>
<tr>
<td>County</td>
<td>11 080 (49.6)</td>
<td>3 749 (50.8)</td>
<td>1 211 (43.6)</td>
</tr>
<tr>
<td>District</td>
<td>5 598 (25.0)</td>
<td>1 067 (14.5)</td>
<td>398 (14.3)</td>
</tr>
</tbody>
</table>

Baseline characteristics of patients ≥18 years old admitted to Swedish ICUs with Covid-19 between 6th of March and 16th of June 2021 or admitted to Swedish ICUs with non-Covid-19 Sepsis or non-Covid-19 ARDS between the years 2011 and 2016. Data are presented as numbers with percentages or medians with interquartile ranges as appropriate. The table was originally used in Paper III and is adapted and reprinted under a Creative Commons Attribution 4.0 International License.
### Figure 13. Odds ratio of 60-day mortality with sepsis (a) or Covid-19 (b) in a logistic regression model.

A p-value for interaction <0.05 denotes a differential effect for that variable between sepsis and Covid-19. The figure was originally used in Paper VI and is adapted and reprinted under a Creative Commons Attribution 4.0 International License.
Figure 14. Odds ratio of 60-day mortality with ARDS (a) or Covid-19 (b) in a logistic regression model.

A p-value for interaction <0.05 denotes a differential effect for that variable between ARDS and Covid-19. The figure was originally used in Paper VI and is adapted and reprinted under a Creative Commons Attribution 4.0 International License.
5.3 Results – Long-term recovery after severe Covid-19

We identified 1405 eligible ICU patients, 6895 hospital patients and 5575 population control individuals for Paper V. These individuals, of working age, were analyzed for the primary outcome, sick-leave-free days alive one year after inclusion. After exclusion of individuals deceased during the first year after inclusion, 1179 ICU patients, 6726 hospital patients and 5562 population controls were included in the analysis for the secondary outcome, being on sick leave one year after inclusion. The groups were numerically different in most baseline characteristics (Table 13). We found a marked difference in proportion of individuals on sick leave on any given day during the first year after inclusion (Figure 15). At one year, 364 (30.4%) of ICU patients, 1,156 (17.2%) of hospitalized patients and 516 (9.3%) of population controls were on sick leave at any degree (p<0.001 for ICU patients compared to the other groups). Analogous to this, we found that affiliation to the ICU group was associated with lower odds of having one or more sick-leave-free days alive in multivariable ordinal logistic regression compared with both the hospital (OR 0.18, 0.16–0.20, p<0.001) and population control groups (OR 0.034, 0.029–0.040, p<0.001) (Figures 16 and 17). The findings were similar in the models on being on sick leave one year after inclusion.

| Table 13. Baseline characteristics of ICU patients, hospital patients, and population controls. |
|-------------------------------------------------|-------------------|-------------------|
| Number of patients | ICU patients | Hospital patients | Population controls |
| Age | 53 (46–59) | 50 (39–57) | 53 (46–59) |
| Sex, female | 384 (27) | 3059 (44) | 1530 (27) |
| CCI | 0 (0–0) | 0 (0–0) | 0 (0–0) |
| SAPS 3 | 49 (44–55) | – | – |
| IMV | 1004 (72) | – | – |
| NIV | 250 (18) | – | – |
| CRRT | 225 (16.0) | – | – |
| Baseline sick leave (one year before inclusion) | 232 (16.5) | 1,057 (15.3) | 521 (9.3) |

Data are presented as numbers with percentages or medians with interquartile ranges, as appropriate. Hospital patients were not admitted to an ICU. Population controls were not admitted to a hospital with Covid-19. The table is adapted from the manuscript of Paper IV. NIV: Non-invasive ventilation.
Figure 15. Proportion of individuals on sick leave per day, stratified by group. The shaded area represents the 99% confidence interval, calculated with the Clopper-Pearson method. The figure is adapted from the manuscript of Paper V.

5.3.1.1 Sensitivity analyses
None of the sensitivity analyses altered our conclusions.
Figure 16. Forest plot of an ordinal logistic model on odds ratio for having one or more additional sick-leave-free days alive during the first year after inclusion. ICU patients and hospital patients.

The figure is adapted from the manuscript of Paper V.
Figure 17. Forest plot of an ordinal logistic model on odds ratio for having one or more additional sick-leave-free days alive during the first year after inclusion. ICU patients and population controls.

The figure is used in the manuscript of Paper V.
6 Discussion

6.1 Ethical considerations

The research in Papers I and II was endorsed by the Regional Ethics Committee of Uppsala (approval no. 2016/421) and that in Papers III, IV, and V by the Swedish Ethical Review Authority (approval no. 2020-02144, with revisions 2021-01170, 2021-02824, and 2021-03395). Informed consent was waived by the authority, but there is an opt-out clause in the SIR, although not in the governmental registries.

In these projects we used already collected data from routine healthcare and did not include any additional interventions. The main risk for the participating patients and population controls is a breach of privacy by loss of data to a third party or reporting outcomes on small enough groups for the individuals to be identified. To minimize these risks, we have had no access to any directly identifying information in our data, as it is pseudonymized with the keys stored at the National Board of Health and Welfare or Statistics Sweden. Furthermore, the datasets are stored and used on secure servers in encrypted file containers. Finally, we have only reported data and outcomes on a sufficiently large group level.

We have not identified any potential benefits for the included individuals. However, our findings, given that they are accurate, might benefit future patients with Covid-19, sepsis or ARDS admitted to the ICU, in that we have a greater understanding of risk factors and outcomes related to ICU admission. Subsequently we find that the risk-benefit balance is favorable, as the actual risk to privacy is low, and we are generating new knowledge in this group of grim diseases.

