Biomarkers and outcomes in critically ill COVID-19 patients

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LUND
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DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on November 14 at 13.15 in Agardhsalen, Clinical Research Centre, Jan Waldenströms gata 35, Malmö, Sweden.

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Abstract: This thesis investigates the survival and long-term outcomes of critically ill COVID-19 patients admitted to intensive care units (ICUs) in the Skåne region of Sweden between May 2020 and May 2021. The study aimed to address knowledge gaps by conducting a prospective, multicentre cohort study following 498 ICU patients over 3 years, evaluating mortality, functional, physical and mental outcomes, as well as Health-Related Quality of Life (HRQoL) and disease severity biomarkers.

Paper I examined factors associated with 3-month mortality in 498 critically ill COVID-19 patients. At 3 months, mortality was 39%, increasing significantly in patients aged over 60 years. A higher ICU burden (>50 patients) was independently associated with a two-fold increase in the odds of mortality, whereas a higher BMI was not associated with increased mortality. A longer ICU stay was associated with a lower Glasgow Outcome Scale (GOSE) score at 3 months.

Paper II investigated recovery patterns between 3 months and 1 year post-ICU. The percentage of patients with a good functional outcome (GOSE ≥ 7) increased from 35% to 64%. Physical HRQoL improved significantly whilst mental health remained stable. A shorter duration of mechanical ventilation and higher age were associated with a better functional outcome at 1 year.

Paper III identified plasma calprotectin as a potential biomarker for mortality and long-term outcomes. Increasing calprotectin levels during the first week of ICU care were independently associated with 1-year mortality, unfavourable functional outcome (GOSE ≤ 5) and organ failure. Day 7 calprotectin combined with age was a good predictor of 1-year mortality.

Paper IV extended the follow-up period to 3 years, revealing a decline in functional outcome and mental health despite stabilised physical health. The proportion of patients experiencing incomplete recovery (GOSE ≤ 6) increased from 32% to 45% between the first and third year post-ICU. Younger age and higher baseline frailty were associated with incomplete recovery at 3 years, indicating the need for individualised follow-up.

Key words: **COVID-19, Critical Illness, Intensive Care Units, Calprotectin, Outcome, Quality of Life**

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"Intensive Care is the Fine Art of Being There

"-Anders Ersson, my first ICU mentor.

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List of Publications

This thesis is based on the following papers, referred to in the text by their Roman numerals:

I. Didriksson, I., Leffler, M., Spångfors, M., Lindberg, S., Reepalu, A., Nilsson, A., Cronqvist, J., Andertun, S., Nelderup, M., Jungner, M., Johnsson, P., Lilja, G., Frigyesi, A., & Friberg, H. (2023). Intensive care unit burden is associated with increased mortality in critically ill COVID-19 patients. *Acta Anaesthesiologica Scandinavica, 67*(3), 329–338.

II. Didriksson, I., Frigyesi, A., Spångfors, M., Leffler, M., Reepalu, A., Nilsson, A. C., Annborn, M., Lybeck, A., Friberg, H., & Lilja, G. (2025). Long-term recovery in critically ill COVID-19 survivors: A prospective cohort study. *Acta Anaesthesiologica Scandinavica, 69*(1), e14550.

III. Didriksson, I., Lengquist, M., Spångfors, M., Leffler, M., Sievert, T., Lilja, G., Frigyesi, A., Friberg, H., & Schiopu, A. (2024). Increasing plasma calprotectin (S100A8/A9) is associated with 12-month mortality and unfavourable functional outcome in critically ill COVID-19 patients. *Journal of Intensive Care, 12*(1), 26.

IV. Didriksson, I., Töniste, D., Hultgren, M., Spångfors, M., Göbel Andertun, S., Nelderup, M., Reepalu, A., Frigyesi, A., Friberg, H., & Lilja, G. (in submission). Three-year functional, physical and mental health outcomes in critical COVID-19 survivors: A prospective study**.** [In submission August 2025]

Publication Not Included in Thesis

Hultgren, M., **Didriksson, I**., Håkansson, A., Andertun, S., Frigyesi, A., Mellerstedt, E., Nelderup, M., Nilsson, A. C., Reepalu, A., Spångfors, M., Friberg, H., & Lilja, G. (2024). Prolonged fatigue and mental health challenges in critical COVID-19 survivors. *Journal of Intensive Care Medicine.*

Johnsson, P., Sievert, T., **Didriksson, I**., Friberg, H., & Frigyesi, A. (2024). Plasma bioactive adrenomedullin predicts mortality and the need for dialysis in critical COVID-19. *Scientific Reports, 14*(1), 23787.

Engström, J., Koozi, H., **Didriksson, I**., Larsson, A., Friberg, H., Frigyesi, A., & Spångfors, M. (2024). Plasma neutrophil gelatinase-associated lipocalin independently predicts dialysis need and mortality in critical COVID-19. *Scientific Reports, 14*(1), 6695.

Koozi, H., Engström, J., Zwawi, A., Spångfors, M., **Didriksson, I**., Larsson, A., Friberg, H., & Frigyesi, A. (2025). Plasma endostatin at intensive care admission is independently associated with acute kidney injury, dialysis and mortality in COVID-19. *Intensive Care Medicine Experimental, 13*, 1–11.

Sievert, T., **Didriksson, I**., Spångfors, M., Lilja, G., Blennow, K., Zetterberg, H., Frigyesi, A., & Friberg, H. (2023). Neurofilament light chain on intensive care admission is an independent predictor of mortality in COVID-19: A prospective multicenter study. *Intensive Care Medicine Experimental, 11*(1), 66.

Abbreviations

ACE2 - Angiotensin-Converting Enzyme 2
ARDS - Acute Respiratory Distress Syndrome
AUC - Area Under the Curve
CFS - Clinical Frailty Scale
CRRT - Continuous Renal Replacement Therapy
GOSE - Glasgow Outcome Scale Extended
HADS - Hospital Anxiety and Depression Scale
HADS-A - Hospital Anxiety and Depression Scale - Anxiety
HADS-D - Hospital Anxiety and Depression Scale - Depression
HRQoL - Health-Related Quality of Life
ICF - International Classification of Functioning, Disability and Health
IMV - Invasive Mechanical Ventilation
LOS - Length of Stay
MCS - Mental Component Summary
MFIS - Modified Fatigue Impact Scale
MID - Minimally Important Difference
NETs - Neutrophil Extracellular Traps
PCL-5 - PTSD Checklist for DSM-5
PCS - Physical Component Summary
PICS - Post-Intensive Care Syndrome
PROM - Patient-Reported Outcome Measure
PTSD - Post-Traumatic Stress Disorder
ROC - Receiver Operating Characteristic
SAPS 3 - Simplified Acute Physiology Score 3
SARS-CoV-2 - Severe Acute Respiratory Syndrome Coronavirus 2
SF-36v2® - Short Form Health Survey Version 2
SGRQ - St. George's Respiratory Questionnaire
SOFA - Sequential Organ Failure Assessment
SWECRIT - Swedish Critical Care Research Platform
TLR - Toll-Like Receptor

Preface

It was late February 2020, just as news of the highly contagious coronavirus outbreak in northern Italy began to dominate headlines. The virus that had emerged in Wuhan, China, had now reached Italy just as my husband and daughters were skiing in the Aosta Valley. After returning to Malmö, my eldest daughter and I caught severe colds. Concerned that we might have contracted the feared new virus, I consulted an infectious diseases specialist, who reassured me since my family hadn't been in the Lombardy hotspots. In the end, it was just an ordinary cold. But none of us could have foreseen that within weeks, the very crisis we had been watching unfold on the news would arrive at our doorstep, completely transforming our ICU and the world around us.

The initial warning came when a friend shared tweets from an Italian emergency doctor describing chaotic conditions at his hospital. Days later, a colleague arranged an online meeting with an intensive care physician from Bergamo. Around 40 staff members gathered to hear him describe what sounded like an inferno. At that moment, we collectively realised our hospital needed to take immediate action to prepare for the coming surge of critically ill patients.

As a senior intensive care physician, I was asked to join a small team to establish a specialised COVID-19 ICU. Within a week, we opened our doors to admit the first patients. What followed was a wave of critically ill patients, unlike anything we had seen before, placing enormous strain on patients, their families and our entire healthcare system. Witnessing the devastating impact of this new virus, I wanted to contribute to our understanding of the disease.

The SWECRIT COVID-19 study was established through the dedicated collaboration of colleagues across six intensive care units in southern Sweden, led by Professor Hans Friberg. The four papers comprising this thesis are part of that research and represent our evolving understanding of COVID-19 critical illness. Patient journeys are documented from initial mortality factors to three-year recovery patterns, and the findings identify factors relevant to both clinical practice and future pandemic planning.

Above all, I am deeply grateful to the patients and their families for their participation during this challenging period, and to the healthcare professionals who supported this research alongside their dedicated patient care.

Introduction

The COVID-19 Pandemic

The Coronavirus Disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), created an unprecedented global health crisis. First identified in December 2019, the virus rapidly spread worldwide, resulting in millions of deaths [1]. The World Health Organization (WHO) declared COVID-19 a pandemic on March 11, 2020, triggering an extraordinary response from healthcare systems worldwide.

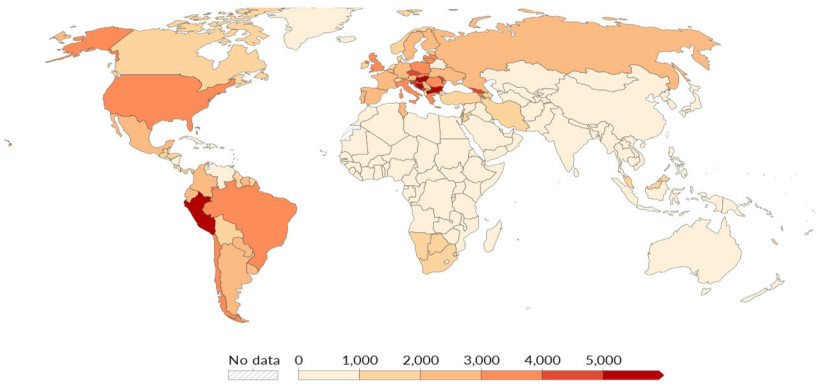

Figure 1: Cumulative confirmed COVID-19 deaths per million people (June 2024). Source: World Health Organization (WHO) COVID-19 Dashboard [1]. Licensed under CC BY-NC-SA 3.0 IGO

As shown in Figure 1, COVID-19 deaths varied widely between countries, reflecting differences in healthcare infrastructure, demographics, and pandemic responses. Sweden's strategy focused on recommendations rather than mandated restrictions, which initially sparked considerable debate [2]. The impact of the pandemic reached far beyond healthcare, profoundly affecting social, economic and psychological aspects of society [3, 4]. The immense strain on healthcare resources, particularly critical care, exposed systemic weaknesses and required rapid adaptation in clinical practices [5, 6]. This was particularly challenging for Sweden, which had among Europe's lowest ICU capacity per capita [7, 8].

Acute COVID-19 and Short-term Outcomes

While most individuals infected with SARS-CoV-2 experienced mild to moderate symptoms, approximately 1–5% [9, 10] developed critical illness [11]. These cases were characterised by acute respiratory failure, multi-organ dysfunction and carried a high risk of death [12].

Acute Respiratory Distress Syndrome (ARDS)

ARDS is a life-threatening condition marked by severe pulmonary inflammation and alveolar damage, leading to impaired gas exchange and respiratory failure. Traditionally, ARDS diagnosis was based on the Berlin criteria, which required invasive mechanical ventilation (IMV) and specific oxygenation thresholds [12] (Figure 2).

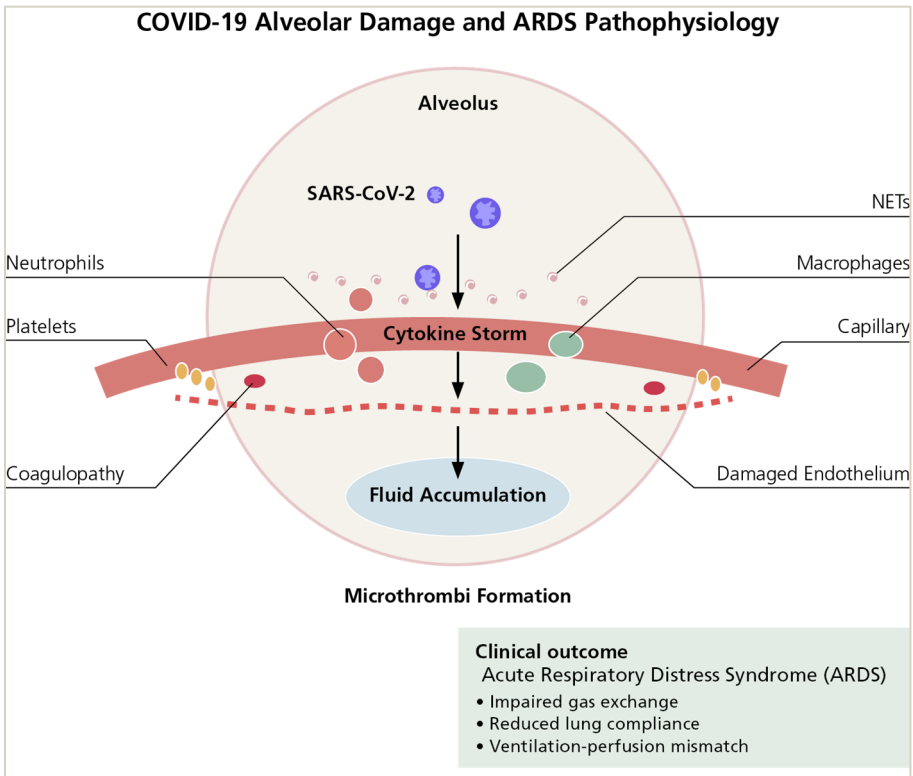

Figure 2: Pathophysiology of COVID-19-induced acute respiratory distress syndrome (ARDS). SARS-CoV-2 infection triggers inflammatory cell infiltration and cytokine storm, leading to endothelial damage, alveolar fluid accumulation and microthrombus formation, resulting in impaired gas exchange and ARDS. Arrows indicate the sequential pathophysiological cascade from viral infection to the development of ARDS.

During the COVID-19 pandemic, clinical observations challenged this definition. Many patients exhibited ARDS-like features while receiving high-flow nasal oxygen (HFNO), prompting a global redefinition in 2023 to include non-intubated patients [13]. COVID-19 ARDS differs from classical ARDS in its immunothrombotic profile, with distinct patterns of coagulopathy, lymphopenia, and neutrophil hyperactivation [14, 15].

Immunopathology of Critical COVID-19

SARS-CoV-2 enters host cells by binding to angiotensin-converting enzyme 2 (ACE2) receptors, which are highly expressed on epithelial and endothelial cells. This interaction leads to elevated levels of angiotensin II. Once inside the cell, the virus activates components of the innate immune system, particularly Toll-like receptors (TLRs).

TLRs are essential elements of the innate immune system, responsible for recognising pathogen-associated molecular patterns (PAMPs), such as viruses, and triggering immune responses. Among these, TLR7 and TLR8 are endosomal receptors that detect single-stranded RNA viruses [16]. TLR7 typically triggers antiviral defence by promoting type I interferon production, a crucial mechanism for early viral clearance. In contrast, TLR8 activation leads to the release of proinflammatory cytokines [17].

In SARS-CoV-2 infection, TLR8 is preferentially activated, leading to suppression of type I interferon responses and enhanced cytokine release via NF-κB [18, 19]. This TLR8-dominant immune activation drives neutrophil hyperactivation, which plays a central role in the pathogenesis of critical COVID-19 by contributing to respiratory failure, acute kidney injury and multiorgan dysfunction [20, 21]. In contrast, individuals who generate an early and robust interferon response through TLR7 usually clear the virus effectively and experience mild symptoms [21-23].

Elevated angiotensin II levels further amplify TLR8-driven inflammation [24], creating a systemic hyperinflammatory state known as a "cytokine storm" characterised by neutrophilia, lymphopenia and dysregulated inflammatory pathways [15, 25, 26]. A major downstream effect is the release of large amounts of calprotectin by hyperactivated neutrophils [27-31]. The described inflammatory response is reflected in elevated biomarkers, including C-reactive protein (CRP), interleukin-6 (IL-6) and calprotectin.

Neutrophil Extracellular Traps (NETs)

A key consequence of neutrophil hyperactivation is the formation of Neutrophil Extracellular Traps (NETs) [32, 33]. NETs are produced during NETosis, a specialised form of neutrophil cell death in which neutrophils release their

chromatin and granular contents into the extracellular space, forming web-like structures composed of extracellular DNA, histones, antimicrobial peptides, and cytoplasmic proteins such as calprotectin [34, 35]. SARS-CoV-2 can directly induce NET formation by binding to ACE2 receptors expressed on neutrophils [36].

While NETs are normally part of the host defence, excessive NET formation contributes to alveolar damage, hyperinflammation and coagulopathy [37, 38]. In severe COVID-19, NETosis is driven by multiple stimuli, including viral exposure, inflammatory cytokines, activated platelets and complement components, creating a self-sustaining inflammatory cycle [39-41].

COVID-19 ARDS has been associated with higher levels of NETosis markers than conventional ARDS [33, 37]. In pulmonary tissue, NETs contribute to alveolar capillary injury and fibrotic remodelling, while in the vasculature, they promote endothelial dysfunction, increased permeability, and complement activation [38, 42].

NETs have been implicated in both acute organ failure and persistent post-viral complications [43, 44]. The persistence of NETs in circulation for months may underlie both acute mortality and long-term outcomes, including post-COVID-19 condition [45, 46].

Calprotectin (S100A8/A9)

Calprotectin (S100A8/A9) is a heterodimeric protein that makes up nearly half of the cytosolic proteins in neutrophils and is released during neutrophil activation and NETosis [47]. Once released, it binds to TLR4 and Receptor for Advanced Glycation End-products (RAGE), triggering inflammatory cascades that sustain ongoing NET formation [48].

Calprotectin has been linked to neutrophil activation, NETosis [49], as well as clinical outcomes, suggesting it could serve as a biomarker for predicting disease progression in severe COVID-19 cases [30, 31, 50]. Its stability in plasma makes it suitable for monitoring [51], and serum calprotectin offers improved sensitivity and specificity compared to conventional markers, such as CRP and procalcitonin [52].

