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RESEARCH ARTICLE

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Intensive care unit burden is associated with increased mortality in critically ill COVID-19 patients

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Abstract

Background: Traditional models to predict intensive care outcomes do not perform well in COVID-19. We undertook a comprehensive study of factors affecting mortality and functional outcome after severe COVID-19.

Methods: In this prospective multicentre cohort study, we enrolled laboratory-confirmed, critically ill COVID-19 patients at six ICUs in the Skåne Region, Sweden, between May 11, 2020, and May 10, 2021. Demographics and clinical data were collected. ICU burden was defined as the total number of ICU-treated COVID-19 patients in the region on admission. Surviving patients had a follow-up at 90 days for assessment of functional outcome using the Glasgow Outcome Scale-Extended (GOSE), an ordinal scale (1–8) with GOSE ≥5 representing a favourable outcome. The primary outcome was 90-day mortality; the secondary outcome was functional outcome at 90 days.

Results: Among 498 included patients, 74% were male with a median age of 66 years and a median body mass index (BMI) of 30 kg/m^2. Invasive mechanical ventilation was employed in 72%. Mortality in the ICU, in-hospital and at 90 days was 30%, 38% and 39%, respectively. Mortality increased markedly at age 60 and older. Increasing ICU burden was independently associated with a two-fold increase in mortality. Higher BMI was not associated with increased mortality. Besides age and ICU burden, smoking status, cortisone use, P_aCO_2 >7 kPa, and inflammatory markers on admission were independent factors of 90-day mortality. Lower GOSE at 90 days was associated with a longer stay in the ICU.

Conclusion: In critically ill COVID-19 patients, the 90-day mortality was 39% and increased considerably at age 60 or older. The ICU burden was associated with mortality, whereas a high BMI was not. A longer stay in the ICU was associated with unfavourable functional outcomes at 90 days.

KEYWORDS
90-day mortality, age, COVID-19, functional outcome, ICU burden

Editorial Comment

In this prospective observation study in COVID-19 ICU patients from ICU's in southern Sweden, the 90-day mortality was 39%. Increased ICU burden (mechanical ventilation), and age ≥60 years were the two most important determinants for mortality.

1 | INTRODUCTION

On March 11, 2020, COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organisation (WHO). As of June 2022, 19,075 deaths have been associated with the disease in Sweden.[1] Patients infected with SARS-CoV-2 can experience various clinical manifestations, from no symptoms to critical illness. The WHO broadly defines critical illness in COVID-19 as individuals experiencing respiratory failure, septic shock and/or multiple organ dysfunction.[2] The mortality rate is high for older patients and those needing high-level care in the intensive care unit (ICU), ranging from 16% to 78% between centres and over time.[3] Furthermore, frailty is associated with increased mortality in elderly COVID-19 patients.[4] For patients needing invasive mechanical ventilation (IMV), mortality was particularly high in the early phase of the pandemic[5] when optimal ventilatory and critical care strategies were more uncertain. In addition, the impact of health care burden on clinical outcomes has been addressed and may have played a significant role at the height of the pandemic.[6] Multiple national and international collaborations have reported outcome data in critically ill patients,[7–9] including long-term functional outcomes.[10]

Our objectives were (a) to evaluate factors on ICU admission associated with 90-day mortality and (b) to describe factors during the ICU stay associated with functional outcomes at 90 days. We hypothesised that high age, body mass index (BMI) and ICU burden were associated with increased 90-day mortality, longer ICU stay and worse functional outcomes.

2 | MATERIAL AND METHODS

This prospective multicentre cohort study included critically ill adult (≥18 years old) patients with laboratory-confirmed SARS-CoV-2 infection where COVID-19 was the primary cause of ICU admission at six intensive care units in the Skåne region, Sweden, between May 11, 2020, and May 10, 2021. Participating units were one cardiothoracic ICU, two general ICUs and an ICU for infectious diseases at a University Hospital (Skåne University Hospital Lund and Malmö). The remaining two were general ICUs at regional hospitals (Helsingborg Hospital and Kristianstad Hospital). The participating units had 30–36 general ICU beds pre-pandemic. The total ICU capacity in the region was assessed daily and patients were admitted and transferred based on available ICU beds. The virus strain SARS-CoV-2 B.1.1.7 (alpha) prevailed throughout the study.[11]

Written informed consent was obtained from participants on admission, before discharge or up to 1 year after inclusion; for deceased patients, consent was presumed. Exclusion criteria were patients treated in the ICU without COVID-19 being the primary cause of admission or where consent was not obtained. The manuscript was prepared in adherence to the STROBE guidelines for observational studies.[12]

The primary outcome was all-cause mortality at 90 days. The secondary outcome was functional outcome assessed by the Glasgow Outcome Scale-Extended (GOSE) obtained at a follow-up at 90 days, performed face-to-face, or via telephone when necessary. GOSE is categorised on an ordinal scale (range 1–8) for assessment of disability and social participation. GOSE 1 represents death, and 8 represents full recovery. A score of ≤4 was considered unfavourable, and a score of ≥5 was deemed favourable.[13]

The SARS-CoV-2 infection was verified with a real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay on nasal or pharyngeal swabs or lower respiratory airway aspirate.