6.2 Discussion in relation to other studies

6.2.1 Sepsis morbidity and mortality

In Papers I and II we studied the explicit effect of Sepsis on severe long-term outcomes, dementia and mortality. The main finding is that we could not demonstrate any effect from Sepsis on incident dementia and that the effect of Sepsis on long-term mortality was small. Thus, our studies do not strongly
support the theories regarding a major long-term impact on future health specifically from the Sepsis syndrome (15); however, the differences in causes of death between Sepsis and Non-sepsis patients are intriguing.

6.2.1.1 Dementia

Our findings on incident dementia are not consistent with several other studies. In a Taiwanese study which, after exclusions, covered 5955 of 16 620 patients with dementia and 5955 age- and sex-matched population controls, the OR of having had sepsis within five years of inclusion was higher in the dementia patients than in the controls after adjustment for comorbidities and socioeconomic factors (109). In another Taiwanese study focusing on the risk of AD development, 20 466 sepsis patients were compared with age- and sex-matched controls in a 1:2 ratio. Patients with a previous dementia diagnosis were not included, but the time frame was not specified. The sepsis patients had more comorbidities, and their risk of dementia was higher in a Cox proportional hazards model (159). However, the study design in these two studies did not differentiate between a sepsis effect and the effect of general critical illness.

Guerra et al. conducted two studies on cohorts of ICU-treated Medicare patients aged >65 years. Patients with a diagnosis of dementia or who underwent cardiac surgery in the previous year were excluded. Patients who did not survive the inclusion quarter were also excluded. The remaining 25 368 patients were included in a Cox model in which several comorbidities, demographics and factors related to the intensive care episode were included, based on data-driven criteria. Infection and, in particular, sepsis was found to be significantly associated with dementia development within four years of inclusion (107). In the second study by Guerra et al. on a similar ICU survival cohort, patients were matched for age, sex and race to Medicare population controls. Exclusion criteria were previous a dementia/mild cognitive impairment diagnosis code or cardiac surgery in the preceding year. The cohorts were monitored for three years, with 40% of dementia diagnoses coded during the first year in the ICU survivors. There was an increased risk of dementia in the ICU cohort after adjusting for demographics and comorbidities. Of note, sepsis was a significant risk factor in that model. However, if comorbidities diagnosed during the inclusion quarter were included in the model, sepsis was no longer a significant risk factor. The main criticism of these studies is that previous diagnoses of dementia may have been overlooked, as only a dementia diagnosis over the past year was assessed. This issue is important because dementia may be a risk factor for sepsis (160). In addition, because dementia is usually a slowly developing syndrome, there is a risk that, by using dementia diagnoses documented early after ICU admission, some of the incident dementia might have been in individuals with a trajectory toward dementia not causally related to the sepsis episode but rather, the patient might have had a sepsis episode.
related to the dementia not yet diagnosed. In addition, the maximum follow-up time was three years, which is substantially shorter than in Paper I.

In a cohort of 161,567 patients without a diagnosis of sepsis or dementia in the previous two years before start of follow-up, the incident diagnosis of dementia was related to a preceding diagnosis of incident sepsis. Using Cox models encompassing demographics and comorbidities, the researchers found an increased HR for dementia in the first two years after the diagnosis of sepsis, but not in later time periods (161). These findings parallel ours, but the authors conclude that future studies should focus on interventions reducing the risk of dementia development in sepsis, thereby overlooking that the dementia syndrome usually is caused by progressing diseases.

6.2.1.2 Mortality

We found a surprisingly low effect from Sepsis on long-term mortality in an adjusted Cox-model, despite a large crude mortality difference between patients with and without Sepsis in the ICU. Moreover, the association exhibited variations across assessment periods, with Sepsis showing a protective effect in the first 30 days and later emerging as a risk factor up to five years after admission. The diminishing effect from Sepsis in the last two assessment periods may be due to depletion of frail individuals (susceptibles) and as such a selection effect or it may represent a truly diminishing effect from Sepsis. The finding of a slightly increased risk of mortality in Sepsis compared to Non-sepsis is in contrast to a large systematic review where an observed increased mortality in one-year sepsis survivors disappeared after adjustment for relevant confounding in ICU patients (162). However, the underlying studies reported inconsistent results and had different inclusion strategies (from hospital or ICU admission or from alive ICU or hospital discharge) (163-166). Also, a recently published study investigated five-year survival in a German cohort of hospital-admitted patients with infection, who had survived hospital discharge. Infected, non-sepsis patients had a five-year mortality of 52.4%, sepsis patients (according to Sepsis-3 definitions) 62.1% and septic shock patients 56.1%. These differences were also evident in multivariable Cox regression. Thus, in the German cohort, sepsis was associated with a substantially increased mortality and the mortality in all groups was remarkably high (167).

The most prominent findings regarding causes of death over the full study period were higher risk for infectious, urogenital and tumor-related causes of death in Sepsis patients. In Sepsis patients, infectious causes of death were markedly increased during the first and second assessment periods, given that infection is an inherent element of the sepsis definition. However, the risk for infectious causes of death was increased in all eight assessment periods, which may indicate a persistent effect on the immune response from Sepsis (15, 168). Other reports of causes of death in ICU-admitted sepsis patients are scarce.
Nevertheless, in a study by Wilhelms et al., one-year ICU survivors with sepsis had a higher degree of infectious causes of death than non-sepsis patients (169). In a US cohort, infectious causes of death were more common in sepsis than non-sepsis patients during a six-year follow-up (170). Urogenital causes of death are not reported by others, but might be linked to the increased risk for chronic renal failure evident in sepsis (171). The increase in mRR for tumor-related deaths over the full study period is almost completely driven by a high mRR in the first 30 days of follow up. The early deaths in sepsis patients are likely associated to reverse causation, as cancer is a risk factor of sepsis (172).

