Long-Term Survival of Mechanically Ventilated Patients with Severe COVID-19: An Observational Cohort Study

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Abstract

Background: Information is lacking regarding long-term survival and predictive factors for mortality in patients with acute hypoxemic respiratory failure due to coronavirus disease 2019 (COVID-19) and undergoing invasive mechanical ventilation. We aimed to estimate 90-day and 180-day survival of patients with COVID-19 requiring invasive ventilation and to develop a predictive model for intensive care unit mortality.

Methods: Retrospective, multicentre, national cohort study between March 8 and April 30, 2020 in 16 intensive care units (ICU) in Spain. Participants were consecutive adults who received invasive mechanical ventilation for COVID–19. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection detected in positive testing of a nasopharyngeal sample and confirmed by real time reverse-transcriptase polymerase chain reaction (rt-PCR). The primary outcomes were 90-day and 180-day survival after hospital admission. Secondary outcomes were length of ICU and hospital stay, and ICU and in-hospital mortality. A predictive model and a nomogram were developed to estimate the probability of ICU mortality.

Results: 868 patients were included (median age, 64 years [interquartile range [IQR], 56-71 years]; 72% male). Severity at ICU admission, estimated by SAPS3, was 56 points [IQR 50-63]. Prior to intubation, 26% received some type of noninvasive respiratory support. The 90-day and 180-day survival rates were 69% (95% confidence interval [CI] 66%-72%) and 59% (95% CI 56%-62%) respectively. The predictive factors associated with ICU mortality were: age (odds ratio [OR] 1.049 [95% CI 1.032-1.066] per 1-year increase), SAPS3 (OR 1.025 [95% CI 1.008-1.041] per 1-point increase), neutrophil to lymphocyte ratio (OR 1.009 [95% CI 1.002-1.016]), a failed attempt of noninvasive positive pressure ventilation previous to orotracheal intubation(OR 2.131 [95% CI 1.279-3.550]), and use of selective digestive decontamination (OR 0.587 [95% CI 0.358-0.963]).

Conclusion: The long-term survival of mechanically ventilated patients with severe COVID-19 reaches more than 50% and may help to provide individualized risk stratification and potential treatments.

Trial registration: ClinicalTrials.gov Identifier: *NCT04379258.* Registered 10 April 2020 (retrospectively registered).

Background

The coronavirus disease 2019 (COVID-19) pandemic is one of the most serious health crises in recent decades (1) with over 138 million infections being reported worldwide. As a result, health care resources in many countries are facing unprecedented challenges (2). This context has been especially dramatic in intensive care units (ICU) in view of the high daily incidence of acute hypoxemic respiratory failure (AHRF) secondary to pneumonia by SARS-CoV-2. Reports show that between 14 and 17% of hospital admissions for COVID-19 require transfer to the intensive care unit (ICU) (3, 4).

Currently available information about critically ill adult patients is heterogeneous because of the case-mix of patients, and in-hospital mortality rates differ between countries (5–9). Specific data on patient characteristics and long-term survival in critically ill COVID-19 patients are needed to inform decision-making regarding resource allocation, critical care capacity, and therapeutic options. Inter-hospital variation and international clinical variability in treatments and outcomes also needs to be assessed.

We conducted a multicenter cohort study to analyze the long-term survival of patients who required invasive mechanical ventilation for severe COVID-19 pneumonia and to assess a predictive model of ICU mortality.

Methods

This observational cohort study was conducted in 16 surgical and medical ICU at 12 university hospitals in Madrid and Barcelona, the Spanish cities most affected by COVID-19 (a complete list of participating sites is provided in the Supplement). We included all patients who were admitted to the participating ICUs between March 8, 2020 and April 30, 2020, and who required invasive mechanical ventilation for acute hypoxemic respiratory failure secondary to SARS-CoV-2 pneumonia. The diagnosis was confirmed by a positive result of real-time reverse-transcriptase polymerase chain reaction (RT-PCR) testing of a nasopharyngeal swab sample or from a lower respiratory tract sample (11). SARS-CoV-2 pneumonia was also diagnosed when there was a compatible clinical condition, and when typical abnormalities on chest X-ray were present in absence of an alternative diagnosis (10, 11). Patients were excluded from the analysis if any data regarding relevant variables were missing.