Recent studies have shown that calprotectin levels remain elevated for months in some patients, especially those with persistent pulmonary dysfunction and exercise intolerance [53]. While calprotectin and other inflammatory markers indicate acute disease severity [27, 29], the potential prognostic value of calprotectin for long-term outcomes in COVID-19 survivors warrants investigation (Figure 3).

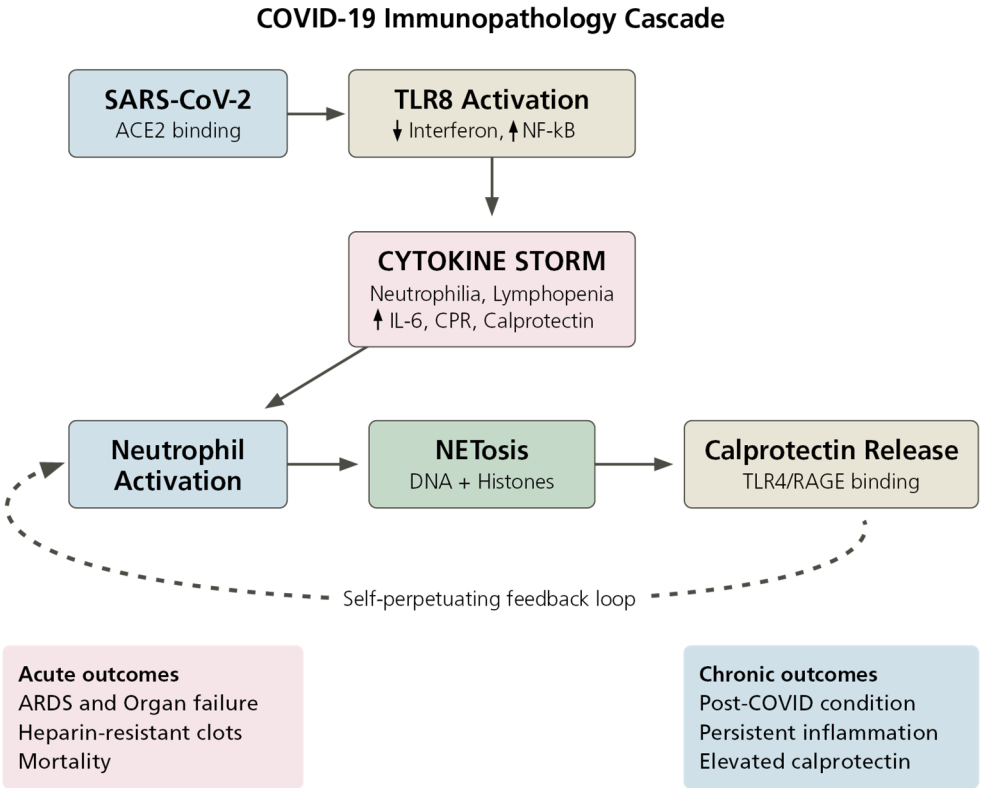

Figure 3: COVID-19 immunopathology cascade. SARS-CoV-2 infection, mediated by ACE2 binding and TLR8-induced immune dysregulation, triggers a cytokine storm, leading to neutrophil activation and NETosis. Calprotectin released during NETosis initiates a self-perpetuating inflammatory cycle through TLR4/RAGE binding, potentially contributing to both acute and chronic COVID-19 outcomes.

Treatment strategies for COVID-19

Management of critically ill COVID-19 patients evolved rapidly during the pandemic. Early clinical debates focused on the timing of intubation and invasive mechanical ventilation (IMV). Some advocated for early intubation to prevent deterioration, while others favoured extended trials of non-invasive respiratory support [54-56]. These differing approaches reflected the heterogeneity of COVID-19 presentations. They contributed to a broader understanding of ARDS phenotypes, informing both diagnostic criteria [13] and treatment strategies [54]. Prone positioning became a cornerstone of care and was increasingly applied even in non-intubated patients [57, 58].

As the understanding of COVID-19 pathophysiology deepened, treatment strategies expanded beyond respiratory support to include immunomodulatory interventions

targeting the dysregulated inflammatory response. Corticosteroids emerged as a central component of therapy, with dexamethasone demonstrating significant mortality benefits in oxygen-requiring patients [59]. Subsequent studies reinforced the role of corticosteroids in severe cases, highlighting their ability to dampen hyperinflammation and reduce organ damage [60-63].

Targeted therapies were also introduced to modulate specific immune pathways. IL-6 receptor antagonists, such as tocilizumab, have been evaluated for their potential to reduce cytokine-mediated injury and improve outcomes in select patients [64-67]. Janus kinase (JAK) inhibitors offered an alternative route to immune modulation, with some studies reporting benefits in reducing inflammation and improving survival [68, 69]. Antiviral agents such as remdesivir were investigated for their ability to limit viral replication and shorten disease duration [70].

Anticoagulation strategies were widely implemented to address the high incidence of thrombotic complications in critical COVID-19. However, standard prophylactic heparin often proved insufficient [71, 72]. Excessive NET formation contributed to heparin-resistant clots, a phenomenon known as immunothrombosis, which was particularly prominent in COVID-19 ARDS [36, 73, 74].

Mortality and Early Clinical Outcomes in Critical COVID-19

While evolving treatment strategies improved management approaches, mortality among critically ill COVID-19 patients remained substantial and varied widely, ranging from 16% to 78% across different centres and time periods [75, 76]. These differences were influenced by patient demographics, healthcare system capacity and evolving treatment strategies [77]. Older age was consistently associated with higher mortality risk [78].

In critically ill patients with COVID-19, respiratory failure was the most prominent and defining feature, and acute respiratory distress syndrome (ARDS) was present in over 70% of those treated in intensive care [79]. Although mortality in COVID-19-associated ARDS was similar to non-COVID ARDS (45% vs 40%) [80], COVID-19 ARDS exhibited distinct clinical and pathophysiological characteristics[14].

Large cohort studies report that acute kidney injury occurred in about 17% of hospitalised COVID-19 patients, with mortality rates of 52%, rising to nearly 80% in those needing renal replacement therapy [81, 82]. Thrombotic complications were also common, with pulmonary embolism reported in 26% of ICU patients and associated with a 45% mortality rate [83]. Neurological and cardiac dysfunction further complicated clinical management [84, 85].

Frailty in Critical COVID-19

Frailty has been recognised as a significant determinant of outcomes in critically ill patients [86]. In COVID-19 ICU populations, its impact varies across age groups. In patients over 70, frailty predicts mortality more accurately than age or comorbidity [87]. To assess frailty, the Clinical Frailty Scale (CFS) is commonly used. It is a validated 9-point tool that evaluates baseline vulnerability based on physical fitness, comorbidities and functional status [88] (Figure 4).

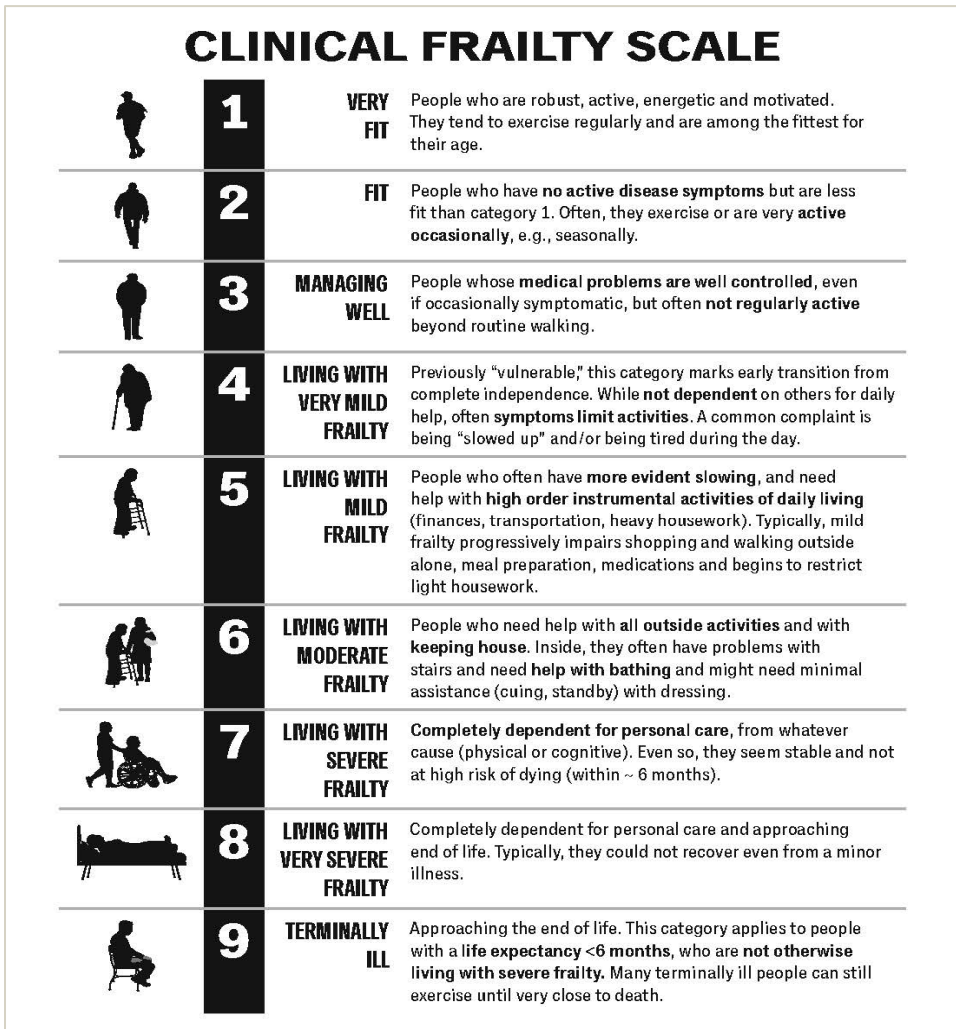

Figure 4: The Clinical Frailty Scale (CFS) ranges from 1 (Very Fit) to 9 (Terminally Ill), providing a standardised assessment of frailty in clinical settings. Source: Rockwood et al., 2005 [88].

Recovery

Recovery patterns in COVID-19-associated ARDS share many similarities with those seen in non-COVID ARDS, particularly in the initial phase. Survivors of non-COVID ARDS typically show early functional improvement followed by stabilisation [89-93]. COVID-19 survivors often follow comparable trajectories, but recent longitudinal studies [94-98] suggest that a subset may experience delayed deterioration in mental health, distinguishing COVID-19 from other forms of respiratory failure.

Post-Critical Illness Sequelae

Survivors of critical illness, including COVID-19, often experience lasting health challenges that affect recovery and quality of life. Two symptom-based classifications help explain these long-term sequelae: Post-Intensive Care Syndrome (PICS) and post-COVID-19 condition. PICS refers to new or worsening impairments following any critical illness requiring intensive care [93], whereas post-COVID-19 condition can occur after SARS-CoV-2 infection, regardless of initial disease severity [99]. Critically ill COVID-19 survivors may present with features of both syndromes simultaneously [100, 101]. The core domains and symptom profiles of these conditions are summarised in Table 1.

Post-Intensive Care Syndrome (PICS)

PICS, formally defined in 2010 [93], encompasses persistent or new symptoms after intensive care, typically affecting physical, cognitive, and psychological domains. These symptoms are common among ARDS survivors and are associated with increased one-year mortality and reduced long-term Health-Related Quality of Life (HRQoL) [90, 102-104]. Fatigue is particularly prominent and often coexists with disturbances across domains, affecting independence, return to work, and overall well-being [105] (Table 1).

Post-COVID-19 Condition

As defined by the WHO, the post-COVID-19 condition is defined by persistent symptoms that develop within 3 months of SARS-CoV-2 infection, last at least 2 months, and cannot be attributed to other diagnoses[99, 100, 106]. These symptoms commonly affect physical, cognitive, and psychological functioning, as detailed in Table 1.

Table 1: Post-Intensive Care Syndrome and Post-COVID-19 Condition: Core domains

Comparison of Post-Critical Illness Syndromes

Post-Intensive Care Syndrome (PICS)	Post- COVID-19 Condition
• New/worsening impairments after critical illness • Persisting beyond acute hospitalisation	• Symptoms within 3 months of infection • Lasting ≥2 months • Not explained by other diagnoses
Physical domain	
ICU-acquired weakness ☑ (40%)	–
Profound fatigue ☑ (70%)	☑ (60%)
Respiratory limitations ☑	☑
Mobility limitations ☑	–
Exercise intolerance –	☑
Activities of daily living issues ☑	☑
Autonomic dysfunction –	☑
Cognitive domain	
Memory deficits ☑ (30–80 %)	☑ (20–70 %)
Attention problems ☑	☑
Executive function issues ☑	☑
Processing speed deficits ☑	☑
Psychological domain	
Anxiety ☑	☑
Depression ☑	☑
PTSD* ☑	☑
Sleep disturbances ☑	☑

* Post-traumatic stress disorder

PICS: Post-Intensive Care Syndrome; PTSD: Post-traumatic stress disorder.

Overlapping Syndromes

Recent research suggests that PICS and post-COVID-19 condition share notable similarities in pathophysiology and clinical presentation. The overlap makes differentiation challenging, particularly in critically ill COVID-19 survivors who may exhibit features of both syndromes [107, 108].

Theoretical Frameworks for Understanding Recovery

The Biopsychosocial Model

To better understand post-critical illness recovery, it is useful to have frameworks that address multiple health dimensions. The biopsychosocial model [109] proposes that health outcomes result from the interplay between biological, psychological and social factors [110] (Figure 5).

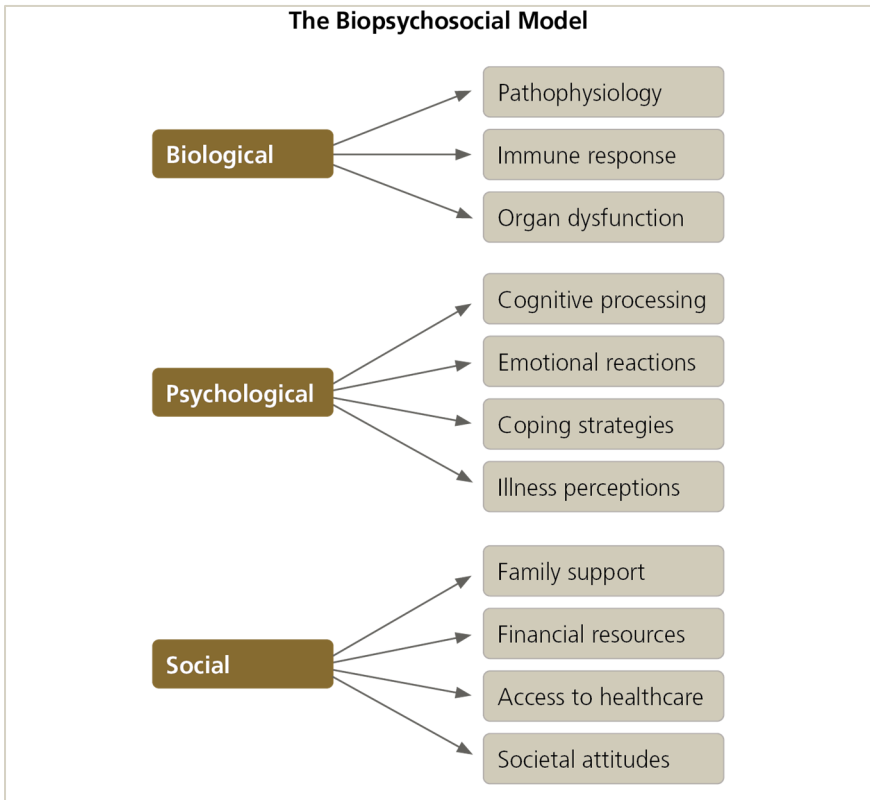

Figure 5: Biopsychosocial Model (Engel, 1977), showing biological, psychological and social domains.

In critical illness, the biological aspects encompass pathophysiology, immune response and organ dysfunction. The psychological aspect includes cognitive processing, emotional reactions, coping strategies and perceptions of illness. The social aspect addresses family support, financial resources, access to healthcare and societal attitudes [111].

Importantly, the model suggests that progress in one domain does not necessarily translate to progress in other domains, which may explain the often variable recovery after critical illness. Previous research in ARDS survivors has demonstrated that physical and psychological recovery often follow different timelines, with psychological symptoms sometimes persisting or emerging later in the recovery process [112].

The International Classification of Functioning, Disability and Health (ICF)

The WHO's ICF framework applies biopsychosocial principles to define and measure health and disability [113]. Figure 6 shows how health conditions affect body functions, activities, participation, and context. Unlike models that focus solely on disease, the ICF examines how people function in real life, making it especially useful for evaluating recovery after critical illness [93]. Studies of critical COVID-19 survivors using the ICF framework have demonstrated that physical recovery often follows a different timeline than functional recovery and social reintegration [114, 115].

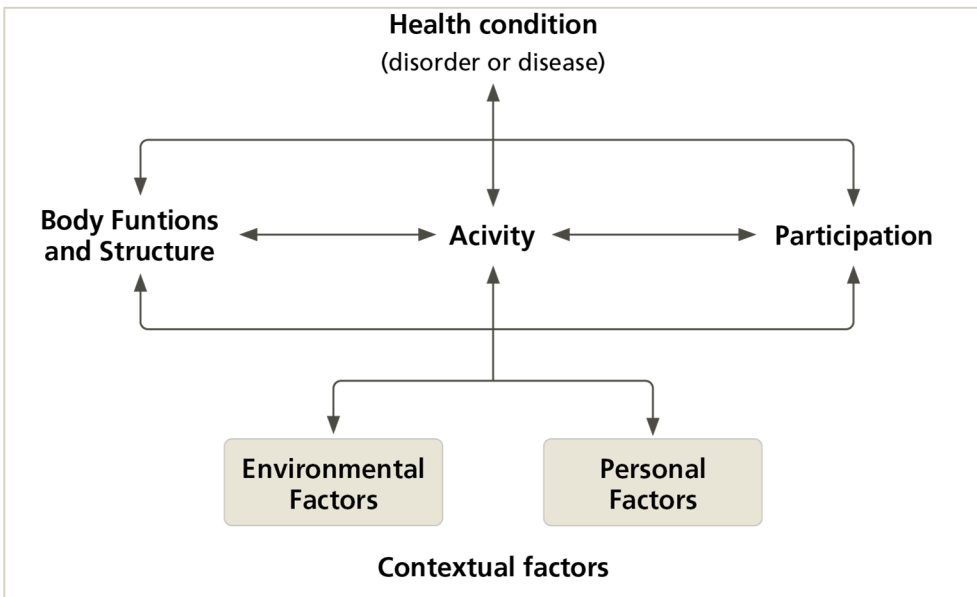

Figure 6: WHO's ICF framework [113], illustrating how health conditions interact with body functions, activities, participation and contextual factors.