6.2.2 Covid-19 ICU admission and mortality

In Papers III and IV we studied risk factors for severe Covid-19 surrogated by ICU admission and short-term mortality in ICU patients and also the relative importance of these risk factors between common ICU syndromes. This research field has evolved very rapidly, and many studies exploring different aspects of our research questions have been published.

6.2.2.1 Risk factors for ICU admission and mortality in Covid-19

A major finding from Paper III, a case-control and cohort study on 1891 ICU-admitted patients, was that, apart from age, sex and acute disease severity, several comorbidities and medications were associated with the risk of ICU admission, ICU mortality, or both. In a similar study, by Chew et al., on an overlapping cohort, only chronic lung disease, out of several comorbidities, was linked to mortality (173). However, while data on comorbidities and medications were prospectively collected in our study, the data collection was retrospective in the latter study (174). Nevertheless, like Chew et al., we found that COPD was linked to ICU mortality, a finding in line with the observations of others. A cohort study of 331 298 SARS-CoV-2 positive patients in Mexico found an association between COPD and mortality (175), paralleling a large meta-analysis of 59 studies including 109 367 patients with Covid-19 (176). The weakness of this meta-analysis is that COPD was not analyzed in a multivariable model, thereby not assessing the COPD as an independent risk factor. Moreover, the largest study (89 756 patients) in the meta-analysis was retracted by the journal (177). In the second-largest study of the meta-analysis, COPD was an independent risk factor for ICU admission and mortality (178). In a more recent meta-analysis, COPD was associated with ICU admission and death in hospitalized patients (179). The conflicting results from large cohort studies, e.g., (180-183), are possibly due to different statistical modeling techniques, choice of covariates and the varying characteristics of the underlying populations. We also found an indication that asthma is an important risk factor for severe Covid-19 and ICU mortality. Other studies partially support our finding. In a UK multicenter study on 8950 hospitalized Covid-19
patients, asthma was associated with an increased risk for critical care admission but not mortality (184). However, several other studies reached a different conclusion. In a Korean study that included 7272 COVID-19 patients (686 had asthma) there was no link found between asthma and mortality (185). A similar finding was reported in a large Mexican cohort (175). In addition, two meta-analyses found no difference in ICU admission or mortality between Covid-19 patients with and without asthma (186, 187) In the latter, a secondary analysis revealed an increased risk for ventilator treatment for patients with asthma in European studies. Again, differing sampling procedures and varying underlying populations may explain the discrepancies, along with diverse statistical methods.

In our cohort, ongoing treatment with an oral anticoagulant was protective of ICU admission, but not ICU mortality. This finding had not been previously reported and contrasts with the results in a case-control study on patients with positive SARS-CoV-2 polymerase chain reactions. Some 139 patients on chronic anticoagulation were compared with 417 propensity score-matched controls for mortality risk. After excluding 102 patients due to lack of matching controls, there was no significant association between anticoagulation and the need for hospitalization, mechanical ventilation, or the risk of death (188). Nevertheless, our results align with later studies, such as Rentsch et al., who studied 4297 hospital-admitted Covid-19 patients. The authors found that 30-day mortality was significantly lower in patients receiving prophylactic anticoagulation than in those not administered an anticoagulant drug (189). In addition, a multi-clinical trial platform study reported that therapeutic dose Heparin was superior to thromboprophylaxis dosing in hospitalized (190) but not in critically ill patients (191). Finally, Loui et al reported 630 hospital-admitted Covid-19 patients with atrial fibrillation who were or were not receiving oral anticoagulant emboli prophylaxis. Oral anticoagulants were protective of ICU admission as well as mortality.

The potential effects of statins on outcomes in intensive care in general (192) and in Covid-19, in particular (193), has been under debate. In our cohort, statins were associated with an attenuated risk of ICU mortality, but no association with ICU admission. Contrary to our results, in a small case-control study, statin use was linked to a lower risk of ICU admission with Covid-19 than non-use (62). Moreover, the use of atorvastatin was correlated to a lower risk of ICU admission in a large Cox regression model performed on another small cohort (63). Mallow et al. performed a logistic regression model on a large cohort of hospitalized Covid-19 patients. The authors reported that statin use during hospitalization was associated with a lower risk of hospital mortality than non-use. In addition, in parallel to us, they found no link to ICU admission (194). Moreover, in a Danish population of 4842 Covid-19 patients, previous statin use was not correlated to hospital admission or mortality in a Cox model that included demographics and comorbidities (195). Similar
findings were observed in an Italian study of nearly 4000 Covid-19 ICU patients (53). Finally a meta-analysis of 35 studies found a protective effect from statin use on severe illness and mortality. This finding was confirmed in a large case control study on 2 058 249 pairs of statin users and non-users (196).

Obesity was associated with an increased risk of ICU admission but had no impact on ICU mortality in our cohort. This finding confirms those from a 442-patient cohort with Covid-19 infection (197). A meta-analysis of 22 cohort studies reported similar results regarding ICU admission. However, this analysis reported an increased risk of mortality as well (198). The difference in impact on ICU mortality may be accounted for by case selection, as we reported mortality in ICU-admitted patients, whereas the meta-analysis reported mortality in SARS-COV-2-positive patients not necessarily admitted to ICU. Our definition of obesity also differs from the more common body-mass-index-determined obesity definition used in most other studies.