Data collection

Variables recorded were: age, sex, height, weight, severity at admission estimated by the Simplified Acute Physiology Score (SAPS3) [which ranges from 16 points (low severity) to 226 points (high severity)], comorbidities, (previous medication use), mode of respiratory support (high flow nasal oxygen cannula and/or noninvasive positive pressure ventilation [NPPV] as CPAP (continuous positive airway pressure) or BiPAP (Bi-Level Positive Airway Pressure)), use of compassionate medication [antivirals (lopinavir-ritonavir, remdesivir), hydroxychloroquine, and immunomodulatory agents (interleukin-6 receptor antagonists, Janus kinase inhibitor, and corticosteroids)] before admission to ICU, length of hospital stay prior to ICU admission, date of intubation, ventilatory settings within the first week of mechanical ventilation, daily arterial blood gases, concentrations of plasma/serum biomarkers drawn within 7 days of ICU admission, including high-sensitivity C-reactive protein, D-dimer, ferritin, high-sensitivity troponin, procalcitonin, and IL-6, use of adjuvant therapies for acute respiratory failure (neuromuscular blocking agents, inhaled pulmonary vasodilators, ventilation in prone position, and extracorporeal membrane oxygenation), vasopressor agents, renal replacement therapy, antibacterial agents, antiviral agents, and other immunomodulatory agents, complications, and organ failure during the ICU stay.

Patients were followed-up until 180 days after hospital admission. Patients who died were censored at the date of death for the time-to-discharge analysis.

Independent on-site monitoring was performed at each participating center in coordination with the main investigators who verified all data.

All data were monitored and reviewed by four external investigators (OP, AE, CRS, and FFV) to detect erroneous and missing data.

The study was approved by the institutional ethics board at each participating site. The requirement for informed consent from individual patients was waived because the study design was considered minimal-risk research using data collected for routine clinical practice during an ongoing public health emergency.

The study was registered in ClinicalTrials.gov Identifier: *NCT04379258*. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines for observational cohort studies (12).

Statistical analysis

Following the approval of the ethics committee at each participating center, patients were collected retrospectively to allow rapid data collection and over 180 days of prospective follow-up to analyze clinical outcomes (data extraction date: April 16, 2020).

The main outcome was mortality at 90-days and 180-days. Secondary outcomes were duration of mechanical ventilation, duration of ICU and in-hospital stay, reason for death and destiny at hospital discharge.

Mortality outcomes were analyzed using mixed-effects logistic regression and the imputed data. The analysis was fitted with a random effect in which the patients were nested in ICUs to characterize ICU-level variation and to estimate center-specific rates of ICU-mortality.

For the predictive model for ICU mortality and hospital mortality, we used the multivariate imputation by chained equations (MICE) procedure for all missing data (13). Incomplete dichotomous variables were imputed using a logistic regression model, while linear regression was used to impute incomplete continuous variables. We generated 10 imputed data sets.

Variables included in the predictive model were as follows: age, sex, comorbidities (diabetes, hypertension, obesity), and the following pre-admission medications: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and chronic steroids. We also included in the model non-invasive respiratory support before orotracheal intubation, time from hospital admission until intubation, SAPS3, relevant variables determined within the first 48 hours of admission to the ICU (neutrophil to lymphocyte ratio, PaO_2 to FiO_2 ratio, D-dimer, ventilatory ratio (14), tidal volume and positive end-expiratory pressure (PEEP), treatments given within in the first 48 hours of mechanical ventilation (vasopressor support, antivirals, immunomodulatory therapy, steroids, anticoagulants, neuromuscular blocking agents, selective digestive decontamination, prone position). The fractional polynomial method was used to explore the behavior of continuous variables. We applied stepwise selection with backward elimination of predictors from the full model with $p < 0.05$.