Post-Viral Immunological Dysregulation

Research indicates that acute viral infections can disrupt immune regulation and trigger long-lasting abnormalities, even when the infection appears to have resolved [116]. Multiple concurrent processes drive post-COVID symptoms, including dysregulated NETosis, where neutrophils form excessive extracellular traps, persistent viral particles residing in tissue reservoirs, epigenetically reprogrammed immune cells, and autoantibody production [33, 37, 117].

SARS-CoV-2 readily triggers such dysregulation, with studies identifying autoantibodies, persistent immune activation, and ongoing NET formation in patients with the post-COVID-19 condition [37, 118, 119] (Figure 7).

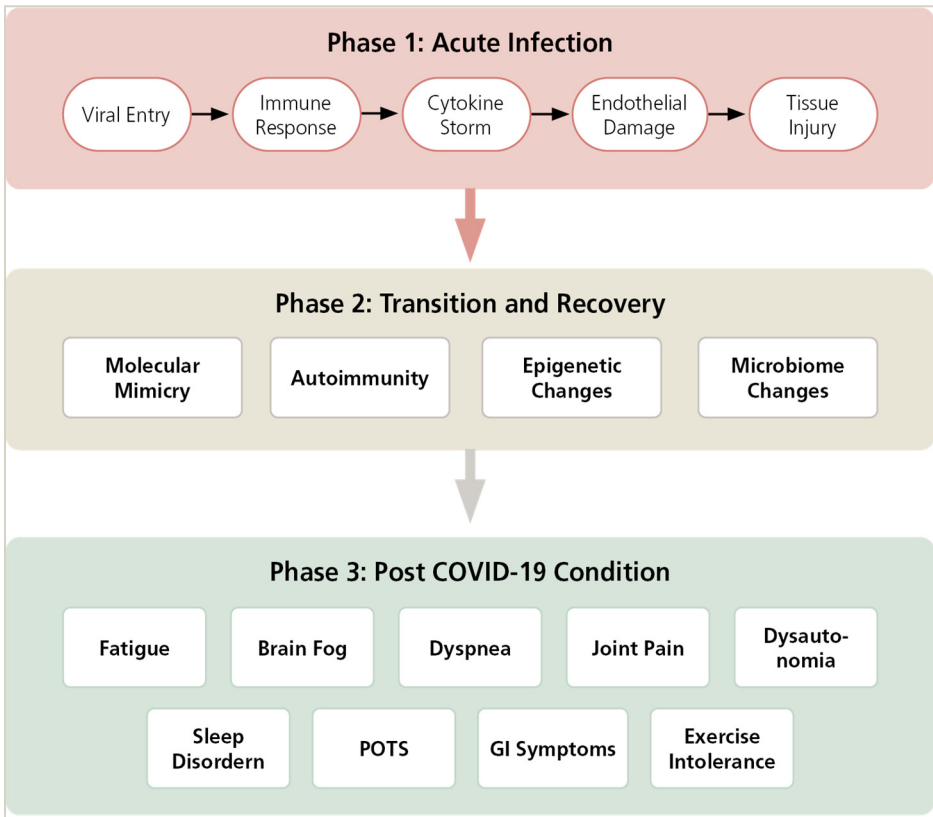

Figure 7: Post-viral immunological dysregulation in COVID-19 [116]: From viral infection to chronic immune dysregulation and long-term symptoms.

Integrating Biological and Biopsychosocial Perspectives

The biopsychosocial model, ICF framework, and post-viral immune dysregulation provide complementary lenses for understanding the long-term effects of critical COVID-19.

These approaches reveal how biological, psychological, and social factors mutually influence recovery. Post-viral immunologic dysregulation establishes the biological foundation, where prolonged immune activation directly impacts neurological and psychological functions through inflammatory pathways [120, 121]. Psychological stress and social adversity can further amplify immune dysfunction via neuroendocrine mechanisms [122]. The ICF framework structures how these factors manifest across life domains, from physical symptoms to functional limitations and reduced social participation [123].

Assessment of Recovery

Patient-Reported Outcome Measures

Patient-Reported Outcome Measures (PROMs) have emerged as essential tools for evaluating recovery from critical illness. These instruments capture the patient's perspective on symptoms, functionality, quality of life and satisfaction with life, reflecting a shift toward more patient-centred healthcare evaluation [124].

Intensive care medicine evolved in the early 2000s to focus on more than just survival. Clinicians and researchers began using PROMs more extensively in critical care and ICU survivorship studies to monitor physical, cognitive and psychological outcomes after discharge [93, 125].

Selecting appropriate post-ICU outcome measures involves balancing comprehensive evaluation against respondent burden [126]. This challenge is particularly important for patients recovering from serious illnesses, who may experience fatigue and cognitive limitations that affect their ability to complete lengthy assessments. Generic health instruments allow comparisons across various conditions but may not be sensitive to the unique challenges faced by ICU survivors. On the other hand, targeted measures may provide greater accuracy for specific domains but reduce comparability [127].

Core Outcome Sets for Critical Illness

International initiatives created standardised core outcome sets to address heterogeneity in outcome measurement in critical care research. The 2017 Core

Outcome Measures (COMs) for Clinical Research in Acute Respiratory Failure Survivors [128] recommend four outcome assessments: the Hospital Anxiety and Depression Scale (HADS) [129], Impact of Event Scale-Revised (IES-R) [130], Short Form 36 Health Survey (SF-36v2®) [131] and EuroQol 5-Dimension (EQ-5D) [132]. These instruments provide a structured approach for comprehensive evaluation across psychological, trauma-related, general health and quality of life domains.

For post-COVID-19 assessment, a developing consensus emphasises the evaluation of physical, cognitive, and psychological domains due to the multisystem nature of the condition [133, 134].

Rationale

In 2020, when this research began, the predictors of mortality and the long-term effects of surviving critical COVID-19 were unknown. The present thesis addresses five key knowledge gaps:

1. **Mortality Risk Factors:** Early data showed varying COVID-19 mortality rates but lacked analysis of factors determining survival, which was essential for clinical decision-making and resource allocation during pandemic surges.
2. **Prognostic Tool Validation:** Established ICU scoring systems (SAPS 3, SOFA) had not been validated for COVID-19 patients, with initial studies suggesting poor predictive accuracy.
3. **Long-Term Outcome Predictors:** Risk factors for functional recovery and symptom persistence after critical COVID-19 were undefined, preventing the development of targeted rehabilitation and follow-up strategies.
4. **Recovery Trajectories:** Systematic long-term studies were needed to track how patients recover across physical, cognitive, and psychological domains following critical COVID-19.
5. **Biomarker Prognostication:** While inflammatory dysregulation was recognised in critical COVID-19, the relationship between specific biomarkers and long-term outcomes remained unexplored. Calprotectin, a marker of neutrophil activation, required investigation for its potential to predict both mortality and long-term functional outcomes.

Aim

The overall aim of this thesis was to identify factors affecting survival and long-term outcome, evaluate calprotectin as a prognostic biomarker, and characterise recovery trajectories over 3 years in critically ill COVID-19 patients.

Paper I

Our objectives were (a) to evaluate factors on ICU admission associated with 3-month mortality, and (b) to describe factors during the ICU stay that were associated with functional outcome at 3 months.

Paper II

The primary objective was to describe changes in functional outcome and Health-Related Quality of Life (HRQoL) between 3 months and 1 year in critically ill COVID-19 survivors. The secondary objective was to investigate factors associated with good functional outcome and HRQoL at 1 year.

Paper III

We aimed to assess whether plasma calprotectin dynamics during the first week of intensive care were associated with long-term mortality, functional outcome, and disease progression in critically ill COVID-19 patients.

Paper IV

The objective was to describe changes in functional, physical, and mental health outcomes between 1 and 3 years among survivors of critical COVID-19 and to identify factors associated with incomplete recovery at 3 years.

Methods

Study Design and Setting

Overall Study Design

We conducted a prospective multicentre cohort study of critically ill COVID-19 patients, with follow-up assessments at 3 months and 1 year after ICU admission. After obtaining consent, we invited participants from the 1-year follow-up to participate in an additional 3-year follow-up.

The study was designed during the early stages of the COVID-19 pandemic, when the long-term effects of the disease had not yet been identified. We intentionally adopted a comprehensive approach to capture both immediate mortality factors and longer-term recovery patterns, enabling evaluation of prognostic factors, biomarker dynamics, and changes in recovery outcomes.

A dedicated biobank was established to enable biomarker studies, including calprotectin analysis. This thesis comprises four papers, each focusing on specific aspects of the outcome of critically ill COVID-19 patients.

Study Setting

Six ICUs across Skåne participated in the research, covering a southern region of Sweden serving 1.4 million residents. Participating sites included both academic and regional hospitals: Skåne University Hospital in Lund (cardiothoracic ICU and general ICU), Skåne University Hospital in Malmö (general ICU and infectious diseases ICU), Helsingborg Hospital (general ICU) and Kristianstad Hospital (general ICU).

These units had a total baseline capacity of 30-36 intensive care beds before the pandemic, which increased significantly during COVID-19 surges. To ensure consistency in clinical management and research protocols, we established weekly online coordination meetings with the research team, including representatives from all sites. We used standardised approaches to patient care, data collection and follow-up protocols.

Table 2: Overview of Study Design and Objectives for Papers I–IV

	Paper I	Paper II	Paper III	Paper IV
Study Design	Prospective multicentre cohort study	Prospective multicentre cohort study	Prospective multicentre cohort study	Prospective multicentre cohort study
Study Population	All critically ill COVID-19 patients admitted to six ICUs in Sweden (May 2020–May 2021)	Survivors from the Paper I cohort participating in follow-up at 3 months and 1 year	Subsample from Paper I cohort with calprotectin measurements	Survivors from Paper III who consented to a 3-year follow-up
Number of Patients	498	264 of 303 at 3 months, 217 of 259 at 1 year	484 on admission, 356 at day 7	191 of 210
Objectives	Assess factors at ICU admission and during ICU stay in relation to 3-month mortality and functional outcome	Evaluate changes in functional outcome and HRQoL between 3 months and 1 year; identify predictors of good outcome.	Investigate the association between calprotectin dynamics and mortality/functional outcome	Assess changes in outcomes between years 1 and 3; identify predictors of incomplete recovery.

HRQoL; Health-Related Quality of Life; ICU; Intensive Care Unit.

Study Period and Timeline

Patients were enrolled between May 11, 2020, and May 10, 2021, during various COVID-19 waves in Sweden.

The alpha (B.1.1.7) variant was dominant throughout the study period, providing virological consistency within the cohort [135, 136]. Vaccination had a minimal impact on the study population, as Sweden's vaccination program began in late December 2020 and did not achieve broad population coverage during most of the recruitment period [136].

As shown in Table 2, the study comprised four interconnected papers examining different aspects of outcomes, with follow-up assessments conducted at 3 time points following ICU admission: 3 months (July 2020-August 2021), 1 year (May 2021-May 2022) and 3 years (May 2023-May 2024).

Participants and Eligibility Criteria

Screening and Enrolment Process

Adults aged 18 years or older with SARS-CoV-2 infection confirmed by Reverse Transcription Polymerase Chain Reaction (RT-PCR) admitted to participating ICUs were eligible for inclusion. Patients were excluded if COVID-19 was not the primary reason for intensive care treatment or if consent could not be obtained. A screening log documented all potentially eligible patients and reasons for non-inclusion.

Consent Procedures

Given the condition of the study population, we used a tiered consent approach:

- Written consent was obtained from participants at ICU admission when possible.
- For patients unable to consent due to illness, deferred consent before discharge or follow-up visits up to one year after inclusion was used.
- Presumed consent for deceased patients as per Swedish Ethical Review Authority approval.
- For the extended 3-year follow-up, additional verbal informed consent was obtained from participants during their 1-year assessment. Only participants who consented to the extended follow-up were contacted at the 3-year time point.
- The study's information and consent forms, originally in Swedish, were translated into English, with certified interpreters available to overcome any language barriers.

Sample Size Considerations

Given the population-based design and predetermined 1-year recruitment period, no formal sample size calculation was performed.

Data Collection

Baseline and Clinical Data

We gathered data from electronic health records, regional registries and case report forms. Demographics included age, sex, Body Mass Index (BMI), level of education, employment and living arrangements. Pre-existing conditions were documented using the Charlson Comorbidity Index (CCI) [137, 138], the Clinical Frailty Scale (CFS) [88], specific comorbidities, smoking status and pre-admission medications.

COVID-19-specific details, including symptom onset date, duration before hospitalisation, SOFA (Sequential Organ Failure Assessment) and SAPS 3 (Simplified Acute Physiology Score 3) were collected [139, 140], respiratory parameters, haemodynamic measurements, neurological status, renal function and ICU interventions and complications. The healthcare system factors tracked included ICU occupancy (ICU burden), inter-hospital transfers and limitation of care decisions.

Quality checks on clinical variables from randomly selected patients (n=50) showed high consistency with minimal discrepancies (<2% variance).

Laboratory Investigations and Biomarkers

Calprotectin Sub-study Methods

Laboratory data were collected at admission and throughout the ICU stay as part of routine clinical care. For the calprotectin sub-study (Paper III), we collected additional blood samples at ICU admission (day 0) and day 7. Peripheral venous or arterial blood was drawn in EDTA tubes and centrifuged within 2 hours of collection (2000g for 10 minutes at 4°C). The plasma was subsequently aliquoted and stored at −80°C in the SWECRIT COVID-19 biobank, which is part of the central biobank of Region Skåne, Sweden (BD-47).

All samples were analysed after the completion of patient enrolment at a certified clinical chemistry laboratory at Uppsala University Hospital. Analysis was performed using a particle-enhanced turbidimetric assay (PETIA) with calprotectin-specific reagents supplied by Gentian AS (Moss, Norway) in a Mindray BS380 chemistry analyser. This methodology has a measuring range of 0.5-50 mg/L and has a detection limit of 0.5 mg/L. It generates results in approximately 10 minutes and has been validated against traditional ELISA techniques for calprotectin measurement [141].

Follow-up Assessment Protocol

Surviving participants were invited to structured assessments at 3 months, 1 year and 3 years following ICU admission. Our systematic approach included sending invitation letters 2-4 weeks prior to appointments and providing telephone reminders for non-responders. Questionnaires were mailed in advance for completion before appointments. A multidisciplinary team of research nurses, occupational therapists and physiotherapists conducted the assessments. Sessions lasted 60-90 minutes, with certified interpreters available for non-Swedish speakers.

The 3-month assessments were predominantly face-to-face (66%), as were the 1-year follow-ups (74%). This allowed us to support participants with interpreters, if needed, and a verbatim reading of the questions to assist them. The 3-year assessments were conducted exclusively via telephone with mailed questionnaires.

All outcome assessors received standardised training in outcome measurement administration, including structured interview formats to increase inter-rater reliability and prevent avoidable missing data.

Lost to Follow-up Management

To minimise loss to follow-up, we used multiple contact methods, including mail and phone calls, with telephone assessments when in-person visits were not possible. When participants remained unreachable despite these efforts, we documented reasons for loss to follow-up where available. We compared baseline characteristics between participants and non-participants at each follow-up time point to assess potential selection bias.

Outcome Measures

Based on the assessment approach discussed in the Introduction, we selected a comprehensive set of standardised assessments with good evidence of being valid for instruments to evaluate multiple recovery domains following critical COVID-19.

Mortality Assessment

Mortality data were collected through two complementary sources: hospital records for in-hospital deaths and the Swedish Population Register [142] for post-discharge deaths.

We assessed mortality at multiple sequential time points: ICU mortality, in-hospital mortality, 3-month mortality (the primary outcome for Paper I), 1-year mortality (the primary outcome for Paper III), and 3-year mortality. For deceased patients, we documented both the date and presumed cause of death when available. The comprehensive Swedish population registration system enabled nearly 100% completeness of mortality data.

Functional Outcome

1	Dead	
2	Vegetative State	Unconscious – unable to obey simple commands or say words. Shows reflex responses and periods of spontaneous eye opening, but no awareness or purposeful behaviour
3	Lower Severe Disability	Conscious but dependent – requires assistance from another person for activities of daily living every day. Cannot be left alone safely for more than 8 hours. Needs frequent help or supervision for basic needs, including washing, dressing, eating, or handling emergencies
4	Upper Severe Disability	Conscious but dependent – requires daily assistance for some activities of daily living, but can be left alone for more than 8 hours. May be unable to shop independently or travel locally without assistance due to physical or cognitive limitations
5	Lower Moderate Disability	Independent at home but unable to participate in one or more major life roles. May be unable to work or can only work in sheltered/non-competitive employment. Severely restricted social participation (rarely takes part) or constant family/relationship problems that are intolerable
6	Upper Moderate Disability	Able to work at reduced capacity; reduced social participation.Independent at home but with reduced capacity in major life roles. Can work but at reduced capacity (part-time, lower responsibility, special arrangements). Participates in social activities much less than before (less than half as often) or has frequent relationship problems
7	Lower Good Recovery	Independent with return to normal life, but with some persisting symptoms or limitations. May participate in social activities somewhat less than before, have occasional relationship problems, or experience symptoms that affect daily life but do not prevent normal functioning
8	Upper Good Recovery	Complete recovery – independent with full return to normal life. No current problems relating to the injury that affect daily functioning. Any deficits are minor and non-disabling

Figure 8: Glasgow Outcome Scale Extended (GOSE). Colour coding represents outcome categories: red (GOSE 2-4) = vegetative state or severe disability, yellow (GOSE 5-6) = moderate disability, green (GOSE 7-8) = good recovery [143, 144].

The Glasgow Outcome Scale Extended (GOSE) [143, 144] served as our primary functional outcome measure at all follow-up points. Originally developed for the assessment of traumatic brain injury, the GOSE has been validated and widely adopted in critical care research [145, 146].

Through structured interviews, this clinician-reported ordinal scale assesses functional outcomes, which include independence, work capacity, societal participation, and the impact of symptoms. Higher scores indicated better recovery. The GOSE adopts a hierarchical approach, where the overall rating is based on the functional domain that is most affected. Figure 8 illustrates GOSE groups, ranging from death (1) to good recovery (8).