RAASi has attracted much attention as a risk or protective factor in Covid-19. We found an association between chronic RAASi use and ICU mortality but not ICU admission. Suspecting that the RAASi effect was mediated through acute renal failure, we performed a post hoc sensitivity analysis adding continuous RRT (CRRT) to the model. In the sensitivity analysis, the RAASi HR decreased but remained linked to mortality. We also divided RAASi into ACEi and ARB, finding that both were linked to an increased risk of ICU mortality. Most studies on Covid-19 and RAASi have a detected SARS-CoV-2 infection as an endpoint or are underpowered to draw conclusions on ICU admission or ICU mortality (199). However, in another large cohort, including ICU-admitted patients with Covid-19, ACEi and ARB were not linked to ICU mortality (53). In a smaller cohort RAASi was a significant risk factor for ICU admission in a model of demographics, comorbidities and ongoing medications. After adding laboratory parameters to the model, the effect of RAASi was no longer evident (200). It may be that the impact of RAASi on mortality in our study is linked to the inability of statistical models to control for confounding from heart or kidney disease, as suggested by Loader et al. (201).

The first treatment proven effective in severe Covid-19 was the glucocorticoid dexamethasone, as evidenced by the RECOVERY trial (202). Even so, we found a link between ongoing immunosuppressive therapy and an increased risk of ICU admission. We performed a pre-planned sensitivity analysis dividing immunosuppressive therapy by ATC-code, finding that only glucocorticoids were associated with ICU admission. We speculate that the association of ongoing glucocorticoid therapy with increased risk of ICU admission despite glucocorticoids being an important therapeutic option in severe Covid-19 is a matter of timing. In RECOVERY there was a trend toward harm with dexamethasone treatment in patients without respiratory compromise. Moreover, long-term adverse effects of chronic glucocorticoid treatment on health
are well known (203). Finally, several other cohort studies have later confirmed our findings (204-206).

DM is associated with an increased risk of hospitalization and mortality from Covid-19 (178, 179, 197, 207, 208). Moreover, of studies assessing the separate associations of T1DM and T2DM, one agrees with our finding that T2DM but not T1DM is associated with a worse outcome (53) and one does not (209). However, neither T1DM nor T2DM were associated with ICU mortality in our cohort.

Covid-19 is a thrombotic disease linked to incident ischemic stroke (210) and other thromboembolic events (211). In accordance with the findings of others, we reported an association between previous stroke and ICU mortality (212-214).

6.2.2.2 Differential risk factors for mortality from Covid-19, Sepsis and ARDS

To our knowledge, no-one has previously compared the significance of risk factors in the common syndromes of sepsis and ARDS with those in Covid-19, despite the great attention that was already being given to risk factors in Covid-19 early during the pandemic. Our main finding in Paper IV, was that the significance of risk factors for mortality differed on only one comorbidity between Covid-19 and sepsis and between Covid-19 and ARDS.

The differential effect of comorbid asthma, where the OR for mortality was significantly higher than one in Covid-19 patients, but not in Sepsis patients, follows the previous findings of a protective effect from asthma in sepsis (215) and our finding that asthma but not COPD is linked to a worse prognosis in ICU-admitted patients with Covid-19 (Paper III). Contrary to this, asthma as a risk factor for Covid-19 mortality is not prominent in meta-analyses (186, 187). However, these meta-analyses are not adjusted for relevant confounding. The seemingly protective effect of chronic renal failure in ARDS was surprising and not in line with the findings from the secondary analysis of the LUNG SAFE study (216), where chronic renal failure was non-differential to the outcome.

Greater age was associated with a higher risk of mortality in Covid-19, both compared with sepsis and with ARDS. This finding is not surprising, as greater age has been consistently and strongly connected to Covid-19 mortality in many cohorts (217). We reported the effect of sex on mortality to be differential between Sepsis and Covid-19, as female sex was associated with mortality in Sepsis but not in Covid-19. There are diverse findings in different cohorts regarding the association of female sex with sepsis mortality (23, 24, 218), and the association between sex and mortality in Covid-19 has been under investigation and debate in the literature (219, 220). A higher SAPS 3 box
III was, as expected, associated with mortality in all groups. However, the effect was stronger in Covid-19 than ARDS, possibly due to ARDS being a consequence of an often less severe cause for ICU admission.

6.2.3 Long term recovery after severe Covid-19

As hypothesized in Paper V, we found a lesser degree of recovery in patients with Covid-19 admitted to ICU than in those admitted to hospital. The level of sick leave in the population controls was also substantially lower than in the ICU-admitted patients.

Our findings that agree with others in that the proportion of individuals on sick leave during follow-up increases with increasing disease severity. In a single-center study from Sweden including Sars-Cov-2-positive health and social care workers, 98.6% had, completely, returned to work three months after inclusion (221). A Swiss single-center study followed 61 hospitalized patients of which 84% had fully returned to work after seven months (68). A US multicenter study report 41–64% of hospitalized patients returning to work after six months depending on whether or not they had neurological complications (69). In a Danish registry-based study on individuals working at baseline, return to work at six months was 98.4%, 92.6% and 74% in general population Covid-19 positive individuals, hospitalized Covid-19 patients and ICU-admitted Covid-19 patients, respectively (222). In a single-center study from Italy, 49% of 39 previously working patients returned to work within two months from ICU admission (72). In a Swedish single-center study, 83% of ICU-admitted patients with Covid-19, who had not yet retired, was not on sick-leave at 12 months from inclusion (223). In Australia, a multicenter study followed 114 ICU patients surviving for six months and found 11.4% of patients were not able to return to work for health reasons (73). In a cohort of 30 ICU patients in a Dutch center, 57% had returned to work at six months (74). In an Italian cohort of Covid-19 ICU patients, 64% had returned to work at any point after six months and 86% after 12 months. However, the proportion of followed-up individuals fell dramatically with time due to Covid-19 restrictions (75). In a similar Italian cohort, 73% had returned to work at six months (224). The largest cohort studies on hospital-admitted Covid-19 patients were reported from a single center in Wuhan, China (70, 71). They reported that 88% of previously employed patients returned to work after 12 months and 89% after 24 months; however, only 8% were admitted to an ICU. Regarding our findings in the setting of the above-reported research, it is important to understand that returning to work is a different outcome from being on sick leave. An individual who is not on sick leave is not necessarily working. Moreover, return to work is usually reported for individuals working at any degree, while our outcome was being on any degree of sick leave. Finally, although we reported the proportion of patients on sick leave, we also investigated the effect of Covid-19 admission in statistical models, thus aiming to eliminate the
effects of confounding factors such as age and comorbidities. This has not, to our knowledge, previously been reported.