The final model was then validated by bootstrapping. Using this procedure we sampled 100 samples for each imputed data set with replacement. Discrimination of the model was evaluated using the *c-statistic*: for a binary outcome, *c* is identical to the area under the receiver operating curve (AUROC). Calibration was evaluated studying the calibration slope and calibration-in-the-large (CITL). Calibration-in-the-large (CITL) indicates the difference between the observed prevalence of death and the predicted mean probability. In a perfect model, the CITL should be equal to zero, but our CITL value was small and the confidence interval contained 0.

The calibration slope tells us if the model coefficients are underfitted (slope > 1) or overfitted (slope < 1). In our case, the slope was below 1, so it was insufficient to obtain the data from our model. However, this is not entirely negative because as a predictive model we want the model to be able to explain future data from other patients and units, not just our data. Furthermore, 1 is included in the confidence interval, so we can consider it to be a good model in terms of calibration. (15).

Subsequently, coefficients were used to generate a nomogram to predict the adjusted probability of ICU mortality individually.

To account for differences in patient-level characteristics and illness severity between ICUs, we calculated the median odds ratio (MOR) (16).

Lastly, in a sensitivity analysis for the multilevel model, further adjustments were made for the number of ICU beds at each hospital before the COVID-19 pandemic (≤50, and > 50 ICU beds).

The 90-day survival and 180-day survival outcomes were calculated using a Kaplan-Meier survival plot in an overall cohort and by predefined subgroups (age categorized in ≤ 70 or > 70 years; SAPS3 categorized in ≤ 50 or > 50 points; ratio PaO_2/FiO_2 categorized according to the acute respiratory distress syndrome (ARDS) Berlin definition (17)).

The differences between survival curves were evaluated by log-rank test. To identify the optimal cut-point value in ROC analysis we used the Youden index approach. Statistical significance was considered at $p < 0.05$.

Analyses were performed using Stata, version 16.1 (StataCorp LLC).

Results

Description of the population included in the analysis

During the study period, 868 of the 1,170 patients who were admitted to the participating ICUs were included in the analysis. A flow chart of study patients is provided in Additional file 1, Figure S1 and clinical characteristics of excluded patients are summarized in Additional information in Table S1. Patients' baseline patient characteristics are shown in Additional file 1, Table S2. Seventy-two per cent were males and mean (standard deviation [SD]) age was 62 years (11 years). The median number of days from onset of symptoms to admission to hospital was 7 days and the median length of stay in the hospital before ICU admission was 3 days. The most common comorbidity was cardiovascular disease (49%).

During ward stay before ICU admission, most patients (75%) received some antiviral and/or immune-modulatory therapy, and noninvasive respiratory support was attempted before orotracheal intubation was initiated in 28% of patients (cannula nasal high-flow oxygen in 14% and NPPV in 14%), while 68% received conventional oxygen by venturi or reservoir mask, and 4% received a combination of cannula nasal high-flow oxygen and NPPV.

Severity at admission to the ICU estimated by SAPS3 was a mean 57 points (SD, 11 points) (predicted mortality was 29%). At admission to the ICU, serum biomarkers and ventilatory settings, arterial blood gases, adjuvant therapies within the first week of mechanical ventilation (Additional file 1: Table S3, Table S4, and Figure S2). According to ARDS Berlin criteria, 231 patients (27%) had severe ARDS when mechanical ventilation was started.

Additionally, level of serum biomarkers, ventilatory settings and complications within the first week of ICU stay are shown in Additional file 1: Table S5, Table S6, Table S7, Figure S2 and Figure S3.

Analysis of Mortality

Overall ICU mortality was 38.5% (confidence interval for 95%: 35% – 42%). Table 2 and Table S2 shows the comparison between survivors and non-survivors. The most significant difference was found in management before admission to the intensive care unit. Patients who received a NPPV attempt before orotracheal intubation had a significantly higher mortality than patients who were not treated with NPPV: 49% vs 37% (p = 0.011).