GOSE Thresholds

Our analysis focuses on three key thresholds (Figure 9):

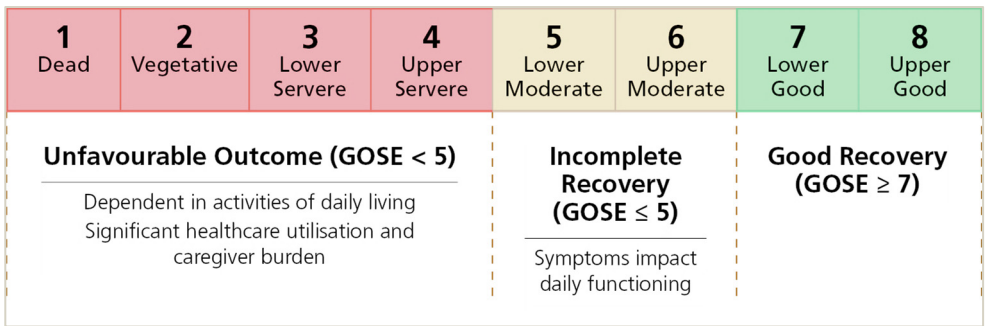

Figure 9: Glasgow Outcome Scale Extended (GOSE) with recovery thresholds. Thresholds shown are: Unfavourable Outcome (GOSE < 5), Incomplete Recovery (GOSE ≤ 6) and Good Recovery (GOSE ≥ 7). Dashed lines indicate threshold boundaries [128, 143].

The GOSE ≥ 7 threshold for "good recovery" was chosen based on previous critical illness literature [128] and represents the point where persistent symptoms no longer significantly impact daily functioning.

The GOSE ≤ 6 threshold for "incomplete recovery" captures patients who maintain independence in basic activities but continue to experience limitations that affect work capacity, social participation, or quality of life [104].

The GOSE < 5 threshold for "unfavourable outcome" reflects patient dependence in certain activities of daily living. This has notable consequences for healthcare resource utilisation, caregiver demands, and overall quality of life [143]. For trajectory analysis over 3 years, we present good recovery rates (GOSE ≥ 7), as this better illustrates recovery patterns over time (Figure 9).

Health-Related Quality of Life Assessment (HRQoL)

We assessed HRQoL using the Short Form Health Survey version 2 (SF-36v2®) [131], a well-established patient-reported outcome measure completed in 10-15 minutes. This instrument generates two main summary measures [147]: Physical Component Summary (PCS) and Mental Component Summary (MCS).

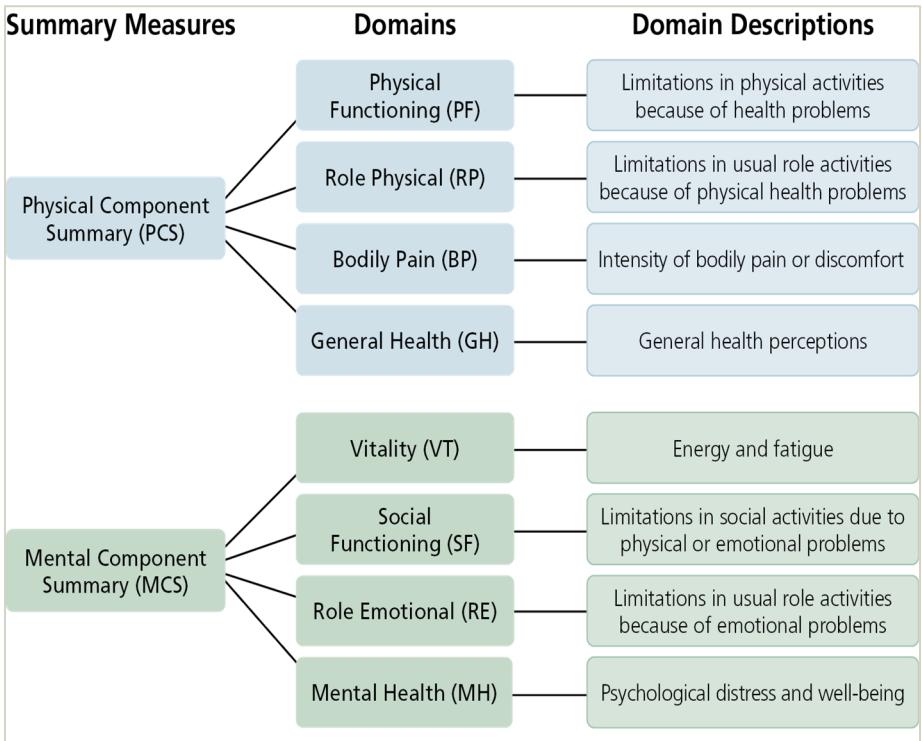

Figure 10: SF-36v2® Health Survey. This diagram categorises the eight health domains into two main component summaries: Physical Component Summary (PCS), Mental Component Summary (MCS). It demonstrates how the 36 items evaluate various facets of health-related quality of life. Additionally, vitality influences the PCS, while General Health affects the MCS [131].

The PCS and MCS are derived from eight health domains, as illustrated in Figure 10. Raw scores are transformed to standardised T-scores where 50 represents the population mean with a standard deviation of 10. Higher scores indicate better health status. T-scores ≥ 45 are considered indicative of good health at the individual level, and ≥ 47 at the group level. The Minimally Important Difference (MID) represents the smallest change in score that is clinically meaningful, defined as >2 points for PCS and >3 points for the MCS [131].

Domain-Specific Outcome Measures

We included several domain-specific measures to evaluate key aspects of post-COVID recovery (Table 3):

-**MFIS:** Modified Fatigue Impact Scale, a 21-item questionnaire covering physical, cognitive and psychosocial impacts [148]

-**HADS**: Hospital Anxiety and Depression Scale, 14 items with anxiety (HADS-A) and depression (HADS-D) subscales [129, 149]

-**PCL-5**: PTSD Checklist for DSM-5 [150, 151]

-**SGRQ**: St George's Respiratory Questionnaire, a 50-item instrument covering symptoms, activity limitations and psychosocial impacts [152-154]

-**Life Satisfaction**: Single-item Visual Analogue Scale from 1-10 [155]

Additionally, we collected data on employment status and rehabilitation needs and conducted simplified physical examinations. Participants requiring further care were referred appropriately and their primary care providers were notified.

Table 3 Outcome measures and scoring criteria

Measure	Domain Assessed	Items	Score Range	Cut-off	MID
GOSE	Functional outcome	N/A	1-8	< 5, <7	1
SF-36v2®	Health-Related Quality of Life	36	T-scores: 50±10	< 45	2-3
Life Satisfaction	Overall wellbeing	1	1-10	< 7.3	-
MFIS	Fatigue	21	0-84	≥ 38	4
HADS-A	Anxiety	7	0-21	≥ 8	1.7
HADS-D	Depression	7	0-21	≥ 8	1.7
PCL-5	Post-traumatic stress	20	0-80	≥ 33	6
SGRQ	Respiratory symptoms	50	0-100	> 8.4	4

Higher scores indicate better outcomes for GOSE, SF-36v2® and Life Satisfaction. Higher scores indicate worse outcomes for MFIS, HADS-A, HADS-D, PCL-5 and SGRQ.

Ethical Considerations

Ethical Approval

The study received ethical approval from the Swedish Ethical Review Authority (reference numbers 2020-01955, 2020-03483 and 2021-00655). These approvals covered the initial study protocol, subsequent amendments for extended follow-up, and the biobank establishment for storing biological specimens. A separate KVB approval was obtained to access data from the COVIDIR quality registry.

The research was conducted in accordance with the Declaration of Helsinki and adhered to Good Clinical Practice guidelines, ensuring scientific integrity, participant safety and ethical conduct. It was registered on ClinicalTrials.gov (Identifier: NCT04974775) before the first follow-up assessment.

Data Protection and Confidentiality

All participants received a unique study identification number. Identifying information was stored separately from study data. Electronic data were maintained in secure, password-protected databases with access limited to authorised study personnel. Paper forms were stored in locked cabinets within restricted-access research areas. The study complied with the European General Data Protection Regulation (GDPR) and Swedish data protection legislation.

Biobanking Procedures

Blood samples for calprotectin analysis were managed according to biobanking protocols: Samples were coded with study IDs without personal identifiers. Informed consent included storage and future use of biological materials. The SWECRIT COVID-19 biobank is part of Region Skåne's central biobank (BD-47) under regulatory oversight. Future research access to samples requires additional ethical review.

Ethical Challenges in COVID-19 Research

Research during the COVID-19 pandemic presented unique ethical challenges, requiring a balance between the rapid generation of knowledge and adherence to ethical and scientific standards [156, 157].

A significant concern was informed consent, as many patients presented with severe hypoxemia while maintaining apparent cognitive clarity, which raised questions about their decision-making capacity.

Language barriers further complicated comprehension for non-native Swedish speakers. We addressed these challenges through a tiered consent approach that allowed for deferred options, revisiting consent during follow-up visits, and engaging qualified interpreters while keeping research separate from clinical care.

Rapidly establishing research protocols during the pandemic crisis could have compromised the quality of data collection. We mitigated this risk through rigorous data verification, standardised procedures across sites and weekly coordination meetings. To minimise conflicts between research and clinical priorities, we designed protocols requiring no additional procedures beyond standard care during acute treatment.

Statistical Methods

General Statistical Approach

Non-parametric statistics were used throughout due to non-normal data distributions. Continuous variables are reported as medians with interquartile ranges (IQRs), while categorical variables are presented as frequencies and percentages. For patient-reported outcomes, means with 95% confidence intervals are also provided to enable comparison with established minimally important differences.

For comparative analyses, the Mann-Whitney U test was applied for independent continuous variables, while the Chi-square or Fisher's exact test was used for categorical variables. For longitudinal comparisons, the sign test or Wilcoxon signed-rank test was employed for dependent continuous variables and the McNemar test was used for paired categorical variables.

Variables for the multivariable regressions were selected using a purposeful selection approach [158], incorporating established clinical relevance from previous literature, the strength of univariate association ($p < 0.10$), low multicollinearity (Variance Inflation Factor, VIF < 5) and clinical interpretability. Statistical significance was generally defined as $p < 0.05$, with $p < 0.01$ used in Paper I for a more conservative interpretation.

We computed pairwise Spearman correlations and constructed an undirected network by retaining edges with $|\rho| > 0.40$, excluding self-loops and duplicates. Node size reflects the degree, and edge colour encodes the sign and strength of the correlation.

Sample Selection by Analysis Type

For longitudinal analyses comparing changes between time points (Papers II and IV), we included only participants with data at both relevant time points to ensure

valid paired comparisons. For cross-sectional outcome reporting in this thesis summary, we included all available participants with valid data at that specific assessment.

Missing Data and Sensitivity Analyses

Different approaches were employed based on analytical requirements. Papers I-II used multiple imputation for variables with <20% missingness, Paper III used complete case analysis due to biomarker temporal dynamics, and Paper IV excluded participants with >20% missing data. Sensitivity analyses assessed the robustness of the findings using alternative outcome thresholds, various missing data approaches, and a comparison of baseline characteristics between participants and those lost to follow-up.

Table 4: Statistical methods employed across the four papers, showing the analytical approaches used for different types of research questions and data structures.

Paper	I	II	III	IV
Descriptive & Clinical Significance				
Median (IQR) for continuous; n (%) for categorical	✓	✓	✓	✓
Mean (95% CI) for PROMs with MID comparison		✓		✓
Missing Data				
Multiple imputation (missForest)	✓			
Multivariate imputation (MICE)		✓		
Exclusion if > 20% missing				✓
Statistical Tests				
Non-parametric comparisons[1]	✓	✓	✓	✓
Paired comparisons[2]	✓			
Multivariable logistic regression	✓	✓	✓	✓
Cox proportional hazards			✓	
Model Assessment				
ROC curve analysis[3]	✓		✓	
Specialised Techniques				
Network analysis[4]				✓
Sensitivity analysis	✓	✓	✓	✓

[1]Mann-Whitney U, Chi-square/Fisher's, [2]Wilcoxon signed-rank, McNemar, [3]Includes AUC, DeLong test, Hosmer-Lemeshow, Youden index, [4]Includes Fruchterman-Reingold algorithm for correlation network visualisation

Results

Participants and Study Flow

From May 11, 2020, to May 10, 2021, 607 patients were screened across six ICUs in southern Sweden, and 498 were included in the study (Figure 11).

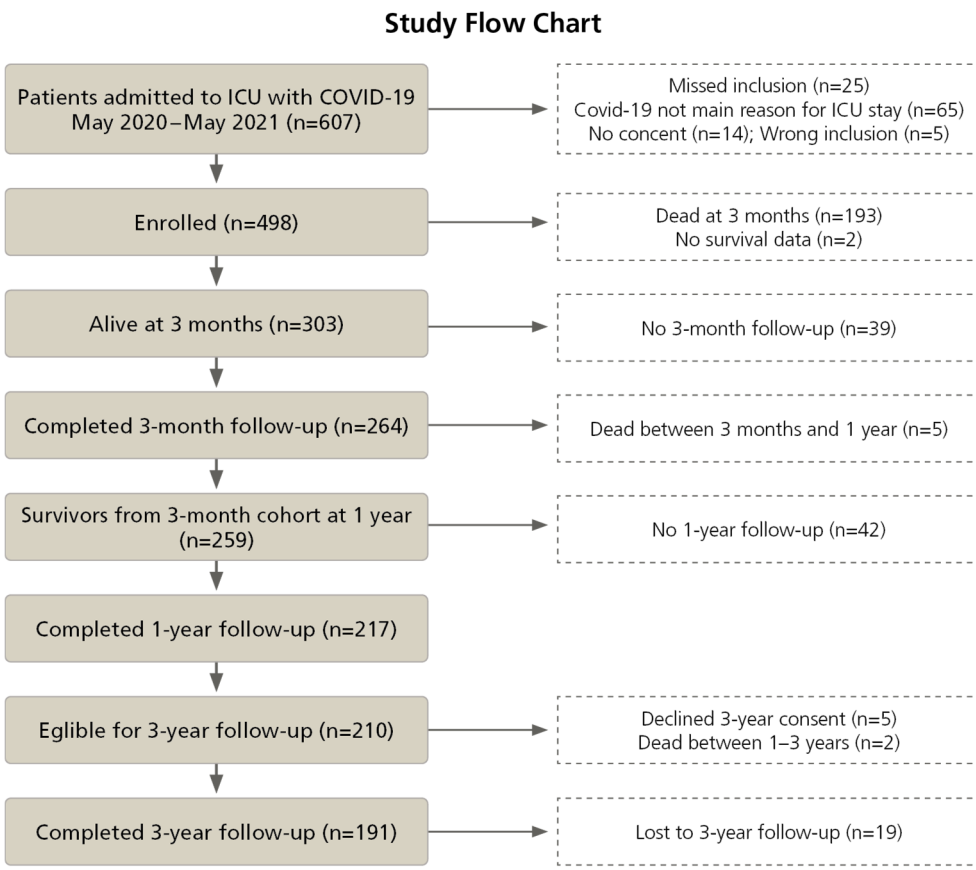

Figure 11*:* Study Flow Chart.

Paper I: Outcomes in the Acute Phase

Cohort Characteristics and Acute Interventions

Table 5: Baseline characteristics, clinical interventions and outcomes stratified by 3-month survival status (n = 498)

	Overall (n = 498)	Survivors (n = 305)	Non-survivors (n = 193)	p-value
Age (years) IQR	66 [56-73]	61 [52-68]	72 [66-77]	< 0.001
Male	74%	74%	74%	0.990
BMI (kg/m2) IQR	30 [27-35]	31 [27-36]	29 [26-33]	0.001
Diabetes mellitus	31%	28%	35%	0.140
Hypertension	55%	50%	62%	0.015
Clinical Frailty Scale	3.0 [2-4]	3 [2-3]	3 [2-4]	< 0.001
SAPS 3	60 [50-69]	56 [47-65]	66 [56-75]	< 0.001
P/F ratio Day 1 (kPa)	10 [8-12]	10 [8-13]	9 [7-12]	0.016
Clinical interventions				
IMV	72%	66%	81%	< 0.001
CRRT	14%	9%	23%	< 0.001
Outcome measures				
IMV total days	9.4 [5-18]	7.5 [4-15]	13 [7-20]	< 0.001
LOS ICU	9.5 [5-17]	7.8 [4.6-15]	12 [5-20]	0.015
ICU Burden	29 [29-52]	27 [20-42]	36 [23-55]	< 0.001
Mortality ICU	30%	N/A	N/A	N/A
Hospital mortality	38%	N/A	N/A	N/A
Mortality 3-month	39%	N/A	N/A	N/A
Mortality 1-year	40%	N/A	N/A	N/A
Mortality 3-year	41%	N/A	N/A	N/A

BMI; body mass index; ICU; intensive care unit; SAPS 3; Simplified Acute Physiology Score; P/F; PaO_2/FiO_2 ratio; IMV; invasive mechanical ventilation; CRRT; continuous renal replacement therapy; LOS; length of stay; ICU burden; number of regional COVID-19 ICU patients on day of admission.

Follow-up rates were 87% at 3 months, 73% at 1 year and 65% at 3 years. The cohort had a median age of 66 years and was predominantly male (74%). Most patients were classified as fit (CFS 1–3, 74%) before COVID-19, while 17% were pre-frail (CFS 4) and 8% were frail (CFS ≥ 5). Median SAPS 3 and SOFA scores were 60 and 8, respectively. Severe ARDS was common, with a median PaO_2/FiO_2 ratio of 10 kPa on ICU admission. We used IMV in 72% of patients. Non-survivors had higher IMV rates (81% vs. 66%, $p < 0.001$) and longer IMV duration (13 vs. 8 days, $p < 0.001$). Continuous renal replacement therapy (CRRT) was more frequent among non-survivors (23% vs. 9%, $p < 0.001$) (Table 5).

Mortality and Risk Factors

Mortality at 3 months was 39%, with most deaths occurring during hospitalisation. Age was most strongly associated with mortality (OR 1.11 per year; 95% CI: 1.08–1.14; $p < 0.001$), with rates rising from 17% in patients under 60 to over 90% in those aged 80 and above (Tables 5-6, Figure 12).

Pre-ICU care limitations were associated with very high mortality (86%), and all patients with ICU treatment withdrawal died before discharge.