Data were prospectively collected in a master file containing the patient study number, the inclusion date, consent date, and follow-up date. Clinical data were retrieved from the electronic medical record system Melior and the regional quality registry CovidIR, extracting daily data from the hospital patient administrative system for intensive care units (PASIVA) and indirectly the Swedish Intensive care Registry (SIR). Demographics and patient characteristics on ICU admission according to Sequential Organ Failure Assessment (SOFA) and Simplified Acute Physiology Score 3 (SAPS 3) were collected.[14,15] We used the Swedish 2016 calibration of SAPS 3.[16] Laboratory tests were collected on admission to the ICU. Baseline creatinine was retrieved from medical records. We manually collected data on sex, height, weight, BMI, Charlson Comorbidity Index (CCI),[17,18] Clinical Frailty Scale (CFS),[19] smoking habits, time of onset of symptoms, pharmacological treatment prior to ICU admission. We subdivided CFS into three categories: fit (CFS1-3), vulnerable (CFS 4) and frail (CFS 5–9).[20] Daily use of IMV, number of days in prone positioning, continuous renal replacement therapy (CRRT), extracorporeal membrane oxygenation (ECMO) referral and tracheotomy were collected and so were complications, pneumothorax, pulmonary embolism and cardiac arrest. The use of steroids and other immunomodulation during ICU care were manually retrieved. Radiological assessments were collected, including chest radiographs, pulmonary computed tomography (CT) scans and CT angiograms. Decisions on limitation of care were registered and retrieved from CovidIR.

As a proxy for ICU burden, we used the total number of ICU-treated COVID-19 patients in the region on the day of admission. Transportation of patients between ICUs due to shortage of ICU beds was registered.

For data quality, an experienced ICU physician assessed collected clinical variables from 50 randomly selected patients (10%). The variables checked were decided by group consensus and included pharmacological treatments prior to admission to the ICU, CFS and CCI.

2.1 | Statistics

Study enrolment was predetermined to close after 1 year, no power analysis was performed. Continuous variables are presented as a median and interquartile range (Q1–Q3), while categorical variables are expressed as percentages. Differences in categorical variables between survivors and non-survivors were compared using Chi-square or Fisher's exact test if there were any cells with an expected count <5. Differences in continuous variables between the two groups were compared using the Mann–Whitney *U* test. Variables with more than 20% missing values were excluded from further analysis. The remaining data set was imputed using the missForest package,[21] and a multivariable logistic regression was performed. We used available variables on ICU admission to evaluate risk factors associated with 90-day mortality. These variables were age, sex, BMI, smoking status, ICU burden, comorbidities (diabetes mellitus, hypertension, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular disease, rheumatic disease, peptic ulcer disease, malignancy, chronic obstructive pulmonary disease, baseline creatinine level), previous medication (statins, immunosuppression, anticoagulants, steroids) variables on admission (pH, arterial oxygen partial pressure ratio to fractional inspired oxygen, P_aO_2/F_iO_2 (P/F), P_aCO_2, C-reactive protein (CRP), Procalcitonin (PCT), Interleukin-6 (IL-6), neutrophil count, lymphocyte count, platelet count, ferritin, bilirubin, D-dimer, heart rate, temperature and vasopressors). Highly skewed variables were log-transformed: ICU burden, creatinine, IL-6, platelet count (PLC), P_aO_2/F_iO_2 (P/F), ferritin and D-dimer.

Variables with a non-monotonous relation to mortality, BMI, P_aCO_2, CRP, neutrophil count and lymphocyte count were categorised with pre-determined cut-offs motivated by clinical experience. The reference levels were as follows: BMI 25–30 kg/m^2, P_aCO_2 4–7 kPa, CRP 80–180 mg/L, neutrophil count 2.5–8 $\times$ 10^9, lymphocyte count 0.8–70 $\times$ 10^9. For smokers, the reference was non-smoking. Backward stepwise regression was performed using the stepAIC function of the MASS package in R version 4.1.3.[22]

For the multivariate ordinal logistic regression of GOSE at 90 days, in addition to ICU admission data, we added variables obtained during the ICU stay: Length of stay in the ICU, IMV, steroid treatment, immunomodulator treatment, tracheotomy, pneumothorax, pulmonary embolism and cardiac arrest.