6.3 Strengths and limitations

There are several strengths and limitations to our studies, some related to observational and registry research in general and some related to the specific circumstances for each paper.

6.3.1 Strengths

All papers included in this thesis are registry studies and as such carry some inherent strengths. The size of the cohort is large or very large, which gives a high power to detect even small differences, but also many degrees of freedom to be used in the adjustment for confounding in statistical models. Also, the national character of the SIR and the governmental registries we have employed is important, as our reports are representative of different regions and socioeconomic groups in a developed country. Moreover, the data is always prospectively collected in the registries, eliminating the risk of recall bias in retrospective research (135, 225). Using the Swedish PIN system, registries can be combined, which allowed us to use the most reliable data source for each variable (e.g., the SIR contains data on ICU mortality, but by using the CDR we were able to follow the patients’ vital status beyond both ICU and hospital discharge. Moreover, the data was procured without loss to follow up in individuals who did not emigrate). The long follow-up in Papers I and II is an important strength, particularly when researching dementia, which is primarily a slowly evolving syndrome (81).

Sepsis, an exposure variable in Papers I, II and IV, Covid-19, an exposure variable in Papers III–V, and ARDS, an exposure variable in paper IV, are, by SIR, treated as especially important diagnoses (in Swedish “För intensivvårdens viktiga diagnoser”), thus already highlighted to the treating physicians during the ICU admission, in an effort to improve the coding. The quality of the diagnostic coding in sepsis and septic shock has been challenged by Lengquist et al. in a study on 5990 ICU admissions, where sepsis coding in the SIR was compared to data from chart reviews (226). In the cohort, 1654 admissions were found to fulfill sepsis criteria despite only 31% having a sepsis code in the SIR. However, the study’s sepsis criteria were a SOFA score ≥2 at ICU admission, blood cultures drawn, and antibiotic administration within a four-day time window. This definition of sepsis is extremely wide, as there are few admissions to ICU where SOFA <2, and most ICUs employ liberal culture strategies and liberal empirical antibiotic treatment in critically ill patients where sepsis cannot be ruled out at the initial stages of the admission. The mean SOFA for all admissions to the including hospitals was 6
(IQR, 3–9) (227) during the inclusion period. However, the proportion of sepsis in our cohort is lower than previously reported. Regarding the studies on Covid-19, Papers III–V, a low degree of exposure misclassification was assured, as reliable diagnostic criteria were established by the SIR (ultimately the WHO through the Board of Health and Welfare) before the first cases were admitted to Swedish ICUs. Also, the validation of the U07.1 diagnostic code in SIR by comparing it to the reports to the sub-registry SIRI, which had a separate, and faster, mode of data collection, increased the precision. For Paper III and V we used a robust control population consisting of random individuals from the Swedish population. This approach did not expose us to the selection challenges inherent in utilizing a control population comprising only Covid-19 positive individuals during a period when testing was limited to healthcare professionals, the elderly, and those already hospitalized (228), a strategy used by others (199, 229). This dilemma is discussed further in section 6.4.2.

6.3.2 Limitations

Registry studies carry some inherent limitations, not all of which are amendable by methodological choices. As we had no control over the data collection, we had to rely on the data collection procedures of the registries. However, the registries employ several methods for data curation such as allowed intervals for continuous variables and automated checks for data completeness (230). Moreover, the observational nature of registry studies comes with the issue of residual confounding, i.e., confounding not addressed in the statistical models. This is aggravated in registry studies as the researchers are limited to using variables available from the registries, in addition to running the risk of not understanding the mechanisms of confounding for the research question under study. Furthermore, as association is not causation the use of observational methods precludes firm conclusions about causal effects, especially when a target trial methodology is not used (231). Finally, registry research allows for the planning of which individuals to include and which analyses to perform after the data is acquired, thus introducing the risk for bias from data-driven analysis and introduction of a type 1 error. We managed this risk by prospectively registering the studies in online databases of clinical trials. Papers I and II were registered with the Australian New Zealand Clinical Trials Registry, and Papers III, IV and V were registered with ClinicalTrials.gov. Thus, we specified the analyses before accessing the data.