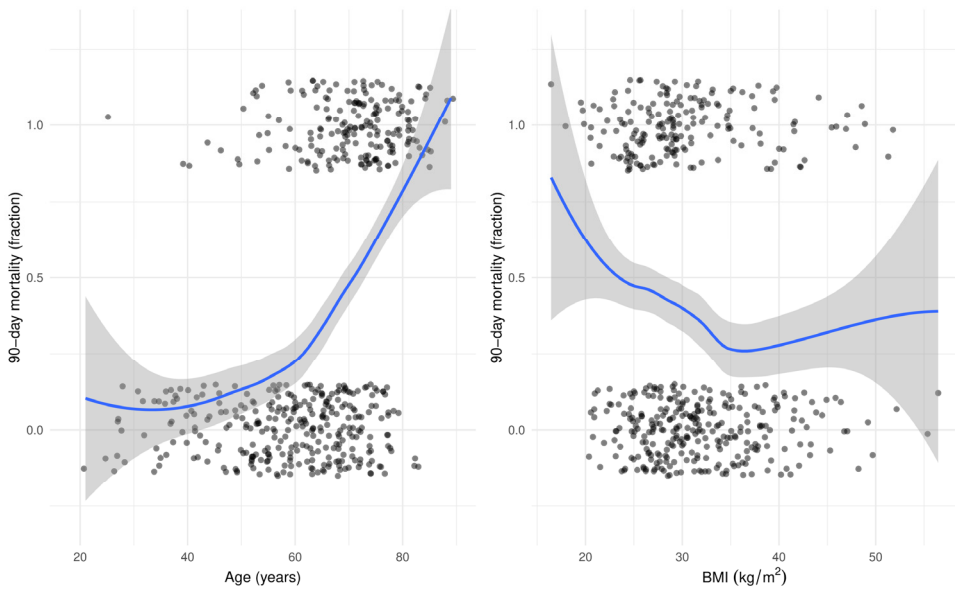

Figure 12: Association between patient characteristics and 3-month mortality. Scatter plots display individual patient outcomes (1 = death, 0 = survival) at 3 months post-ICU admission for (A) age and (B) BMI. Blue lines represent predicted probability of mortality with 95% confidence intervals.

BMI and Mortality

BMI showed a U-shaped relationship with mortality. Patients with BMI <25 kg/m² had increased risk (OR 1.95, 95% CI 1.19–3.20, $p = 0.008$), while moderate obesity (BMI ~35 kg/m²) was associated with reduced mortality (OR 0.60, 95% CI 0.38–0.93, $p = 0.024$) (Figure 12).

Healthcare System Impact

ICU burden, defined as the number of regional COVID-19 ICU patients on the day of admission, was independently associated with 3-month mortality (OR 1.02, 95% CI 1.01–1.04, $p = 0.001$). Regional ICU occupancy peaked at 62 COVID-19 patients in January 2021. Mortality exceeded 50% during high-burden periods (> 50 ICU patients) compared to 25% during low-burden periods (Figure 13, Table 6).

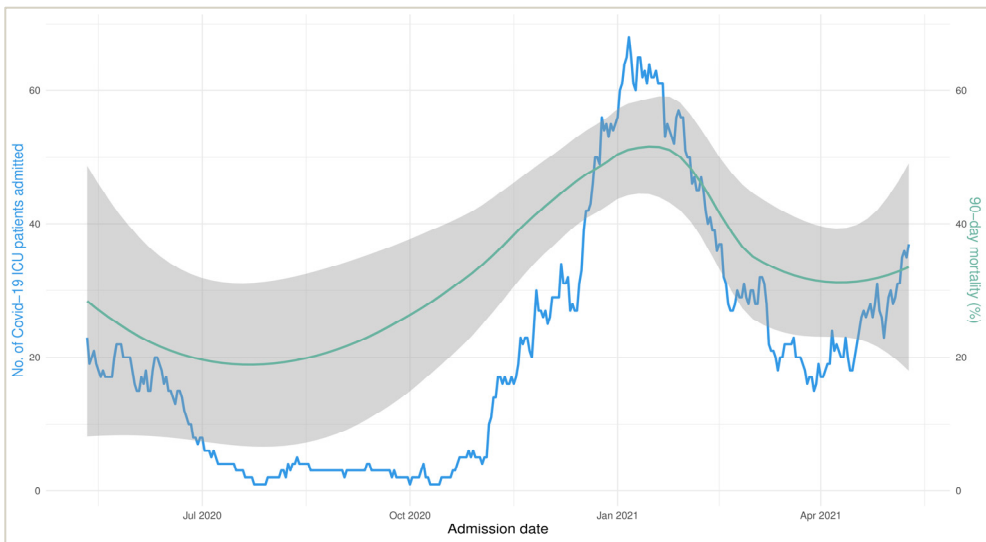

Figure 13: COVID-19 ICU admissions and 3-month mortality (May 2020-May 2021). The blue line shows daily COVID-19 ICU admissions (left y-axis) and the green line shows 3-month mortality rates with 95% confidence intervals (right y-axis).

Frailty and Survival

Baseline frailty assessment using the CFS revealed 74% classified as fit (CFS 1–3), 18% as having very mild frailty (CFS 4), and 8% as frail (CFS ≥5). Survival over 3 months (90 days) differed significantly across frailty categories (log-rank $p < 0.001$), with survival rates of 67% for fit patients, 51% for vulnerable patients, and

28% for frail patients (Figure 14). The hazard ratio for mortality was 1.8 (95% CI 1.3-2.5) for vulnerable patients and 3.9 (95% CI 2.6-5.8) for frail patients compared to fit patients.

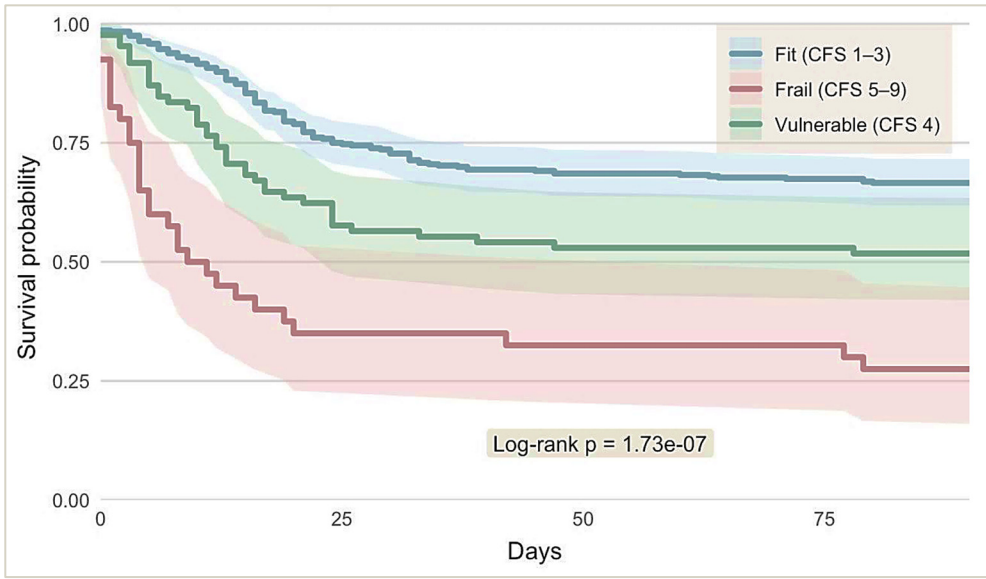

Figure 14: Kaplan-Meier survival curves stratified by baseline frailty in critically ill COVID-19 patients. Survival curves display 90-day outcomes for fit (CFS 1-3, n = 367), very mild frailty (CFS 4, n = 87) and frail (CFS ≥ 5, n = 40) patients. Log-rank test p < 0.001. CFS = Clinical Frailty Scale. ***Note: "Very mild frailty" corresponds to the current CFS 4 label, previously termed "vulnerable.***

Table 6 Multivariable regression for 3-month mortality

Variable	OR [95% CI]	P-value
Age (years)	1.11 [1.08-1.14]	< 0.001
Sex (male)	0.89 [0.51-1.54]	0.671
Clinical Frailty Scale	1.25 [0.98-1.59]	0.067
Hypertension	0.76 [0.46-1.27]	0.298
Diabetes	1.33 [0.69-2.57]	0.391
Smoker	1.56 [0.97-2.53]	0.068
ICU Burden	1.02 [1.01-1.04]	0.001
SOFA at admission	1.06 [0.99-1.14]	0.119

OR=odds ratio; CI=confidence interval; ICU=intensive care unit; SOFA=Sequential Organ Failure Assessment. Variables with p < 0.05 were considered statistically significant.

Predictive Models

SAPS 3 [159], which is normally used to predict hospital mortality, had an Area Under the Curve (AUC) of 0.71 for predicting 3-month mortality in our cohort, while age alone had an AUC of 0.78. AUC values range from 0.5 (no predictive ability) to 1.0 (perfect prediction), with values greater than 0.7 considered acceptable and those greater than 0.8 considered good discriminatory performance. Our multivariable model, which incorporated age, ICU burden, smoking status, creatinine, $PaCO_2$, inflammatory markers, and corticosteroid use, had an AUC of 0.87 for 3-month mortality prediction (Figure 15).

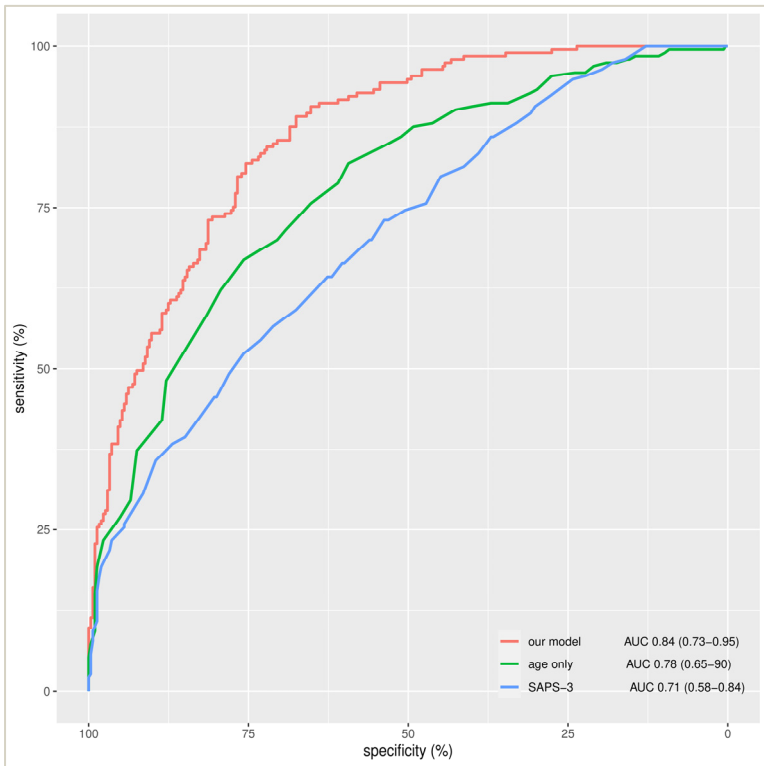

Figure 15: ROC curve comparison of 3 predictive models for 3-month mortality: Multivariable model (red), age alone (green) and SAPS-3 (blue). The multivariable model showed superior performance (AUC 0.87) compared to age alone (AUC 0.78) and SAPS-3 (AUC 0.71). AUC = Area Under the Curve; SAPS-3 = Simplified Acute Physiology Score 3.

Paper II: First-Year Recovery Trajectories

Outcomes at 3 months

At the 3-month follow-up, survivors of critical COVID-19 showed notable functional impairments. Only 36% achieved a good functional outcome (GOSE ≥ 7), while 20% had unfavourable outcomes (GOSE < 5), indicating dependency in daily activities.

Health-related quality of life (HRQoL) was significantly reduced, particularly in physical domains. The mean Physical Component Summary (PCS) score was 40. The proportion of participants with below normal physical HRQoL (PCS < 45) was 70%. Mental HRQoL was comparatively less affected, with a mean Mental Component Summary (MCS) score of 47, and 44% of participants scoring below the normative threshold. Among the SF-36v2® subdomains, Physical Functioning and Role-Physical were most impaired, reflecting limitations in mobility and the ability to perform usual activities due to physical constraints (Table 7).

Table 7: The mean T-scores of the eight domains and the Physical component summary score (PCS) and Mental component summary score (MCS) of SF-36v2®.

Outcome Measure	3-Months	1-Year	Mean difference (MID)	p-value
Summary Scales				
Physical Component Summary (PCS)	40 (39-42)	44 (42-45)	**3.6** (2)	< 0.001
Mental Component Summary (MCS)	46 (45-48)	48 (47-50)	1.9 (3)	0.05
Sub-domains				
Physical Functioning	39 (38-41)	44 (42-45)	**4.4** (3)	< 0.001
Role-Physical	37 (35-38)	43 (42-45)	**6.4** (3)	< 0.001
Bodily Pain	44 (43-46)	46 (44-48)	1.6 (3)	0.13
General Health	46 (45-48)	46 (44-47)	-0.8 (2)	0.42
Vitality	45 (43-47)	47 (45-49)	**2.1** (2)	0.05
Social Functioning	42 (40-44)	47 (46-49)	**5.2** (3)	< 0.001
Role-Emotional	42 (39-44)	44 (42-46)	2.7 (4)	0.004
Mental Health	48 (46-49)	49 (47-51)	1.3 (3)	0.10

All scores are T-scores (population mean = 50, SD = 10). Values in parentheses in the first two columns represent 95% confidence intervals. Values in parentheses in the "Mean difference (MID)" column indicate Minimally Important Differences. Bold values exceed MID thresholds and are considered clinically significant. Higher scores reflect better health.

Changes in Outcomes Between 3 months and 1 year

Between 3 months and 1 year, survivors demonstrated substantial improvements in functional outcome. Median GOSE scores increased from 6 to 7 ($p < 0.001$), and the proportion of patients with good functional outcomes (GOSE ≥ 7) nearly doubled from 36% to 64% ($p < 0.001$). Conversely, the percentage with unfavourable outcomes (GOSE < 5) declined from 20% to 7% ($p < 0.001$).

Improvements in HRQoL were domain-specific. The proportion of participants with normal physical HRQoL (PCS ≥ 45) rose from 30% to 55%. Mental HRQoL remained relatively stable, with mean MCS scores increasing modestly from 46 to 48. The percentage of participants with normal mental HRQoL increased from 56% to 65%; this change did not exceed the threshold for clinical significance (Table 7).

Among participants aged 20–64 years who were employed prior to ICU admission (n = 106), return-to-work rates increased from 55% (58/106) at 3 months to 68% (72/106) at 1 year ($p < 0.001$). The proportion of all survivors (n = 217) receiving ongoing rehabilitation decreased from 32% at 3 months to 16% at 1 year ($p < 0.001$).

Factors Associated with 1-year Outcomes

Multivariable regression analyses identified several factors that were independently associated with favourable outcomes at the 1-year follow-up after critical COVID-19. Shorter IMV duration was consistently associated with better outcomes across all measures, including functional outcome (GOSE), physical HRQoL (PCS), and mental HRQoL (MCS). Higher age was associated with improved functional outcome. Better PCS was associated with lower baseline frailty and absence of diabetes mellitus (Table 8).

Table 8: Factors independently associated with good 1-year Outcomes.

Outcome measure	Variable	OR (95% CI)	p-value	Effect Direction
Good Recovery (GOSE ≥ 7)	Age (per 10-year increase)	1.49 (1.03-2.17)	0.03	↑ Better with increasing age
	IMV Duration	0.24 (0.08-0.71)	0.01	↓ Worse with longer duration
Normal Physical Health (PCS ≥ 45)	CFS score	0.52 (0.29-0.90)	0.02	↓ Better with lower frailty
	Diabetes mellitus	0.10 (0.01-0.89)	0.04	↓ Worse with diabetes
	IMV Duration	0.20 (0.06-0.66)	0.008	↓ Worse with longer duration
Normal Mental Health (MCS ≥ 45)	IMV Duration	0.32 (0.11-0.96)	0.04	↓ Worse with longer duration
	Tracheostomy	6.2 (1.2-32)	0.03	↑ Better with tracheostomy

GOSE: Glasgow Outcome Scale Extended, PCS: Physical Component Summary, MCS: Mental Component Summary, IMV: Invasive Mechanical Ventilation, CFS: Clinical Frailty Scale.

Paper III: Calprotectin as a Prognostic Biomarker

Calprotectin Levels and Outcomes

Plasma calprotectin was measured in 484 patients at the time of ICU admission and in 356 patients on day 7. Median levels were higher in non-survivors than in survivors, both at admission (8.62 vs 6.72 mg/L, $p < 0.001$) and on day 7 (6.01 vs 3.52 mg/L, $p < 0.001$) (Figure 16).

Between ICU admission and day 7, 39% of patients had increasing calprotectin levels. This subgroup had higher odds of 1-year mortality, poor functional outcome (GOSE < 5), and need for IMV and CRRT (Table 9).

Day 7 calprotectin showed moderate discriminative ability for predicting 1-year mortality (AUC 0.70), which improved when combined with age (AUC 0.79). The combined model had higher predictive accuracy than age alone (AUC 0.74, $p = 0.004$) (Figure 17).

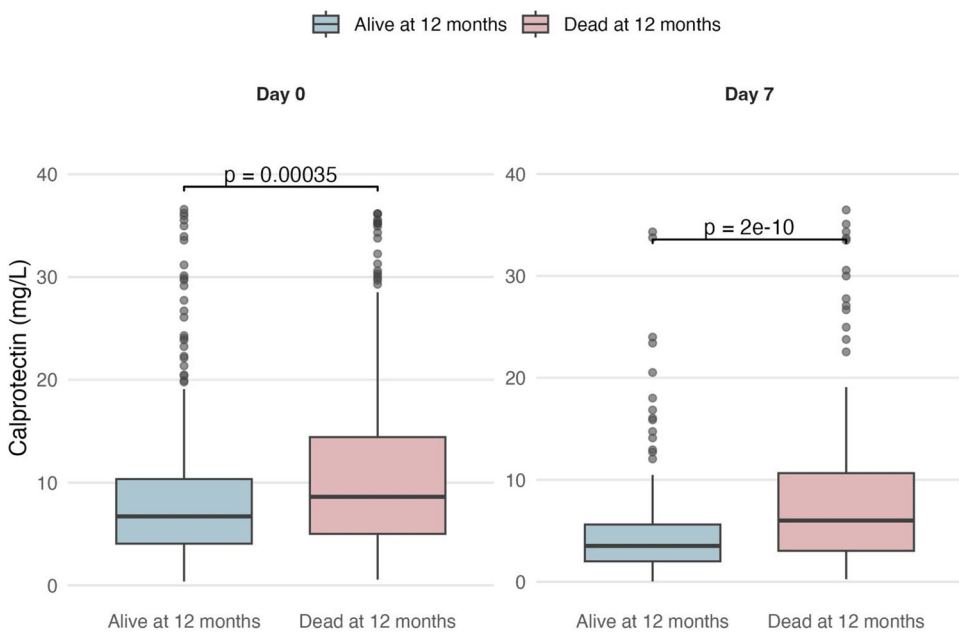

Figure 16:Calprotectin Levels at ICU Admission and Day 7 Stratified by 1-Year Survival. Box plots show calprotectin concentrations (mg/L) at ICU Day 0 and Day 7 for patients who survived (blue) and those who did not survive (red) within 12 months. Significant differences at both times, with higher levels in non-survivors.