The performance of the multivariable logistic regression models for 90-day mortality was evaluated using the area under the curve (AUC) of the receiver operator characteristics curve (ROC).[23] The AUC was calculated using 10-fold cross-validation with 50 repeats.[24] Differences in AUC were tested using the method of DeLong et al.[25] We performed a backward, multivariate ordinal logistic regression of GOSE 2–8 using the polr function in the MASS package.[22] The $p < .01$ level of significance was used.

3 | RESULTS

During the study period, 607 patients were screened, of whom 498 were included (Figure S1, Table 1). In 65 patients, COVID-19 was not the reason for the ICU-stay, 25 were missed to inclusion and 19 did not give consent. Data on the missing 25 patients are described in Table S1. Mortality in the ICU, in-hospital and at 90 days was 30% ($n = 151$), 38% ($n = 190$) and 39% ($n = 193$), respectively. In 72% ($n = 356$) IMV was employed with a corresponding mortality of 44% at 90 days, compared with 26% in patients without IMV. Demographics, admission characteristics, clinical interventions, and complications, stratified by mortality at 90 days are summarised in Table 1. There was a significant difference in CFS between survivors and non-survivors 3 (2, 3) versus 3 (2–4) ($p < .001$). Among fit patients ($n = 367$) 90-day mortality was 33%, mortality increased to 49% and 72% in vulnerable ($n = 87$) and frail patients ($n = 39$), respectively. No patients with CFS 8–9 were included.

The ICU burden varied between 1 and 62 at its peak on January 11, 2021 (Figure 1). On that specific day, the total number of ICU patients including COVID-19 patients was 84, an increase of almost 200% compared with the normal number of ICU beds (Figure S3). A lower ICU burden carried a 90-day mortality of 25%, while a higher ICU burden was associated with a 90-day mortality exceeding 50% (Figure 1). Age was associated with 90-day mortality with a linear increase in mortality from age 60 (Figure 2A). Lower BMI was associated with increased 90-day mortality, a BMI of 35 kg/m^2 was associated with the lowest mortality (Figure 2B).

In 29 patients (6%), a limitation of care existed prior to ICU admission, with a 90-day mortality of 86% ($n = 25$). A decision to withdraw life-sustaining treatment in the ICU was made in 129 patients, out of whom 119 (92%) died in the ICU and all 129 died in-hospital.

Among the 305 survivors, 264 (87%) participated in the 90-day follow-up. Complete GOSE were retrieved from 260 patients. The median GOSE was 6 (5–7), and no patient presented a GOSE of 2. An unfavourable GOSE of 3–4 was seen in 23% of the patients, while a favourable GOSE of 5–8 was seen in 77%. A full recovery, GOSE 8, was reported by 7% (Figure 3). Patients who were missed at the detailed follow-up ($n = 41$) did not differ to those who participated regarding pre-disease characteristics (age, sex, BMI, CFS), IVM or LOS (data not shown).

There were few missing data and good coherence between the three parameters checked in the quality control. CFS from one patient was reassessed and adjusted, and two patients' CCI values were adjusted from CCI 2 to CCI 3.

TABLE 1 Admission characteristics, clinical interventions, complications, and outcomes stratified by 90-day mortality