As our studies on sepsis were performed on data from 2005 to 2017, the diagnostic coding has been based on the Sepsis-2 (9) and not the present Sepsis-3 criteria (10). However, Sepsis-2 and Sepsis-3 criteria identify similar cohorts, differing mainly in the proportion with septic shock (23), and long-term follow-up is precluded by using Sepsis-3 definitions in cohorts defined by diagnostic codes.
The outcome, incident dementia, in Paper I, is defined by diagnostic codes in the NPR (inpatient section), which risks overlooking patients not allocated to inpatient care. In order to miss fewer dementia diagnoses we added data from the SveDem covering all specialist memory units and an increasing proportion of primary care. An imbalance of missed diagnoses is not likely between Sepsis patients and other ICU patients. Yet, the unknown proportion of overlooked dementia diagnoses could cause non-differential non-dependent misclassification and as such, information bias, which would dilute the exposures effect on the outcome. Moreover, in Paper I, we reported high short- and long-term mortality, with two effects. First, we excluded nearly one third of the patients because of death in the first year after ICU admission. To respond to the impact of the exclusions, we performed a sensitivity analysis with inclusion at ICU admission rather than at one year after admission. Despite this manipulation, Sepsis remained a non-significant variable in the model. Second, dying during follow-up is an important competing event for the eventual development of dementia. To address this issue, we performed a sensitivity analysis on patients with a lower risk of mortality by including only patients of the lowest SAPS 3 quartile. The sensitivity analysis did not change the significance of Sepsis in the model. We chose not to perform a competing events analysis, because the hypothetical population where dead patients could acquire dementia is not realistic and also not relevant to the question of whether Sepsis in the ICU is a risk factor for dementia (232).

We had a high proportion of missing SAPS 3 in Papers I to III and thus, we chose to use multiple imputations by chained equations, rather than excluding the patients with missing data. This avoided the exclusion of many patients and still allowed us to adjust for acute illness severity at ICU admission. The validity of the imputations was tested by sensitivity analyses: complete case analysis, and in Paper I also by performing the model without SAPS 3. In Papers I and III the sensitivity analyses gave similar results to the main analyses, but in Paper II we found a marked difference in that sepsis was protective in a complete case analysis. The latter finding stresses the importance of multiple imputation in situations with significant amounts of missing data in key variables (146).

During the first surge of Covid-19, patient selection for intensive care may not have represented normal circumstances because of strained ICU capacity. The strain might have led to more active work with limitations of life sustaining care than usual, possibly affecting the external validity of the findings in Papers III and IV. Limitations of ICU care are based on patient attitudes, biological age, comorbidities and the acute illness (233) but in a situation with scarce resources limitations might be applied at a lower burden of age, comorbidity and acute illness; this could skew the results compared with other ICU cohorts of the first surge and later Swedish ICU cohorts. Moreover, the admission
criteria could have been changed during the surge, as an increasing number of patients may have been treated with high-flow oxygen and non-invasive ventilation in regular hospital wards. In Paper III we performed a sensitivity analysis that included only IMV patients, to address this possibility. However, the models differed from the main analysis only on oral anticoagulants not being protective against ICU admission with IMV, a finding with a p-value close to 0.05 in the primary analysis. Furthermore, in Paper III we did not match for the region of residence. Region of residence may be important, as Covid-19 was spread unevenly across the country, and the studied comorbidities are unevenly distributed as well (234). This irregularity in comorbidities could, in part, be explained by different age distributions over regions, and age was controlled for in our models. Matching on region of residence was performed in Paper V.

Body mass index above 25 or 30 would have been a more precise and sensitive definition of obesity than the one we used, which was based on previous ICD-10 diagnoses, certain interventions and medications. Regrettably, we did not have access to the body mass index of the included patients in Papers III and IV. For Papers III and IV, we also did not have access to socioeconomic factors which are indicated to affect the risk of Covid-19 infection, hospital and ICU admission and mortality in Covid-19 (235). Finally, we lack information on patient frailty, an important prognostic entity (236), regretfully not reported to the SIR during the study periods.

6.4 Methodological considerations
6.4.1 Bias related to misclassification
As stated earlier, we believe that the coding of Sepsis in the SIR is fairly reliable. Regarding ARDS, compared with prevalence studies, we reported a rather low proportion of ARDS patients in Paper IV, possibly due to less than perfect coding. We do not regard the potential misclassifications of our exposures and outcomes as either dependent or differential. This because the exposures and the outcomes for our studies are recorded at different time points and are collected from different sources.
6.4.2 Bias related to selection of the control group

As there was a pronounced shortage of testing resources during the first wave of the pandemic, we used a control group consisting of general population individuals instead of Covid-19-infected individuals. Doing the latter, in Paper III and V, would have introduced marked selection bias due to conditioning on the collider “tested and positive for Covid-19” (Figure 18). Conditioning on a collider has the same effect as adjusting for a collider in a statistical model (237).

![DAG on the effect of selecting participants based on testing status.](image)

The square symbols selection: i.e., conditioning on Tested and positive for Covid-19. Asthma is the exposure and ICU admission with Covid-19 is the outcome. The figure was produced on the dagitty.net web page.

6.4.3 Missing data

In all Papers we imputed missing SAPS 3, and in Paper IV also time-at-risk data, using multiple imputation by chained equations. SAPS 3 data in the SIR are known not to be missing completely at random (238) and therefore there is a risk of bias if only complete cases were analyzed, especially given the high proportion of missingness (239). We could have omitted the SAPS 3 variable, but for Papers I and II our aim was to separate the potential effect of sepsis from the potential effect of severe illness on the risk of later development of dementia and long-term mortality.