Table 9 Associations with Calprotectin levels and various outcomes.

Outcome	Calprotectin Measurement	Adjusted OR (95% CI)	p-value
1-Year Mortality	Admission	1.51 (1.20-1.90)	< 0.001
	Day 7	1.89 (1.34-2.68)	< 0.001
	Increasing (Day 0-Day 7)	2.10 (1.18-3.74)	0.012
GOSE <5 at 3 Months	Day 7	2.79 (1.51-4.89)	0.001
	Increasing (Day 0-Day 7)	2.53 (1.07-6.10)	0.036
Use of IMV	Admission	1.73 (1.39-2.16)	< 0.001
	Increasing (Day 0-Day 7)	2.23 (1.10-4.53)	0.027
Use of CRRT	Day 7	1.58 (1.04-2.42)	0.034
	Increasing (Day 0-Day 7)	2.07 (1.07-4.00)	0.031

OR=Odds Ratio; CI=Confidence Interval; GOSE=Glasgow Outcome Scale Extended; IMV=Invasive Mechanical Ventilation; CRRT=Continuous Renal Replacement Therapy. GOSE <5 indicates poor functional outcome. Increasing calprotectin levels defined as a rise between ICU admission and day 7.

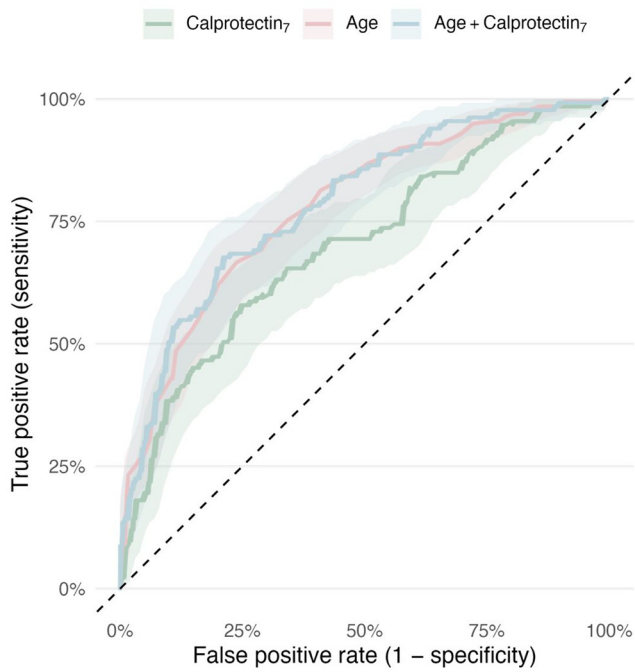

Figure 17: ROC Curve for 1-Year Mortality Prediction Using Age and Calprotectin. ROC curves show that combining age with Day 7 calprotectin (blue) resulted in a higher AUC (0.79) compared to age alone (red, AUC = 0.74, p = 0.004) or calprotectin alone (green, AUC = 0.70, p = 0.003).

Paper IV: Changes Between Years 1 and 3

Functional Outcome (GOSE)

Functional outcome deteriorated between 1 and 3 years post-ICU. Median GOSE scores decreased from 7 [6-8] to 7 [6-7] ($p < 0.001$), with good recovery (GOSE ≥ 7) decreasing from 64% to 55% ($p = 0.001$). Correspondingly, incomplete recovery (GOSE ≤ 6) increased from 36% to 45% between years 1 and 3. This decline primarily reflected patients moving from excellent recovery (GOSE 8) to categories indicating minor problems (GOSE 7) or moderate disability (GOSE 5-6) (Figure 18).

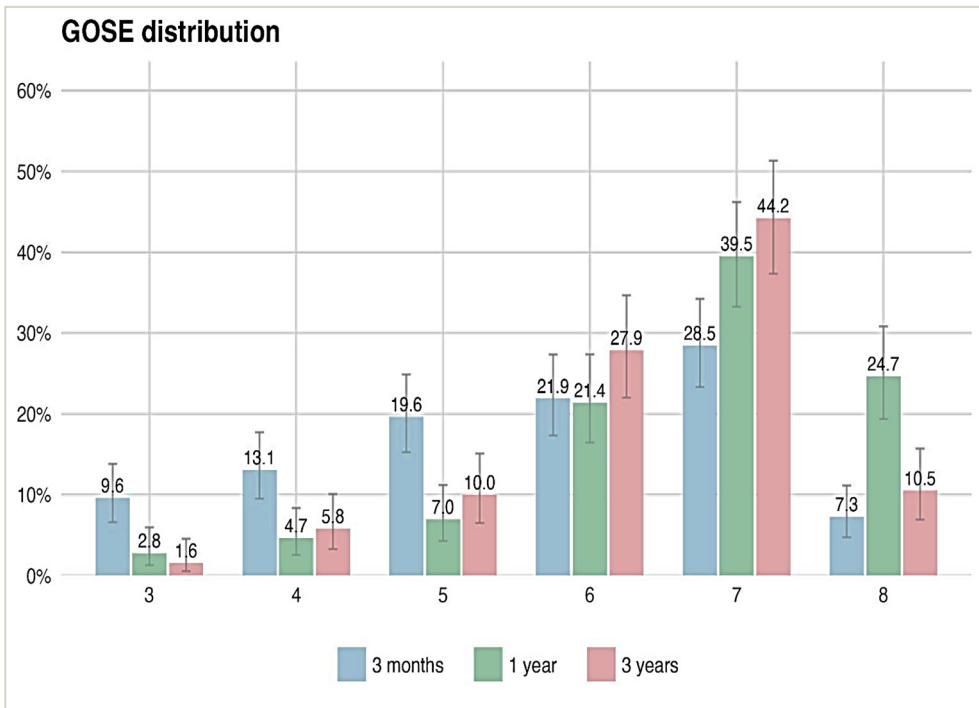

Figure 18: Distribution of Functional Outcomes (GOSE) at 3 Months, 1 Year, and 3 Years After Critical COVID-19. Bar chart showing the percentage of patients in each category of the Glasgow Outcome Scale Extended (GOSE, scores 3–8) at each follow-up. Initial improvement from 3 months to 1 year was followed by a decline between years 1 and 3, with fewer patients achieving excellent recovery (GOSE 8) and more classified with moderate disability (GOSE 5–6). At 3 years, 45% of survivors had incomplete recovery (GOSE ≤6). Data are cross-sectional at each time point.

Health-Related Quality of Life (HRQoL) SF-36v2®

Physical HRQoL remained stable, with PCS scores of 44.2 at 1 year and 44.8 at 3 years ($p = 0.14$), although PCS and most physical domains had mean T-scores below the reference range for a normative population (Figure 19).

Mental HRQoL declined, with MCS scores decreasing from 48.9 to 45.5 ($p < 0.001$), a change exceeding the minimally important difference (MID). The proportion of participants with poor mental HRQoL (MCS < 45) increased from 33% to 48%. Among SF-36v2® domains, Social Functioning and Mental Health showed the largest declines, while Vitality improved (Figure 20).

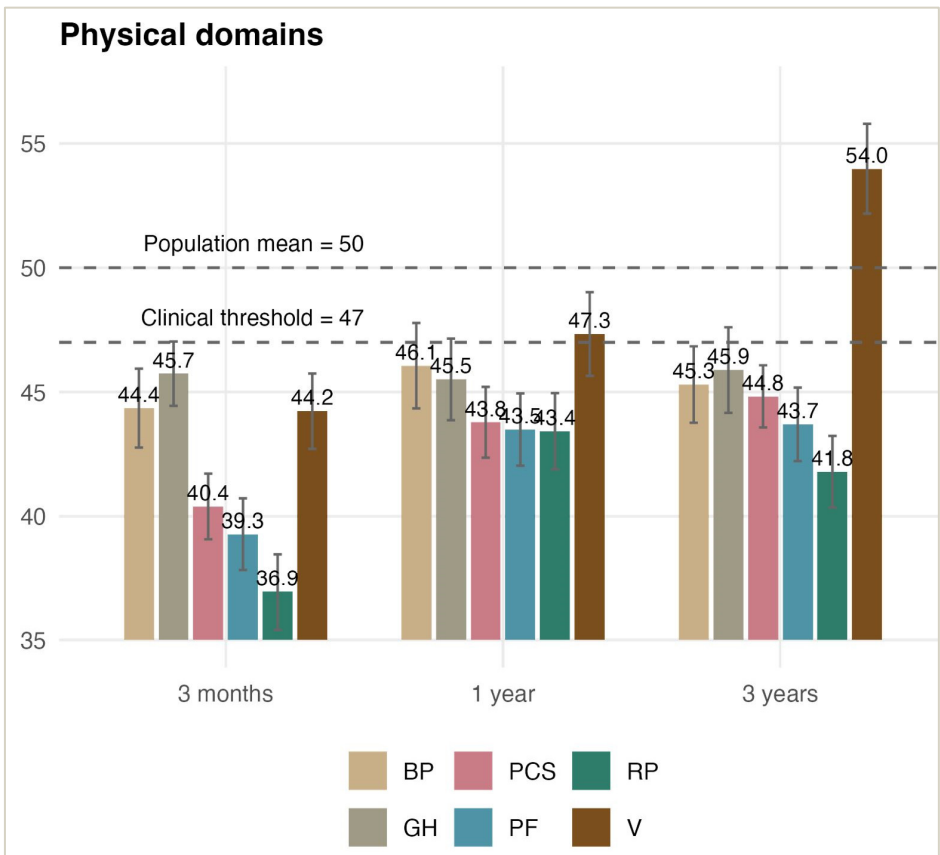

Figure 19: Physical Health-Related Quality of Life (PCS) and Domains at 3 Months, 1 Year, and 3 Years After Critical COVID-19. Bar chart showing mean T-scores for the Physical Component Summary (PCS) and physical health domains of the SF-36v2 (Physical Functioning [PF], Role-Physical [RP], Bodily Pain [BP], General Health [GH], Vitality [V]) at each follow-up. All domains improved from 3 months to 1 year, with slower progress to 3 years. Dashed lines indicate the population mean (T=50) and clinical threshold for impairment (T=47). Data are cross-sectional at each time point.

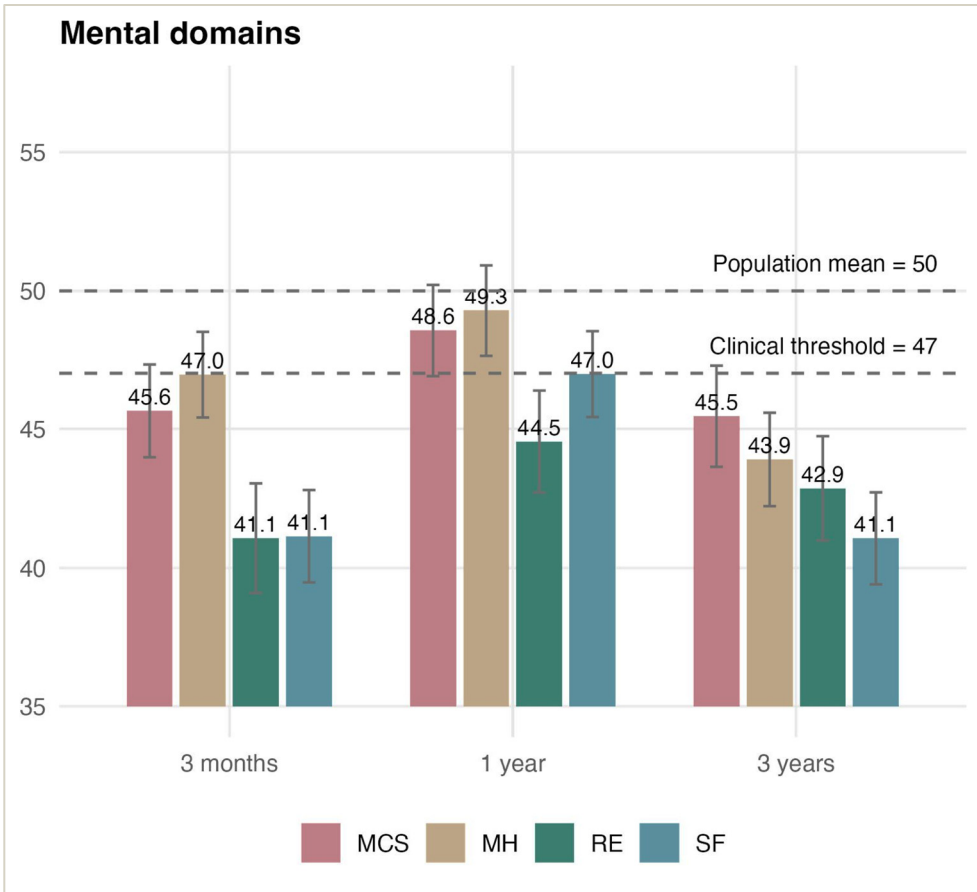

Figure 20: Mental Health-Related Quality of Life (MCS) and Domains at 3 Months, 1 Year, and 3 Years After Critical COVID-19. Bar chart showing mean T-scores for the Mental Component Summary (MCS) and mental health domains of the SF-36v2 (Social Functioning [SF], Role-Emotional [RE], Mental Health [MH]) at each follow-up. MCS and Social Functioning peaked at 1 year before declining by 3 years, while Role-Emotional and Mental Health remained relatively stable. Dashed lines indicate the population mean (T=50) and clinical threshold for impairment (T=47). Data are cross-sectional at each time point.

Fatigue and Psychological Symptoms

Fatigue severity increased, with MFIS scores rising from 31.6 to 34.6 ($p = 0.008$). All subdomains (physical, cognitive and psychosocial) showed significant worsening. The prevalence of clinically significant fatigue (MFIS ≥ 38) rose from 37% to 41%. Symptoms of depression and PTSD also increased (HADS-D: 4.4 to 5.1, $p = 0.006$; PCL-5: 15.1 to 16.7, $p = 0.041$), though these changes did not exceed MID thresholds. Anxiety symptoms remained unchanged, affecting approximately 25% of participants (Figure 21).

Respiratory Symptoms

Overall respiratory symptom burden remained stable (SGRQ total: 29.3 to 29.7, p = 0.35), but the Symptoms subscale worsened significantly (28.0 to 31.0, p = 0.021). The Activity subscale remained elevated, and the proportion of participants with respiratory impairment (SGRQ ≥ 19.7) increased from 59% to 62% among those with complete data at both timepoints (n = 191) (Figure 21).

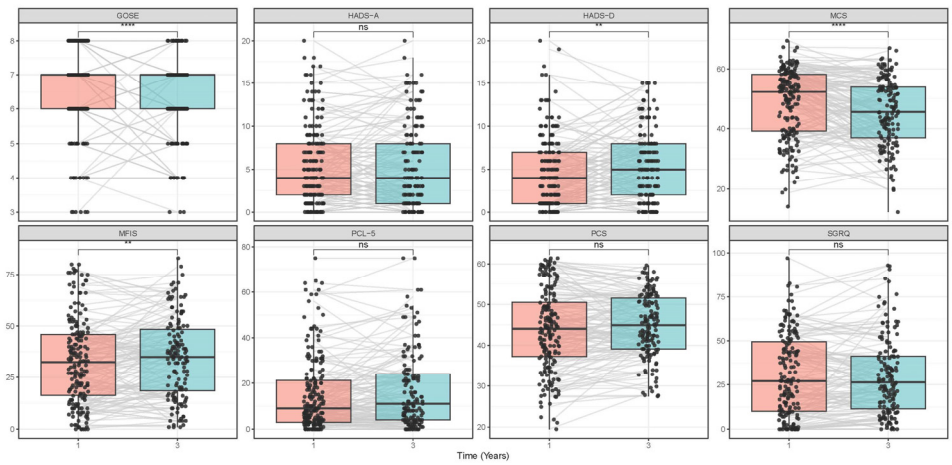

Figure 21 Comparison of clinical outcome measures and biomarkers between two time points. Box plots display the distributions for GOSE, HADS-A, HADS-D, MCS, MFIS, PCL-5, PCS, and SGRQ, with pink boxes representing 1-year data and blue boxes representing 3-year data. Individual data points are overlaid with paired measurements connected by grey lines.

Employment and Return to Work

Among participants aged 24–65 years who were employed prior to ICU admission and who attended both the 1-year and 3-year follow-ups (n = 84), return-to-work rates remained stable at 82% (69/84) at both time points. The number of participants in full-time employment increased from 46 at 1 year to 53 at 3 years, while the number of participants in part-time jobs decreased from 23 to 16 (Figure 22).