	Overall ($n = 498$)	Survivors ($n = 305$)	Non-survivors ($n = 193$)	*p*-value survivors/ non-survivors
Admission characteristics				
Age (years) IQR	66 [56–73]	61 [52–68]	72 [66–77]	***<.001***
Male	74%	74%	74%	.99
BMI (kg/m^2) IQR	30 [27–35]	31 [27–36]	29 [26–33]	***.0010***
Symptomatic days before ICU	11 [8–15]	11 [8–14]	12 [7.4–17]	***.040***
Smokers-ever	44%	38%	55%	***<.001***
Immunosuppression	8%	7%	10%	.19
Systemic steroids (before COVID-19)	5%	3%	9%	***.008***
Charlson Comorbidity Index	3 (2–4)	2 (1–3)	4 (3–5)	***<.001***
Diabetes mellitus	31%	28%	35%	.14
Hypertension	55%	50%	62%	***.015***
COPD and severe asthma	19%	17%	22%	.13
Clinical Frailty Scale	3.0 [2–4]	3 [2–3]	3 [2–4]	***<.001***
SAPS 3	60 [50–69]	56 [47–65]	66 [56–75]	***<.001***
Temperature (°C)	37.5 [37.4–37.6]	37.6 [37.5–37.7]	37.4 [37.3–37.6]	.25
Systolic blood pressure (mmHg)	120 [100–134]	120 [100–137]	115 (95–130)	***.0030***
P/F ratio Day 1 (min) (kPa)	10 [8–12]	10 [8–13]	9 [7–12]	***.016***
P_aCO_2 Day 1 (max) (kPa)	5.8 [5.1–7.2]	5.7[5.0–6.9]	6.3[5.1–8.1]	.38
pH	7.43 [7.36–7.47]	7.44 [7.37–7.47]	7.42 [7.34–7.46]	***.019***
Creatinine (μmol/L)	75 [60–102]	72 [58–91]	81 [65–123]	***<.001***
Platelets ($\times 10^9$/L)	244 [183–324]	259 [192–328]	226 [160–321]	***.0040***
Leukocytes ($\times 10^9$/L)	10.7 [8.0–15.4]	10.3 [7.9–13.8]	12.1 [8.4–17.3]	***.0020***
Lymphocytes ($\times 10^9$/L)	0.6 [0.4–0.9]	0.6 [0.5–0.9]	0.6 [0.4–0.8]	.070
CRP mg/L	151 [87–221]	148 [90–214]	158 [82–240]	.64
PCT (μg/L)	0.4 [0.2–1.2]	0.4 [0.2–1.1]	0.5 [0.2–1.3]	.082
Lactate (mmol/L)	2.2 [1.7–2.9]	2.1 [1.7–2.6]	2.6 [1.8–3.6]	***<.001***
Bilirubin (μmol/l)	9.0 [6.5–13.0]	9.0 [6.0–12.0]	10 [7.0–15.0]	***.0010***
D-dimer (mg/L)	2.0 [1.0–6.7]	1.7 [1.0–4.3]	2.8 [1.1–11.0]	***.0010***
Ferritin (μg/L)	1430 [834–2350]	1430 [705–2260]	1420 [927–2460]	.39
IL-6 (ng/L)	105 [49–247]	92 [43–185]	140 [66–429]	***.0010***
LD (μkat/L)	9.8 [7.5–13.0]	9.5 [7.5–12.0]	10.0 [7.8–14.0]	.062
Clinical interventions				
Invasive mechanical ventilation	72%	66%	81%	***<.001***
Prone position	80%	81%	78%	.35
Tracheotomy	15%	14%	17%	.41
CRRT	14%	9%	23%	***<.001***
ECMO	3%	2%	4%	.39
Complications				
Pneumothorax	11%	7%	17%	***.0010***
Pulmonary embolus	17%	15%	22%	.080
Cardiac arrest	4%	1%	8%	***<.001***
Outcome measures				
IMV total days ($n = 356$)[a]	9.4 [5–18]	7.5 [4–15]	13 [7–20]	***<.001***
LOS ICU ($n = 498$)	9.5 [5–17]	7.8 [4.6–15]	12 [5–20]	***.015***
Mortality ICU	30%	N/A	N/A	N/A
Hospital mortality	38%	N/A	N/A	N/A

TABLE 1 (Continued)

	Overall ($n = 498$)	Survivors ($n = 305$)	Non-survivors ($n = 193$)	*p*-value survivors/non-survivors
Mortality 90-day	39%	N/A	N/A	N/A
GOSE, ($n = 260$)[b]	N/A	6 (5–7)	N/A	N/A

Note: Results are expressed as *n* (%) or median (25th–75th percentiles). Immunosuppression defined as patients on immunosuppressive medication except for corticosteroids. Bold italics is used for statistically significant results (*p*-value < 0.05).

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; GOSE, Glasgow Coma Scale Extended; ICU, intensive care unit; ICU, intensive care unit; IL-6, interleukin-6; IMV, invasive mechanical ventilation; LD, lactate dehydrogenase; LOS, length of stay; P/F ratio defined as P_aO_2 (arterial partial pressure of oxygen)/F_iO_2 (fraction of inspired oxygen); P_aCO_2, arterial partial pressure of carbon dioxide; PCT, procalcitonin; SAPS 3, Simplified Acute Physiology Score.

[a]Limited to patients on invasive mechanical ventilation.

[b]Limited to surviving patients at 90-day follow-up with complete GOSE score.