6.4.4 Matching in case control design

Case control design is used when individuals with an outcome of interest are identified (i.e., cases) and potential differences in exposure between these individuals and individuals of a broader population are compared. It is common, though not without problems, to match the control individuals to the cases on some variables. Matching may introduce selection bias, as the matching process often makes the controls more similar to cases in other aspects than the matching variables (136, 240). There are also conflicting views on the validity of matching as a means to improve efficiency in the analysis. Matching on a
variable makes the controls and cases identical over the matched strata, e.g., sex. (136, 240, 241). Usually the matched factors should be controlled for in the analysis unless there is no association between the matching factor and the exposure. In the case of Paper III, we matched on age and sex and controlled for those variables by performing a conditional logistic regression model (the analyses were stratified on case-control set) advocated by many (242). However, if a stratified analysis is performed, some strata may be identical, not only on the matched variables but also on the rest of the variables in the model. These identical strata provide no information to the model and are thus excluded. A high ratio of controls to cases can alleviate this effect (136, 240, 241). An unconditional logistic regression analysis, also including age and sex, might also have been an appropriate choice of method (240).

6.4.5 Model assumptions
All statistical tests make some assumptions about the data. Below I will discuss some of the assumptions relevant to the research underlying this thesis.

6.4.5.1 The proportional hazards assumption
The proportional hazards assumption of the Cox proportional hazards model is a strong assumption that the hazards are proportional over time between outcomes, i.e., the hazard ratio does not change with time. This is a very demanding assumption, which can be tested in several ways. The most basic test is to draw Kaplan-Meier plots and evaluate whether the lines are crossing, a feature that is strongly suggestive of non-proportional hazards, at least in a non-adjusted model. A statistical test of the correlation of scaled Schoenfeld residuals with time can be performed (243), but like the test of normality with the Kolmogorov-Smirnov test, the suggested statistical test is sensitive to the size of the population. In a large population, even minimal differences are statistically significant. In Papers I, II and III we chose to visually inspect plots of the scaled Schoenfeld residuals against the transformed time, looking for patterns over time. We found no patterns; however, in Paper II it was obvious that the HR of sepsis varied over time, as it was significantly below one in the first 30 days and above one later. Because of this finding, we performed a sensitivity analysis where time was cut at <31 days and all variables suspected to be time varying were reported with two HRs. Some authors, such as Hernán and Stensrud, state that that the proportional hazards assumption is biologically implausible and that HRs should only be interpreted as a weighted average. From this, the conclusion is that testing for proportional hazards is unnecessary. It is further suggested to report restricted survival differences at different, pre-specified, time points during follow-up (244, 245).
6.4.5.2 Non-linear continuous data

Many physiologic variables, such as age or weight, are not linear in relation to the outcome studied in regression analysis. Linearity is a basic assumption in all statistical models used in this thesis; however, neither age nor SAPS 3 can be expected to be linearly linked to any diagnostic or vital outcome (149, 246). Also, where appropriate, visual inspection of plots of Martingale residuals against the tested variable revealed non-linearities (247). Hence, we had to employ strategies to neutralize these non-linear relationships. The most basic strategy is to categorize the variable, e.g. divide age into age spans. There are three problems with that strategy. First, there is a loss of information in the categorization and the loss is larger with fewer categories. Second, if age is categorized into two levels, and the relation between age and the outcome is u-shaped there would, seemingly, be no difference related to age in the outcome. Third, if age is categorized into deciles the underlying assumption is that there is no difference in relation to outcome between age 71 and 79, but there is a difference between age 79 and 80 (248). This assumption is obviously biologically implausible. Another strategy is to use a transformation on the non-linear variable (e.g., a logarithmic transformation). However, this transformation seldom makes a better fit to the linear assumption. Finally, the variable can be fitted to a regression or penalized spline function. Splines allow for the relationship between the variable and the outcome to be non-linear through a series of functions connected at knots, at a loss of degrees of freedom (149, 249). We used restricted cubic and penalized splines and placed the knots at software pre-defined places related to percentiles. Finally, we combined the regression estimates for all parts of the spline into one estimate.

6.4.5.3 Multicollinearity

Multicollinearity is a concept where two or several variables in a model are statistically correlated. In Paper IV we found indications of multicollinearity for age and SAPS 3 box III in the binary logistic models on 60-day mortality. We assessed the impact of multicollinearity in relation to the SAPS 3 box III by performing a sensitivity analysis without that variable and found only minor changes to the model output. The impact of multicollinearity in relation to age was not assessed, as we believed that modelling without age would be pointless. Also, the main consequence of multicollinearity is very large standard errors, which were not found for any of the independent variables in the model (250).

6.4.6 Loss to follow-up

Registry research using Swedish governmental registries has a relatively low loss to follow-up, as basically, only emigrated individuals are lost. We report unexpectedly low numbers of loss to follow-up due to emigration in Papers I, II and V. However, emigration was probably not fully captured. Had the total
population register been used instead of reports to the NPR, the proportion with emigration during follow-up would probably have been higher. Loss to follow-up might induce bias, especially if the loss is related to the exposure and the outcome. However, we believe that emigration status was not linked to the likelihood of being positive for the exposure or outcome in any of the papers. Thus, any outcome misclassification would be non-differential and possibly dilute any effect. The most up-to-date registry source would have been the TPR, from which we regrettably did not get this information.
7 Conclusions

In a large cohort of patients admitted to Swedish ICUs between 2005 and 2016, we found an increased incidence of dementia in patients with Sepsis, i.e., severe sepsis or septic shock. However, Sepsis was not independently associated with incident dementia in one-year survivors. This finding suggests that it is reasonable to think severe illness, rather than the sepsis syndrome itself, is responsible for an apparent increased risk of dementia in sepsis survivors.

In the same cohort we investigated the extended mortality in patients with Sepsis compared to patients without. The 15.5-year follow-up was divided into eight assessment periods and, in Cox models, Sepsis was found to be weakly associated with mortality for the full follow-up and more strongly associated with mortality during the first six assessment periods, i.e., until five years after ICU admission. Furthermore, causes of death differed between patients with and without Sepsis. The adjusted risk for infectious causes of death was increased in Sepsis during all assessment periods. These findings indicate that the sepsis syndrome has a small but statistically significant long-term effect on patients’ survival and that there is a persistent increased susceptibility to mortality from infections.