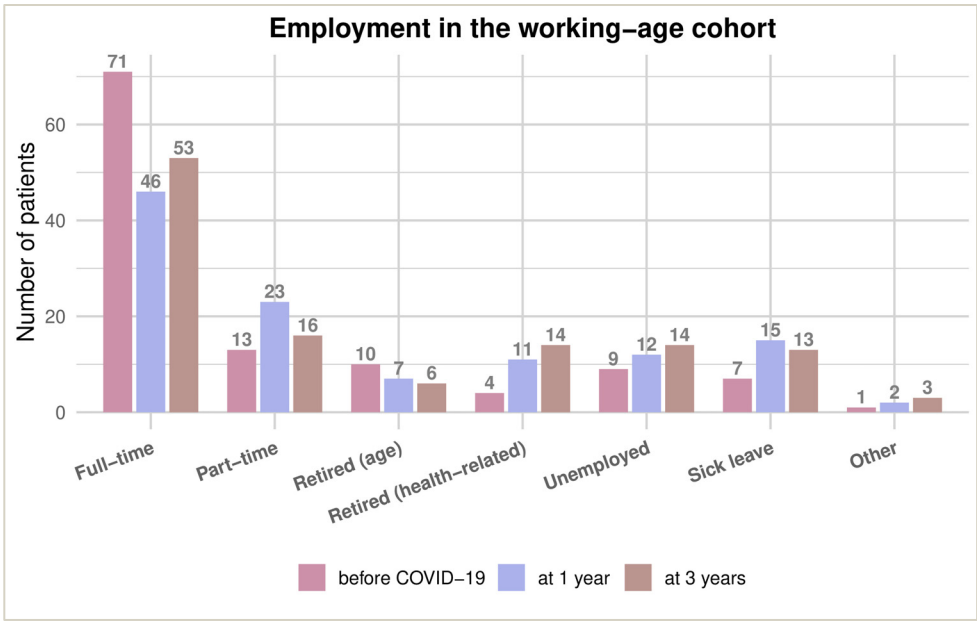

Figure 22: Employment and retirement status before COVID-19 and at 1 and 3 years after ICU discharge among survivors aged 24-65

Correlations Among Variables at 3 Years

Correlation network analysis revealed two distinct symptom clusters. Mental health measures (HADS-A, HADS-D, PCL-5) and fatigue (MFIS) were strongly correlated, with coefficients exceeding 0.7. A second cluster linked functional outcome (GOSE) with fatigue, respiratory symptoms, and both physical and mental HRQoL (Figure 23).

Factors Associated with Outcomes at 3 years

Incomplete recovery (GOSE $\leq$ 6) was present in 45% of survivors at 3 years. Multivariable analysis identified younger age and higher baseline frailty as independently associated with incomplete recovery [OR 0.70 (95% CI 0.54–0.91), p = 0.008 and OR 1.54 (95% CI 1.04–2.28), p = 0.029, respectively]. Baseline comorbidities and COVID-19 severity markers were not significantly associated with recovery at 3 years.

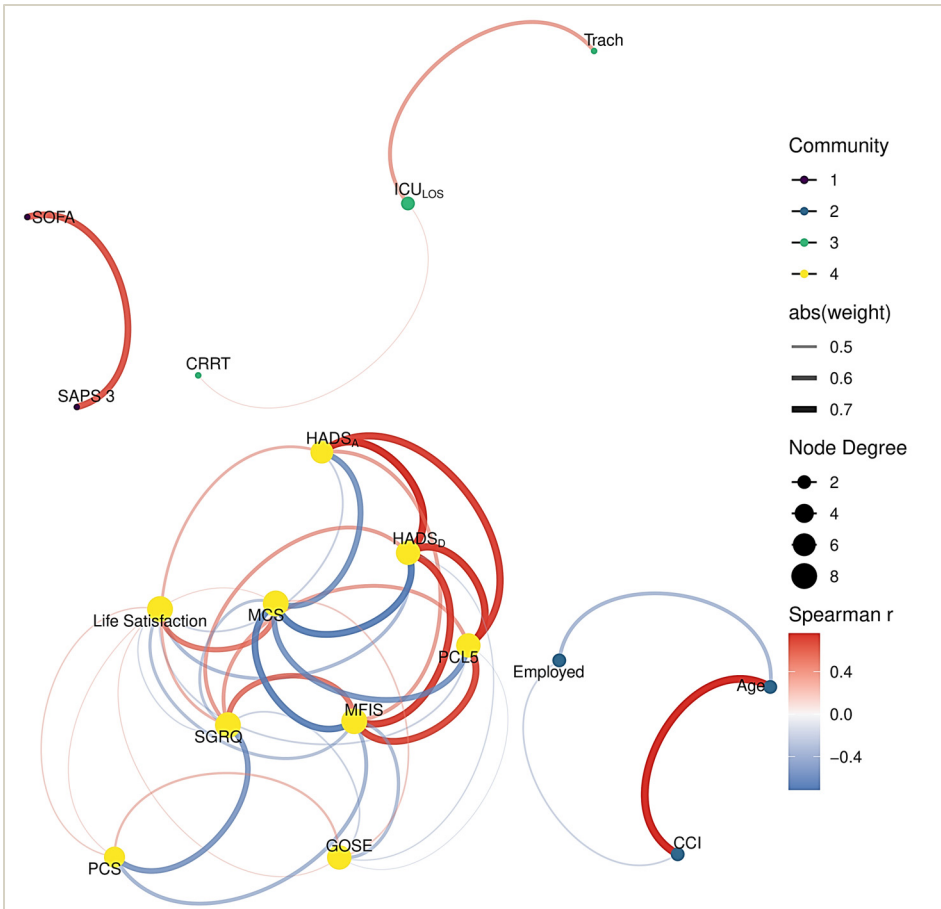

Figure 23 illustrates the network correlation analysis of variables at the 3-year follow-up (n = 191). Node size reflects variable importance, while edge thickness and colour intensity indicate the strength of correlation (Spearman's ρ). Red edges represent strong positive correlations (ρ>0.7); purple edges indicate moderate correlations (0.4<ρ<0.7). Two distinct clusters are evident: one comprising mental health symptoms, including fatigue, and another including functional outcomes and physical health measures, while some demographic and clinical factors remain isolated.

Discussion

Key Findings in Context

This thesis presents a comprehensive, longitudinal analysis of critically ill COVID-19 patients admitted to ICUs across southern Sweden during the first year of the pandemic. Through a 3-year follow-up, it explores mortality determinants, recovery trajectories, and the prognostic value of calprotectin as a biomarker. The findings contribute to our understanding of COVID-19 critical illness and the biopsychosocial mechanisms behind recovery.

COVID-19 Mortality

Age and Mortality

When this study began in 2020, the factors influencing survival in critically ill COVID-19 patients were largely unknown. Traditional ICU severity scores, including SAPS III [140], demonstrated limited predictive accuracy, whereas age consistently emerged as the strongest predictor of mortality. Our observed 3-month mortality aligns with international data [160], with rates rising sharply from age 60 and reaching over 90% among octogenarians. Of the 17 intubated patients aged 80 or older, only one survived to the 3-month mark.

ICU Burden and Mortality

System-level strain also influenced outcomes. Mortality more than doubled during periods when regional ICU occupancy exceeded 50 patients, and this association remained significant after adjustment for individual risk factors. Similar findings were observed in studies of US Veterans Affairs hospitals [5], while other research indicated substantial additional excess deaths when ICU occupancy approached or exceeded capacity [161]. European studies found that limited access to ICU beds was linked to higher COVID-19 death rates [162].

BMI and Mortality

The association between BMI and mortality followed a U-shaped pattern, with increased risk at both low and high extremes. Patients with moderate obesity had more favourable outcomes than those who were underweight or severely

obese. This pattern, often referred to as the obesity paradox, has been described in the broader critical care literature [163, 164].

Several factors may contribute to this finding. Patients with higher BMI might have been admitted to the ICU earlier due to expected respiratory complications. Greater metabolic reserves and improved nutritional status could protect against the catabolic stress of prolonged critical illness. [165]. From a respiratory mechanics perspective, moderate obesity may influence transpulmonary pressure gradients in a way that reduces alveolar damage [166]. Moderate obesity may reduce excessive cytokine responses, which could help lower systemic inflammation [167].

Comparing Patterns Across the 3-Year Timeline

Mortality Patterns

Following an initial 39% mortality rate at 3 months, only seven additional patients died between 3 months and 3 years, indicating a distinct early mortality plateau. This stabilisation pattern differs from that of some broader critical illness studies and may reflect unique pathophysiology or demographics of COVID-19 [168, 169].

Age-Outcome Relationship

Our data revealed contrasting age-related patterns between the acute and recovery phases. During critical illness, increasing age was the strongest predictor of mortality. However, among patients who survived to discharge, older survivors consistently showed better functional outcomes than younger survivors at every follow-up point over the three-year period.

Frailty and Recovery

Frailty, assessed via the Clinical Frailty Scale (CFS), was more strongly associated with long-term outcomes than age alone. While frailty stratification showed associations with 3-month mortality, its relevance became even more apparent in recovery patterns. At 1 year, lower frailty was associated with good functional outcome, and similarly, at 3 years, higher frailty was associated with incomplete recovery. These findings are consistent with previous research, which has shown that baseline frailty is associated with adverse outcomes in critical illness [170]. A recent meta-analysis [171] further supports the relevance of frailty, particularly in older ICU patients, although the strength of association varied across subgroups. Despite being relatively uncommon in our cohort, frailty remained significantly associated with long-term recovery.

Impact of Invasive Mechanical Ventilation

Longer IMV durations were consistently associated with worse outcomes at all assessment points, consistent with the broader literature [172, 173], which

demonstrates higher mortality rates and greater need for post-discharge care among IMV-treated patients [174, 175]. The association between longer IMV duration and worse outcomes may reflect both the severity of the underlying illness and the potential for ventilator-induced lung injury [176].

Recovery Trajectories

Recovery following critical COVID-19 infection was non-linear and varied across health domains. While functional outcomes improved substantially during the first year, a subsequent decline was observed between years 1 and 3. Physical health showed gradual improvement, whereas mental health peaked at 1 year and then deteriorated, returning to levels similar to those seen at 3 months (Figure 24).

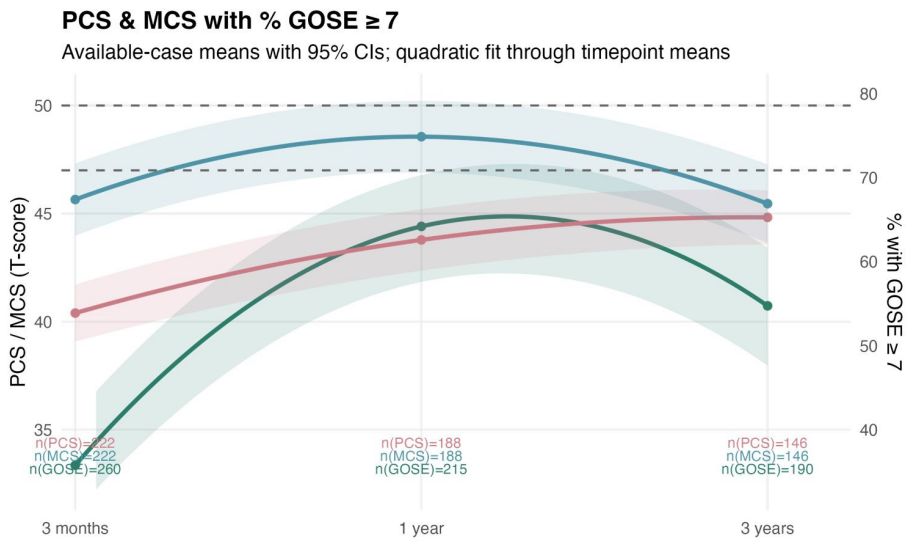

Figure 24: Recovery trajectories following critical COVID-19. The light green line (right y-axis) represents the percentage with a good functional outcome (GOSE ≥ 7). Pink and light blue lines (left y-axis) show physical (PCS) and mental (MCS) health-related quality of life T-scores. Shaded areas show 95% CI. Grey dashed line (47) and black dotted line (50) indicate clinical cutoff and population norm for T-scores. Data represent cross-sectional assessments at each time point.

Although most previous studies report persistent but stabilising psychiatric symptoms up to two years post-COVID-19 [94, 98, 177], our findings align with more recent research [178], indicating progressive deterioration in psychiatric and cognitive health between 2 and 3 years after hospitalisation.

This late decline in mental health may reflect a delayed shift in patient awareness: as physical recovery progresses, individuals may become more conscious of

lingering cognitive and emotional limitations, which can contribute to psychological distress and interfere with both functional recovery and social reintegration [179].

The overall recovery trajectory in our cohort showed initial improvement followed by longer-term challenges, a pattern similar to that observed in non-COVID ARDS survivors [89, 90]. However, the decline in mental health between years one and three appears to distinguish our COVID-19 cohort from other forms of respiratory failure, where psychiatric symptoms typically stabilise after the first year.

Interpreting Long-term Outcome through Conceptual Frameworks

To better understand the varied recovery patterns in our cohort, we drew on two conceptual models previously introduced in the Introduction: the biopsychosocial model and the ICF framework [109, 113]. These frameworks help explain why patients may improve in one domain while deteriorating in another and offer structure for interpreting the multidimensional outcomes observed.

In our data, physical health (Body Functions and Structures) improved initially, while social participation (Activities and Participation) declined over time. This was most evident in the six-point drop in SF-36v2® Social Functioning scores between years 1 and 3, suggesting that lingering symptoms limited patients' ability to re-engage socially, despite stabilisation in physical recovery.

Biological, psychological and environmental factors jointly influenced long-term outcomes. Age is used here to illustrate how the biopsychosocial and ICF frameworks can help interpret outcome patterns across domains.

- Biological: Younger patients may be more vulnerable to prolonged immune dysregulation, possibly due to stronger acute inflammatory responses [116, 120, 121].
- Psychological: Older patients often demonstrate more adaptive coping strategies [180], while younger survivors may face greater disruption to work, family life and identity. This is supported by recent findings showing that individuals under 50 are at higher risk of persistent post-COVID symptoms than those aged 65 and above [181]. Additionally, younger survivors may experience a greater discrepancy between pre-illness functioning and post-COVID limitations, combined with more demanding work and family obligations [182].
- Environmental: System-level factors such as ICU burden and access to rehabilitation services also shaped outcomes, highlighting the importance of context in recovery.

Taken together, these frameworks help explain why recovery was domain-specific and non-linear. They also clarify why younger age, although protective in the acute phase, was associated with poorer long-term outcomes among survivors.

Calprotectin as a Bridge Between Acute Inflammation and Long-term Recovery

Our analysis revealed that patients with elevated or rising calprotectin levels during the first week of ICU care had significantly worse long-term outcomes, including higher 1-year mortality and poorer functional recovery. A sustained increase in calprotectin may reflect a failure to interrupt the self-amplifying inflammatory cycle described earlier, in which calprotectin release triggers further neutrophil activation and NET formation [36, 47]. This cycle represents a shift from an adaptive immune response to a maladaptive NETosis-driven process, potentially contributing to tissue damage across multiple organ systems, as illustrated in Figure 25.

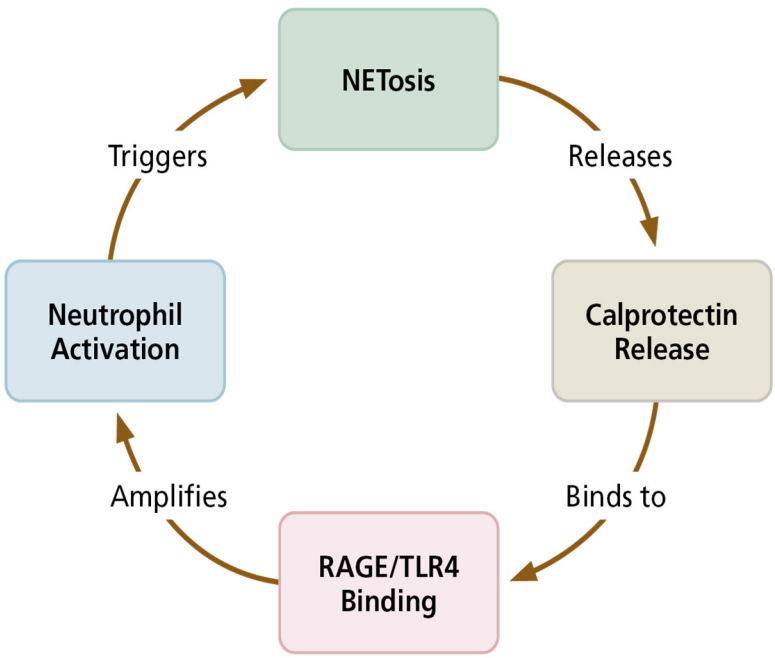

Figure 25: Calprotectin inflammatory amplification loop. Neutrophil activation leads to NETosis and calprotectin release. Calprotectin binds to RAGE/TLR4 receptors, triggering further neutrophil activation in a self-perpetuating cycle.

Persistently elevated calprotectin levels may underlie the multidomain impairments observed over three years, including fatigue, cognitive dysfunction, and psychological symptoms. Our correlation analysis revealed clustering between fatigue and mental health symptoms, which is consistent with neuroinflammatory mechanisms that can disrupt brain function [120, 121] and explain the mental health decline between years one and three.

This proposed mechanism aligns with emerging evidence that COVID-19 can induce lasting immune dysregulation and sustained neural alterations, contributing to long-term cognitive and psychiatric symptoms [183-185]. The association between calprotectin and functional outcomes (GOSE) demonstrates how a single inflammatory biomarker can reflect impairments across physical, cognitive, and psychological domains, effectively bridging acute-phase immune activity with chronic recovery trajectories.

Long-term Sequelae

Three-year follow-up data demonstrate overlapping features of PICS and post-COVID-19 condition among ICU survivors, with some notable differences compared to what is typically observed in either condition alone.

Physical symptoms followed a trajectory consistent with PICS, characterised by early improvement followed by stabilisation. However, respiratory symptoms persisted and worsened in severity, particularly cough and shortness of breath. By year three, 64% of survivors had clinically significant respiratory impairment, compared to 48% at year one. Cognitive fatigue remained prominent, reflecting post-COVID "brain fog" [186].

Mental health followed a more concerning trajectory. Depression and PTSD symptoms increased between years one and three, with marked deterioration in social functioning. This contrasts with typical PICS, where psychological symptoms tend to stabilise after the first year [179].

Fatigue emerged as a central and persistent symptom, worsening across physical, cognitive and psychosocial domains, and frequently co-occurring with impaired physical function, anxiety and depression. Correlation analysis confirmed strong links between fatigue and mental health symptoms, while functional outcome was closely tied to both fatigue and respiratory impairment. These clustering patterns, while prominent in COVID-19, have also been documented in ARDS survivors, where fatigue often exceeds other impairments and co-occurs with them [105]. A meta-analysis further supports this, showing that fatigue and cognitive impairment are among the most prevalent and persistent symptoms in the post-COVID-19 condition [187].

Although these patterns may reflect broader post-critical illness trajectories, the timing, persistence and especially the late decline in mental health may be more specific to COVID-19. It has been proposed that post-COVID-19 condition, PICS and post-sepsis syndrome share common features [107], reflecting what Needham et al. termed "surviving but not thriving" [93].