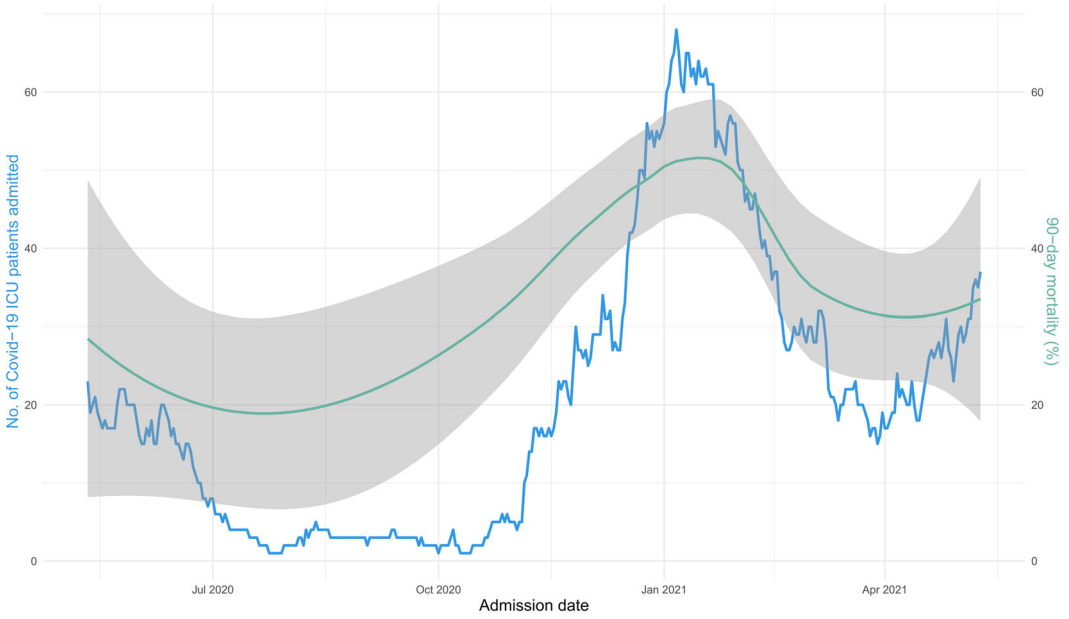

FIGURE 1 Intensive care unit (ICU) burden and mortality. The ICU burden was defined as the total number of ICU-treated COVID-19 patients in the region on admission. The ICU burden is presented in blue and 90-day mortality is shown in green.

3.1 | Regression analyses

The predictive model for 90-day mortality based on SAPS 3 reached an AUC of 0.71 (95% CI: 0.66–0.75) (Figure 4). A simplified logistic regression model for 90-day mortality was created using backward regression with all the variables (Figure S2). This resulted in a simplified model including age, ICU burden, smoking status, P_aCO_2, baseline creatinine, CRP, IL-6, platelet count and ongoing cortisone treatment at ICU admission (Figure 5). The resulting model generated an AUC of 0.87 (95% CI: 0.84–0.90). Age alone predicted 90-day mortality with an AUC of 0.78 (95% CI: 0.74–82). The AUCs of all three models were significantly different ($p < .01$) (Figure 4).

Length of stay in the ICU was associated with unfavourable functional outcome, odds ratio (OR) for LOS ICU 0.14 (95% CI: 0.057–0.33), *p*-value <.001 (Table S2).

4 | DISCUSSION

In this prospective multicentre cohort study of COVID-19 patients requiring ICU care, our main findings were that age and ICU burden were strongly and independently associated with mortality at 90 days, while a high BMI was not. Mortality increased considerably from 60 years of age. Inflammatory markers on ICU admission showed mixed results. Approximately one in four survivors had an unfavourable functional outcome at 90 days, and <1 in 10 had a full recovery. Poor functional outcome was independently associated with a longer ICU stay.

The strong association between mortality in COVID-19 and high age is well established[26,27] and seems to be particularly true in critical disease.[28] In the COVIP study[4] investigating 1346 critically ill COVID-19 patients with a median age of 75 years, the 90-day mortality was