In a national Swedish ICU cohort of Covid-19 patients and population controls, we assessed independent risk factors for ICU admission and ICU mortality in two sets of regression models. In logistic regression, hypertension, T2DM, CRF, asthma, obesity, solid organ transplants, as well as ongoing treatment with immunosuppressants, were linked to ICU admission with Covid-19. In a Cox regression, age, acute illness severity, stroke, COPD, asthma and ongoing treatment with RAASi were independently associated with increased ICU mortality. Ongoing treatment with oral anticoagulants was protective of ICU admission, and statins were protective against ICU mortality. However, when we compared the impact of these comorbidities on 60-day mortality after ICU admission with Covid-19, sepsis and ARDS, we found only a few differences. This finding suggests that comorbidities are mainly risk factors connected to severe illness, rather than specific syndromes.

When we assessed sick leave one year after ICU admission with Covid-19 compared to hospital admission with Covid-19 and population controls, in
working age individuals, we found a marked impeded recovery in the ICU cohort also after adjustment for age, sex, socioeconomic status and comorbidities. From this we conclude that there is a large proportion of Covid-19 patients that have an impeded functional recovery during the first year after ICU admission.
Clinical considerations and future aspects

Our findings regarding long-term causes of death in Sepsis patients warrant confirmation in other cohorts. If, indeed, Sepsis patients have a markedly increased risk of mortality from infectious diseases at a distant point in time, interventions aimed at future infections in connection with the evolving clinics for follow-up after ICU care might be feasible.

Risk factors and preventive factors in Covid-19, but also in Sepsis and ARDS, need to be further explored in order to find possible mechanisms for modifications of the risks. In addition to further refinement of the care delivered in the ICU, the aforementioned follow-up clinics need to focus on the functional recovery of Covid-19 patients, and there is a need to find post-ICU interventions that might help the patients achieve a more favorable outcome than those in our cohort.


10 Acknowledgments

As I put the final words to this doctoral thesis, there are many people to whom I am in debt. I want to express my gratitude to a number of people:

My supervisors. Miklós Lipesey, my main supervisor, who has been vastly supportive since day one, when he pointed out that scientific work is, at best, 10% inspiration and 90% perspiration. Always kind, always swift. Ing-Marie Larsson for her patience and support and Gunnar Strandberg for his attention to detail.;

Moreover, my gratitude is directed toward my co-authors Michael Hultgren for his patience, energy and great knowledge of the regression methods and R programming, and Robert Frithiof for his many ideas and skill with words;

Professor Sten Rubertsson, who gave me advice and pointed me in the right direction when I asked about how to get involved in research;

Inger Mattson, our previous head of clinic, for her personality and her generous support in resolving the catch 22 of obtaining a doctoral position without funding and vice versa. Torbjörn Roos, our head of clinic, for generous support and continuous understanding. Without his excellent leadership during the pandemic waves there would have been a steady stream of quitting co-workers, dying Covid-19 patients and no time to do research. Eva Brolin, our assistant head of clinic, for her generosity and kindness. The former and present heads of the ICU, Lena Moren, for her integrity, frankness and support, Monica Kihlström, for solving every problem you could think of. Lisa Singdén, for swiftness and problem solving and Eva Olsson whom I’m just now getting to know;

Lisa Hårdstedt, who managed to always make sure to remember my research weeks, even in periods with a scarcity of anesthesiologists at the clinic. Jeanette Vestling, my present companion and Magnus Enlund my former companion as medical director at the ICU in Falun, for their never-ending patience and all great discussions. All anesthesiologists at the clinic, for their never-ending dedication to our patients and their forbearance with my divided focus during the last seven years. Nurses, assistant nurses and physiotherapists
of the ICU and all other co-workers on the Op/An/IVA-kliniken for keeping our care up to standards;

The SIR and all those working hard to allow the registry to collect and share data with clinicians and researchers. The ICU patients, for their generous sharing of their data to the SIR;

Henrik Renlund, statistician at Uppsala Clinical Research Center, with great pedagogical skills and Riccardo Lomartire, our in-house statistician at the Center for Clinical Research in Dalarna (CKF), for his sharp methodological thinking, excellent patience and pedagogical skills;

Leslie Shaps and an anonymous editor at Anchor English, for proof-reading which makes my writing more understandable;

Erica Schytt, former director of CKF, and Catharina Gustavsson, present director, for their continuous work in creating a research environment at Nissers väg 3. Björn Ång, director of research in Region Dalarna, for helping Erica and Catharina with the creation of this environment and for stalwart methodological support. The CKF, Region Dalarna, for generous financial aid;

Karin Björling, Isabell Boväng Östman, Sofia Möller Skog and Sara Skoglund and Camilla Ottosson at CKF, and Katja Andersson, Siv Andersson, Elin Eriksson and Birgitta Haglund at the Institution of Surgical Sciences, for making the administrative burdens easy to carry;

Fellows at the Swedish INterdisciplinary Graduate School in register-based research (SINGS) for interesting interactions and dedication to understand the finer aspects of registry research methods;

My friends, for helping me think of other things than the PhD;

Sylvia and Kjell for being supportive and kind;

Mona for being the best mother I could wish for;

Finally, Sara, for your endless patience and understanding when the research work has stolen my time and focus. Eskil and Knut for bringing joy and meaning to my life and for patiently waiting for me to be available again.
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A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)