Despite ongoing symptoms, most participants remained employed, with a gradual shift from part-time to full-time employment. This gap between clinical recovery and workforce participation highlights the complex relationship between health outcomes and societal reintegration [188-190].

Interestingly, life satisfaction remained stable and approached national averages in Sweden [155], indicating psychological adaptation despite lingering symptoms. This discrepancy may reflect psychological adaptation or response shift [191, 192].

Nonetheless, the persistent clustering of symptoms points to ongoing biological processes. Sustained low-grade inflammation and unresolved NET formation [42, 45] may underlie the observed fatigue, cognitive dysfunction and multisystem symptoms [116].

Notably, most baseline comorbidities and COVID-19 severity markers linked to poor 1-year outcomes were no longer predictive at 3 years. This shift may reflect that long-term recovery is shaped more by post-acute factors than by initial disease severity [193, 194].

Strengths and Limitations

This study has several notable strengths. The prospective, multicentre design, combined with a large cohort and comprehensive data collection, provided a robust foundation for evaluating outcomes in critically ill COVID-19 patients.

The use of validated instruments for both clinician-rated and patient-reported outcomes enabled a multidimensional assessment, allowing for meaningful comparisons over time across physical, cognitive, and psychological domains.

Retention rates were high throughout the study, with follow-up rates of 87% at 3 months, 73% at 1 year, and 65% at 3 years. These are figures that exceed those reported in many other post-ICU studies. This strengthens the reliability of longitudinal findings.

Face-to-face follow-up interviews during the first year helped reduce missing data and improve overall data quality. In particular, in-person assessments enhanced the sensitivity of clinician-reported functional outcomes.

The extended 3-year follow-up provided insights beyond the timeframes typically examined in COVID-19 survivorship studies, capturing late-phase changes in recovery trajectories.

Finally, the inclusion of calprotectin as a mechanistic biomarker added biological depth to the clinical and functional analyses, linking acute-phase inflammation to long-term outcomes.

Limitations

- Pre-COVID baseline data were limited in non-survivors, as comprehensive baseline information was only collected during the 3-month follow-up. This affects our ability to accurately assess the degree of functional decline attributable to COVID-19 versus pre-existing conditions.
- Participants lost to follow-up differed from those retained in the study. Non-participants at 3 months had shorter ICU stays, while those lost to follow-up at 12 months were younger and had lower illness severity. Additionally, those who attended the 3-year follow-up were more often native Swedish speakers and had slightly higher SAPS3 scores at admission. This may have introduced selection bias, potentially overrepresenting patients with more complex recovery trajectories and influencing the observed results, such as functional outcome and return-to-work rates.
- Survivorship bias may have contributed to the observed recovery patterns, particularly among older patients. The shift from face-to-face to telephone interviews between years 1 and 3 may also have affected assessment comparability.
- Response shift [192] and recall bias are potential concerns, especially regarding pre-COVID status, as outcomes relied primarily on patient-reported instruments.
- The study lacks detailed information on the length, type and intensity of rehabilitation interventions, which prevents definitive conclusions about the effectiveness of rehabilitation.
- Although this was a multicentre study, it was conducted within the Swedish healthcare system. This context may limit the generalisability of findings to other settings.

In summary, this thesis provides a detailed account of critical COVID-19 across the acute phase, recovery trajectories and biological mechanisms. The findings highlight how patient-level vulnerability, systemic strain and immunological dysregulation interact to shape both short- and long-term outcomes.

Clinical Implications

The findings of this thesis have several clinical implications for both acute care and long-term management of critically ill COVID-19 patients.

Age and frailty

Age was strongly associated with short-term mortality. However, among survivors, older age was not linked to poorer long-term outcomes. Instead, clinical frailty was more closely associated with recovery status at three years. These findings indicate that frailty should be part of prognostic evaluations, and current tools such as SAPS 3 could be improved to better capture patient vulnerability. Chronological age alone should not be used to exclude patients from intensive care.

ICU burden

Mortality was significantly higher during periods of high ICU occupancy, indicating that system strain can affect individual outcomes. When resources are stretched, the timing of admission and bed availability may influence who receives life-saving care, sometimes independently of medical need. This highlights the need for fair resource allocation and transparent triage protocols.

BMI

BMI showed a U-shaped relationship with mortality. Patients with low BMI had higher death rates than those with moderate obesity. This may reflect better metabolic reserves or an enhanced immune response in moderately obese patients, or earlier ICU admission due to anticipated complications. The findings indicate that BMI alone is inadequate for risk assessment in critical illness.

Calprotectin

Calprotectin levels during the first week of ICU care were associated with both short- and long-term outcomes. When combined with age, day 7 levels showed good predictive accuracy for 1-year mortality. As a stable and rapidly measurable biomarker, calprotectin may help identify patients at risk of persistent inflammation and impaired recovery. Although not yet part of routine clinical practice, its prognostic potential merits further investigation.

Recovery and rehabilitation

Our findings support a structured, staged approach to post-ICU care. Early identification of rehabilitation needs, followed by coordinated physical, psychological and social support, may improve outcomes. This aligns with recent recommendations [123], which advocate for assessment and intervention across all ICF domains. A comprehensive evaluation should include psychological health, quality of life, and social participation.

Conclusions

This thesis examined survival and long-term outcomes in 498 critically ill COVID-19 patients admitted to ICUs in the Skåne region between May 2020 and May 2021. Through a prospective, multicentre cohort study with 3-year follow-up, it explored mortality, functional recovery, health-related quality of life, and biomarkers of disease severity. The most important findings are summarised below:

Key findings

- **Age** was most strongly associated with mortality, yet elderly survivors showed better functional outcome.
- High ICU occupancy (**ICU burden**) was independently associated with increased mortality, underscoring system-level effects.
- Being moderately **obese** was linked to the lowest mortality rate in a U-shaped pattern. After adjusting for various factors, obesity was still not found to be associated with higher mortality.
- **Clinical frailty** was more strongly associated with long-term recovery than age alone.
- Early **calprotectin dynamics** predicted mortality and functional outcomes.
- Recovery was **non-linear** and domain-specific: physical health stabilised while mental health deteriorated between the first and third years.

Future Aspects

This research highlighted key lessons for future health emergencies. Establishing structured data collection early is vital for research and clinical decisions. Collaboration across six ICUs, with regular meetings, improved research quality and clinical consistency. Maintaining high research standards despite pandemic pressures ensured the reliable results.

So what?

These findings matter because they reveal how systemic strain, biological vulnerability, and immune dysregulation interact to influence recovery. They demonstrate that survival alone is not enough; many patients continue to live with ongoing impairments. Applying these insights allows for better ICU preparedness, personalised patient care, and the development of more effective rehabilitation pathways.

ICU burden

Future pandemic preparedness requires capacity models that account for the demonstrated relationship between ICU occupancy and mortality. Research should focus on identifying optimal surge thresholds and strategies for maintaining care quality during peak demand periods.

Prognostic models

There is still a clear need to improve prognostic tools for critically ill patients. Adding frailty assessments and inflammatory markers to existing scoring systems, such as SAPS 3, could make predictions more accurate for older or vulnerable groups. Future studies should focus on how these models can be used in everyday clinical practice to support decision-making and improve patient outcomes. Importantly, they need to be validated and tested for real-world impact in ICU settings.

BMI

The observed U-shaped association between BMI and mortality warrants further research. Future studies should investigate how body composition, metabolic reserves, and inflammatory responses impact outcomes in critical illness.

Understanding these mechanisms may help explain why moderate obesity appears protective in some ICU populations.

Calprotectin

Plasma calprotectin has emerged as a promising biomarker for ongoing inflammation and poor outcomes. Prospective studies should evaluate its clinical utility, cost-effectiveness and feasibility in routine ICU workflows. Building on research from the Malmö Diet and Cancer Study [195, 196], it would be valuable to investigate whether changes in calprotectin levels reflect a broader failure to resolve inflammation. Malmö-based cohorts could help validate these findings in other diseases.

Inflammation and long-term effects

The link between persistent calprotectin elevation and poor long-term outcomes suggests that unresolved inflammation may contribute to the post-COVID-19 condition. Future studies should explore the role of NETs, immune dysregulation and other mechanisms that may underlie fatigue, cognitive dysfunction and mental health decline.

Long-Term Follow-Up

The observed decline in mental health between years one and three highlights the importance of extended follow-up. Monitoring this cohort over five to ten years may help distinguish between temporary and persistent impairments. However, maintaining long-term cohorts poses challenges, including participant attrition and resource demands. Comparative studies with non-COVID ICU survivors are also needed to understand which outcomes are specific to COVID-19.

Implementation

To make these findings useful in clinical practice, we must find practical ways to incorporate frailty assessments and biomarker data into ICU routines, standardise post-ICU screening, and create flexible rehabilitation programmes tailored to patient needs. Insights should also guide ICU resource planning, especially during crises. Although calprotectin shows promise as a prognostic marker, its usefulness depends on reliable measurement and whether acting on early risk signals improves outcomes.

Personal Reflections

My understanding of COVID-19 has evolved steadily throughout this research journey. Beginning in March 2020, I regarded critical COVID-19 primarily as an acute respiratory syndrome with devastating mortality. With ICU resources stretched to their limits, our immediate focus was on patient survival and managing scarce resources.

Over time, I have recognised COVID-19 as a complex condition with lasting effects on multiple systems. Non-linear recovery patterns reveal improvement followed by deterioration, alongside varied physical and mental health trajectories, challenging simplistic recovery models. Observations regarding age and frailty inform my clinical practice, highlighting the importance of considering each patient's overall condition rather than focusing solely on individual factors.

My path to this research began unexpectedly in 1987 when, at the age of 19, I was working as an au pair in Paris and attended a presentation by a researcher from the Institut Pasteur discussing HTLV-III (later known as HIV). As fear of AIDS gripped society, I was captivated by his work and thought, "I want to do that". This moment sparked my journey through medical school, taking me to the jungles of Nicaragua, Portland, Oregon, for part of my residency, and eventually to 26 years of specialising in anaesthesia and intensive care.

For most of my career, I focused on clinical work, education, and improving ICU practices. It was not until I was over 50, encouraged by colleagues and especially my supervisor, Professor Hans Friberg, that I dared to consider serious research. Then the pandemic struck, instantly shifting my research focus. In hindsight, COVID-19 represents a modern-day plague. Completing this research at nearly 57 years old has felt like coming full circle, from that young au pair girl inspired by research into one devastating global health crisis to a clinician-researcher documenting one of the most significant health crises of our time.

The COVID-19 pandemic has had a profound impact on patients, healthcare systems and society as a whole. This research has profoundly changed my understanding of critical illness and, perhaps most of all, recovery processes.

I remain deeply grateful to the patients who, despite their hardships, made these discoveries possible by participating in our study.

Summary in Swedish

Tre år efter intensivvården - vad hände med COVID-19-patienterna?

Inledning

När COVID-19-pandemin bröt ut våren 2020 var vår förståelse av sjukdomen i det närmaste obefintlig. Medierna rapporterade om smittspridning och dödstal, men avgörande medicinska frågor förblev obesvarade: vilka faktorer påverkar överlevnad, hur ser återhämtningen ut månader och år senare, och kan tidiga blodprover förutsäga patienternas framtid?

För att belysa dessa frågor genomförde vi en omfattande uppföljning av 498 kritiskt sjuka COVID-19-patienter som vårdades på intensivvårdsavdelningar i Skåne under det första pandemiåret. Patienterna följdes upp efter tre månader, ett år och tre år för att undersöka både faktorer som påverkar överlevnad och långsiktiga återhämtningsmönster.

Mortalitet och riskfaktorer

Mortaliteten var hög och uppgick till 39 % under de första tre månaderna, där ålder identifierades som den mest avgörande riskfaktorn. Dödligheten visade en tydlig ökning från 60 års ålder, och bland patienter över 80 år som var i behov av respiratorbehandling överlevde endast en av sjutton.

Studien påvisade en alarmerande koppling mellan vårdkapacitet och patientutfall. Under perioder med hög belastning (över 50 COVID-19-patienter samtidigt i intensivvård) fördubblades mortaliteten jämfört med perioder med normal belastning. Detta resultat understryker hur systemfaktorer direkt påverkar individuella patienters överlevnadschanser.

En oväntad observation var att patienter med måttlig fetma hade bättre överlevnad än både normalviktiga och kraftigt överviktiga. Det U-formade sambandet mellan kroppsvikt och mortalitet kan delvis förklaras av att måttlig fetma ger större energireserver vid långvarig sjukdom, eller att vissa komplikationer är lättare att behandla i denna grupp.

SYDSVENSKAN 175 år

Ny studie: Ingen koppling mellan högt BMI och ökad dödlighet i covid

21 december 2022 13:43

Under covidpandemins tidiga dagar hörde man ofta att överviktiga personer var en grupp som löpte större risk att dö av sjukdomen. Nu visar en ny studie, utförd bland annat i Skåne, att det sambandet inte tycks finnas.

Johan Lorentzon
Text

Studiens fynd om att måttlig fetma kunde vara skyddande mot kritisk COVID-19 blev stora nyheter när de publicerades. Expressens löpsedel "DINA EXTRAKILON KAN SKYDDA MOT COVID" och Sydsvenskans rapportering "Ingen koppling mellan högt BMI och ökad dödlighet i COVID" visar hur medicinska upptäckter kan nå ut till allmänheten.
Foto: Langvad, E. (2022, 21 december). Sydsvenskan. TT Nyhetsbyrån.

PICS och post-covid-tillstånd

Efter intensivvård för COVID-19 är långvariga symptom, både fysiska och psykiska, vanliga. Det finns två närbesläktade tillstånd: Post-Intensive Care Syndrome (PICS), som innebär nya eller förvärrade problem efter intensivvård, och post-covid-tillstånd. Enligt WHO:s definition innebär post-covid-tillstånd att symptom utvecklas inom tre månader efter infektion med SARS-CoV-2, varar i minst två månader och inte kan förklaras av någon annan diagnos. Vanliga symptom är trötthet, andfåddhet, kognitiva svårigheter, ångest och depression. Många patienter har båda tillstånden samtidigt, vilket gör återhämtningen mer komplicerad och långvarig. Våra resultat visar att symptom ofta kvarstår i flera år efter intensivvården, vilket tydligt visar behovet av långsiktig uppföljning och rehabilitering.

Funktionell återhämtning och livskvalitet

Bland de som överlevde den kritiska fasen väntade i många fall en utdragen och komplex återhämtningsprocess. Genom noggrann uppföljning med validerade mätinstrument för funktionell återhämtning och hälsorelaterad livskvalitet kunde vi identifiera mönster i återhämtningen som tidigare varit okända.

Under det första året skedde en tydlig förbättring, med andelen patienter som hade god funktionell återhämtning som steg från 35 till 64 procent. Detta pekade på en möjlig stegvis återhämtning av hälsan. Dock noterades en oväntad förändring mellan det första och tredje året.

Trots att den fysiska, hälsorelaterade livskvaliteten fortsatte att förbättras under hela treårsperioden kvarstod många specifika symtom. Vid treårsuppföljningen rapporterade 64 procent av patienterna fortsatt andningsbesvär, och 41 procent upplevde uttalad utmattning (fatigue).

Utvecklingen av den psykiska hälsan visade däremot en mer oroande trend. Från att ha värden som var nära den hos normalbefolkningen vid ett år, steg andelen personer med depression och ångest markant vid treårsuppföljningen. Sammantaget visar resultaten att vissa psykiska besvär kan uppträda eller förvärras sent i återhämtningsförloppet, vilket understryker vikten av långsiktig uppföljning även av den psykiska hälsan.

Respiratortid och åldersparadox

En genomgående faktor som påverkade både överlevnad och återhämtning var respiratortid. Patienter som behandlades längre i respirator hade sämre utfall på alla mått, från högre dödlighet till sämre funktion även tre år senare.

Studien påvisade en märkbar åldersparadox: trots att högre ålder var kopplad till högre dödlighet, uppvisade äldre överlevare ofta bättre funktionell återhämtning än yngre patienter. Detta mönster var tydligt vid både ett- och treårsuppföljningen. Denna paradox kan bero på selektionsmekanismer, där endast äldre patienter med låg grad av klinisk skörhet (frailty) klarar sig genom den akuta fasen. Detta förklarar deras bättre återhämtning. Samtidigt kan yngre patienter uppleva en större skillnad mellan sina förväntningar och den nya verkligheten, vilket påverkar deras upplevelse av situationen och återhämtningen.

Kalprotektin som biomarkör

En av studiens viktigaste upptäckter var sambandet mellan inflammationsmarkören kalprotektin och långsiktiga utfall hos COVID-19-patienter. Kalprotektin är ett protein som utgör en stor del av innehållet i neutrofiler (en typ av vita blodkroppar) och frisätts vid inflammation. Patienter vars kalprotektinnivåer steg under den första veckan på intensivvården hade betydligt högre risk att avlida inom ett år, och de

som överlevde hade oftare sämre funktionell återhämtning och behövde mer avancerad vård.

Kalprotektin verkar driva en självförstärkande inflammatorisk process, där aktiverade neutrofiler frisätter kalprotektin som i sin tur aktiverar fler neutrofiler och förlänger inflammationen. Kalprotektin dag 7, i kombination med ålder, förutsäger ettårsmortalitet bättre än ålder ensam och kan därmed utgöra en tidig biomarkör för riskbedömning.

Systemfaktorer, återhämtning och framtida beredskap

Studien visar att återhämtningen efter kritisk COVID-19 är en långvarig och komplex process som påverkar både patienter och deras närstående. Även om många återgår till arbete kvarstår ofta psykiska och fysiska symtom under lång tid, vilket ställer krav på långsiktig planering inom vården.

Resultaten understryker att ålder inte bör vara den enda faktorn vid riskbedömning. Klinisk skörhet och biomarkörer som kalprotektin ger en mer nyanserad bild av patientens prognos och kan bidra till individanpassad behandling. Vårdkapacitet visade sig ha direkt påverkan på överlevnaden, vilket betonar behovet av robusta strukturer för intensivvård och krisberedskap.

Fysisk återhämtning följer ofta förutsägbara mönster, medan den psykiska dimensionen är mer varierad och kräver särskild uppmärksamhet. För framtida pandemiplanering är det avgörande att inte enbart fokusera på den akuta vården, utan även etablera hållbara system för uppföljning, rehabilitering och psykosocialt stöd.

I en värld där framtida pandemier är troliga snarare än möjliga, utgör denna kunskap en viktig pusselbit i förberedelserna för kommande hälsokriser.

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