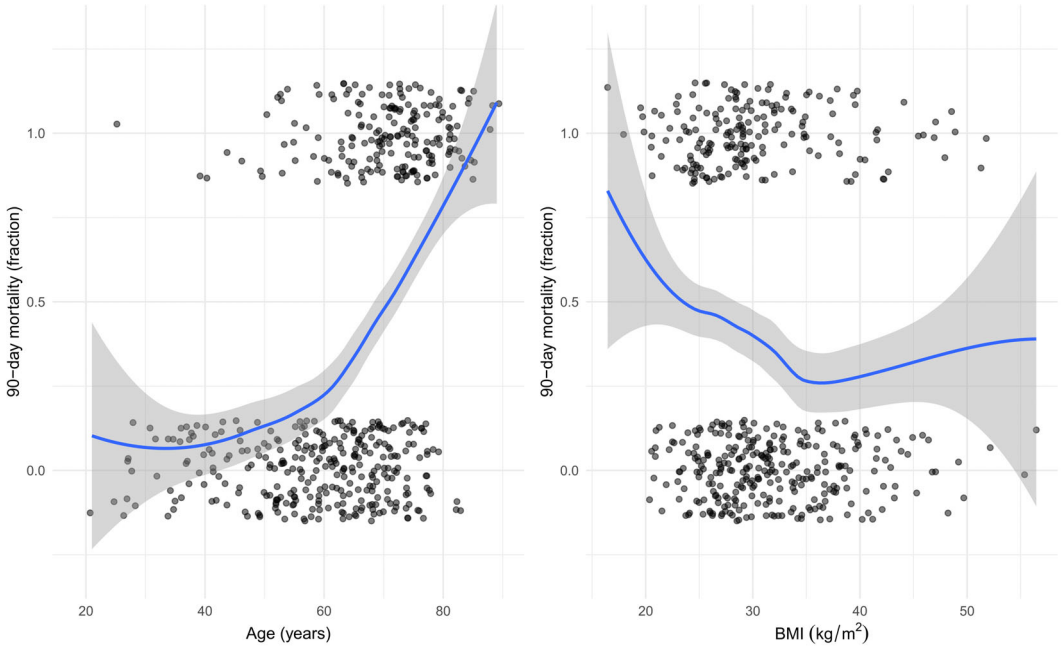

FIGURE 2 The 90-day mortality (blue line) as a function of (A) age (left panel) and (B) body mass index (BMI) (right panel). Individual patients are shown as dots; for clarity, jitter was added so that values in the range of (−0.15,0.15) on the *y*-axis, that is, centred around 0 on the *y*-axis, are 90-day survivors. In contrast, values in the range of (0.85,1.15) on the *y*-axis, that is, centred around 1 on the *y*-axis, are 90-day non-survivors.

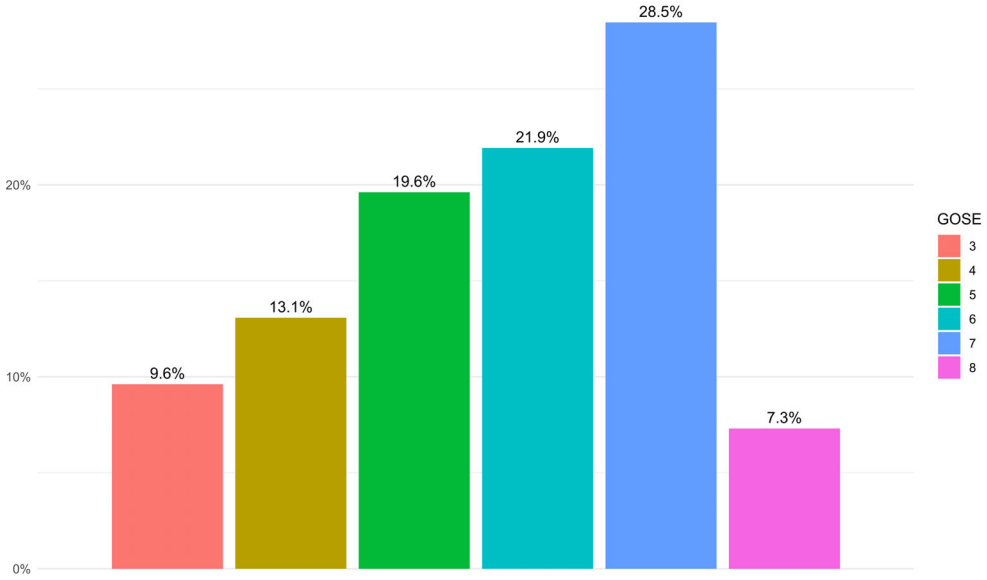

FIGURE 3 Glasgow Outcome Scale-Extended (GOSE) for the 260 surviving patients, with a complete GOSE, participating in the 90-day follow-up.

48%. In our cohort, mortality among the elderly was comparable, with a 90-day mortality of 43% in patients 75 years or older and increased further with higher age.

Age alone was predictive of 90-day mortality with an AUC of 0.78, which outperformed SAPS 3, despite age being an integral part of SAPS 3. This highlights the disproportionate importance of age as a predictor of mortality in severe COVID-19. Current methods of estimating the probability of mortality for ICU patients based on admission variables (SAPS 3) have not been calibrated for COVID-19. Our multivariate logistic regression model achieved good predictive performance with an AUC of 0.87, much better than the 0.71 for SAPS 3.

The burden on the health care systems was unprecedented during the COVID-19 pandemic. Prioritising resources is essential and transcends the responsibility of individual hospitals. Sweden has one of the lowest numbers of ICU beds per capita in Europe.[29] It is therefore of particular interest to investigate any impact on patient outcomes when ICU resources are limited. In line with our results, Bravata et al. demonstrated that increasing ICU health care burden was associated with higher mortality in COVID-19 patients.[6] Toth et al. also found a similar association.[30] In the present study, we defined the number of admitted COVID-19 patients each day as a proxy for ICU burden. This is an arbitrary measure and should be put

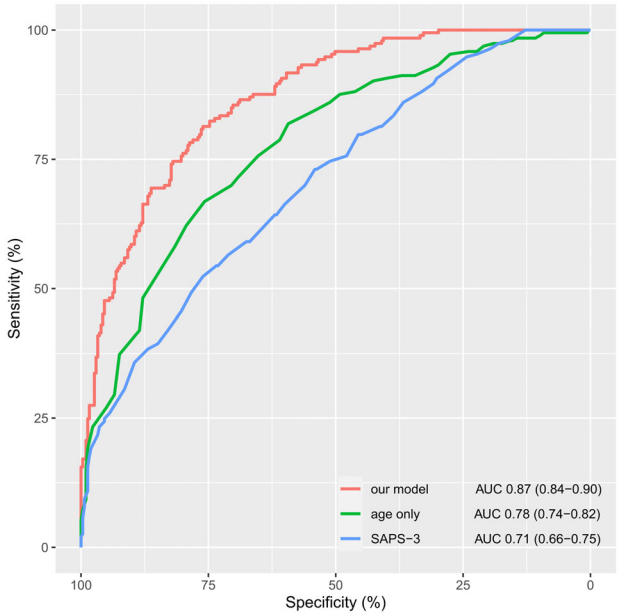

FIGURE 4 Receiver operator characteristic (ROC) curves and their corresponding areas under the curve (AUC) for 90-day mortality prediction in ICU-treated COVID-19 patients. All the AUCs were significantly different ($p < .01$). All the models were based on logistic regression. ICU, intensive care unit; SAPS 3, simplified acute physiology score 3.

in proportion to the number of available ICU beds. We found a strong association between ICU burden and 90-day mortality, which can be explained by several factors, including staffing, nurse/patient ratio, severity of critical illness and shortage of beds. Some studies have demonstrated no additional harm from transporting critically ill patients,[31,32] which is in line with our own unpublished data. This does not, however, exclude harm in patients who were *not* transported. Nevertheless, mortality increased significantly and doubled from 25% to >50% when the ICU burden was high, an important finding that needs further analysis.

In several studies, being overweight has been a risk factor for severe COVID-19.[33,34] Further, there is a general perception that being overweight is a risk factor for mortality in general intensive care.[35,36] Several studies have, however, shown the contrary; an observation called the obesity paradox.[37,38] Notably, the lowest mortality in the present study was associated with a BMI of 35 kg/m^2, whereas a low BMI was associated with increased mortality. A possible explanation could be that a high BMI may lead to earlier ICU admission in critical COVID-19 when the pulmonary disease is not as severe. Simple mechanical factors and a lower functional residual capacity in the obese may lead to earlier respiratory failure and the need for high-level care. In addition, a more ample energy reserve in obese patients may be beneficial in critical disease.[39,40]

Variable		N	Odds ratio	p
Age (years)		498	1.10 (1.07, 1.13)	<.001
Smoker	Never	236	Reference	
	Ex	235	1.96 (1.20, 3.23)	.008
	Active	27	0.96 (0.28, 3.16)	.948
log10(ICU burden)		498	3.56 (1.58, 8.33)	.003
Cerebrovascular insult		498	2.12 (0.88, 5.32)	.099
ACEi		498	0.59 (0.33, 1.03)	.068
log10(Baseline creatinine) (umol/L)		498	6.96 (1.39, 38.43)	.020
Cortisone treatment		498	5.88 (2.16, 17.10)	<.001
$PaCO_2$ (kPa)	(4,7]	346	Reference	
	(0,4]	15	3.05 (0.84, 12.69)	.101
	(7,30]	137	3.04 (1.79, 5.27)	<.001
CRP (mg/L)	(80,180]	220	Reference	
	(0,80]	101	2.25 (1.20, 4.24)	.012
	(180,800]	177	1.35 (0.77, 2.37)	.297
log10(PCT) (ug/L)		498	0.66 (0.42, 1.01)	.056
log10(IL-6) (ng/L)		498	2.69 (1.70, 4.33)	<.001
Neutrophils (x 10^9)	(2.5,8]	182	Reference	
	(0,2.5]	10	2.59 (0.39, 15.38)	.302
	(8,65]	306	1.73 (0.99, 3.04)	.055
log10(Platelet count) (x 10^9)		498	0.09 (0.02, 0.36)	<.001

FIGURE 5 A Forest plot of the simple 90-day mortality model based on information on admission demonstrating adjusted/multivariable odds ratio with a 95% CI (demographics, comorbidities, acute physiology, acute lab: P_aO_2, P_aCO_2, F_iO_2, C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6), platelet count, neutrophil count, angiotensin converting enzyme inhibitor (ACEi).

Mortality in mechanically ventilated COVID-19 patients has been shown to vary over time and in different regions,[5,41] suggesting different viral strains and health care burden as possible determining factors. A vast majority of patients in this study had P/F ratios below 13 kPa on ICU admission, corresponding to severe acute respiratory distress syndrome (ARDS) in mechanically ventilated patients.[42] Eventually, IMV was employed in 72% of the patients and associated with an increased 90-day mortality of 44%, which is comparable to other studies.[8] There has been a debate regarding the appropriate timing of ICU care and initiation of IMV in critical COVID-19 and which patients may benefit.[43,44] In a study by Gonzalez et al.,[45] a delay in intubation was associated with increased mortality and worse pulmonary sequelae at follow-up. The opposite finding has also been described.[46] A conservative approach was practised in our study cohort, which is reflected by a very low median P/F ratio (9 kPa) on ICU admission in the group receiving IMV. Although there was no predetermined age limit, only otherwise healthy patients above 80 years old were eligible for IMV, very few survived (6%).

Pneumothorax was more common in patients receiving IMV and in non-survivors, as reported by others.[47] More complications, including pneumothorax, may be explained by a longer ICU stay. Pulmonary embolism was diagnosed in 17% in this study with no association with increased 90-day mortality, which is in line with results from a recent meta-analysis.[48,49]

Comorbidities and frailty were associated with higher 90-day mortality but not in the adjusted model, presumably due to age-related covariation. Kidney disease was an independent risk factor for 90-day mortality, which aligns with previous studies in critically ill patients.[50] Our finding that ongoing systemic corticosteroid medication increased the risk of 90-day mortality is not surprising. However, we did not find other immunosuppressive treatments to be associated with 90-day mortality, but the numbers were low. A high level of IL-6 on ICU admission was associated with increased 90-day mortality, indicating a more severe manifestation of COVID-19. On the other hand, a low CRP (<80 mg/L) was also associated with increased 90-day mortality, as was a high neutrophil count and low platelets. These diverse findings highlight the complexity of the dysregulated inflammatory response in severe COVID-19. Although this field has been extensively investigated, no consensus exists on the predictive value of the various inflammatory biomarkers.[51–54] A consequence of the RECOVERY study,[55] published in June 2020, was that systemic steroids became part of routine care in critical COVID-19, as demonstrated here.

Few patients in this study had a limitation of care prior to ICU admission, but among them, mortality was very high. A decision to withdraw life-sustaining treatment in the ICU was common, of whom most died in the ICU and the remaining died in-hospital.

Glasgow Outcome Scale-Extended (GOSE) has been used for more than 40 years for assessment of traumatic brain injury patients and is increasingly used in other critical disease as well.[56,57] A favourable functional recovery at 90 days was not associated with age, BMI, or ICU burden in the present study. An unfavourable functional recovery was, not surprisingly, independently associated with a longer ICU stay, indicating a more severely ill patient group. Noteworthy is that at 90 days, patients with longer ICU stays had a shorter recovery time to follow-up, which is why a later follow-up (12 months) will be of particular interest.[58,59]

Strengths of this study include the multicentre design and consecutive enrolment of a relatively large cohort of critically ill COVID-19 patients over 12 months with few missing. We assume that no significant effect of the national vaccination programme was evident until after the termination of the study.[60] Data collection was comprehensive, and data quality was checked with random sampling, showing good compliance and few missing data. Another strength is our detailed follow-up at 90 days after ICU admission, including 87% of all surviving patients. In addition, we had complete data (100%) on the primary outcome, mortality. In a recent review article,[61] difficulties in performing follow-up studies after Intensive Care were addressed, supporting the strength of our follow-up model.

Limitations include the challenges of performing high quality research during a pandemic. Further, our proxy for ICU burden may be a limitation, although we find it as relevant as other arbitrary measures. Also, we have no numbers on nurse/patient ratios during the pandemic. Baseline functional status in all patients was limited to CFS. P/F ratios were calculated from both intubated and spontaneously breathing patients, resulting in possible falsely low P/F ratios. Another limitation is that GOSE has not previously been used in this population.

5 | CONCLUSION

In this multicentre prospective study of ICU-treated COVID-19 patients, mortality was high and increased from the age of 60. A higher ICU burden was associated with a two-fold increase in mortality. A high BMI did not imply increased mortality. Ongoing treatment with cortisone, inflammatory markers and hypercapnia on admission were independent factors of 90-day mortality. A favourable functional recovery at 90-days was independently associated with a short LOS in the ICU.

AUTHOR CONTRIBUTIONS

Hans Friberg and Attila Frigyesi designed the study. Märta Leffler and Mårten Jungner created the ICU registry. Ingrid Didriksson, Märta Leffler and Martin Spångfors collected clinical data. Ingrid Didriksson performed data quality assessment. Gisela Lilja coordinated and supervised the 90-day follow-up. Attila Frigyesi, Martin Spångfors, and Ingrid Didriksson performed the statistical analyses and prepared figures and tables. Ingrid Didriksson, Märta Leffler, Attila Frigyesi, and Hans Friberg wrote the initial manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The datasets used during the current study are available from the corresponding author on request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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