Table 1
Baseline characteristics of included patients in the analysis. Data are n (%), unless otherwise indicated.

	Overall **N = 868**
Age, mean (SD), years [Range]	62 (11) [21–86]
Female sex	243 (28%)
Body mass index, mean (SD), kg/cm^2	29 (5)
Comorbidities	
Hypertension	401 (46%)
Obesity	268 (31%)
Diabetes	209 (24%)
Dyslipemia	144 (16%)
Asthma	69 (8%)
Ischemic Cardiopathy	65 (7%)
COPD	59 (7%)
Chronic Kidney Disease	43 (5%)
Immunodepression	28 (3%)
Ictus	27 (3%)
Autoimmune Disease	26 (3%)
Hematological Malignancy	16 (2%)
Symptoms	
Fever	679 (78%)
Dyspnea	640 (74%)
Cough	439 (51%)
Asthenia	182 (21%)
Myalgias	167 (19%)
Gastrointestinal	139 (16%)
Headache	57 (6.5%)
Previous therapy	
Statins	288 (33%)
Angiotensin-converting enzyme inhibitors	172 (20%)
Angiotensin II receptor blockers	122 (15%)
Antiplatelets	102 (12%)
Beta-blockers	97 (11%)
Calcium Antagonists	59 (7%)
Anticoagulants	48 (5%)

	Overall N = 868
Steroids	34 (4%)
Days from initiation symptoms to admission at Hospital, median (P_{25}, P_{75})	7 (4,9)
Antiviral therapy	
Lopinavir/Ritonavir	602 (69%)
Hydroxychloroquine	751 (87%)
Daily doses Hydroxychloroquine, mean (SD), mg	423 (62)
Remdesivir	57 (7%)
Darunavir	29 (3%)
Immunomodulator therapy	
Steroids	586 (68%)
Doses Steroids	
Methylprednisolone < 1 mg/kg	449 (52%)
Methylprednisolone > 1 mg/kg	389 (45%)
Azithromycin	426 (49%)
Tocilizumab	426 (49%)
Interferon	189 (22%)
Noninvasive Respiratory support at ward	
High-Flow Oxygen Cannula Nasal	126 (14%)
Non-invasive positive pressure ventilation (NPPV)	119 (14%)
Combining NPPV and high flow oxygen nasal cannula	33 (4%)
Conventional oxygen	590 (68%)
Days until intubation, median (P_{25}, P_{75})	3 (1, 6)

Table 2
Univariate and multivariate analysis for ICU-mortality.

	Survivors N = 533	Non-Survivors N = 335	Univariate OR (CI 95%)	P value	Multivariate OR (CI 95%)	P value
Age, mean (SD), years	59 (12)	66 (10)	1.061 (1.046–1.077)	< 0.001	1.049 (1.032–1.066)	< 0.001
Sex, male, No (%)	369 (69.2)	256 (76.4)	1.440 (1.054–1.968)	0.022		
Comorbidities						
Hypertension	223 (41.8)	178 (53.1)	1.576 (1.197–2.075)	0.001		
Obesity	176 (33.3)	92 (26.0)	0.7679 (0.569–1.037)	0.085		
Diabetes	103 (19.3)	106 (31.6)	1.932 (1.410–2.648)	< 0.001		
Inpatient Medication						
Angiotensin-converting enzyme inhibitors	95 (17.8)	77 (23.0)	1.376 (0.982–1.929)	0.064		
Angiotensin II receptor blockers	69 (12.9)	53 (15.8)	1.264 (0.858–1.862)	0.236		
Steroids	15 (2.8)	19 (5.7)	2.076 (1.040–4.145)	0.038		
Respiratory support at ward						
Oxygen mask alone	408 (76.6)	226 (70.5)	*[reference]*		*[reference]*	
High flow oxygen nasal cannula	65 (11.9)	40 (12.1)	1.064 (0.695–1.628)	0.775	1.033 (0.611–1.745)	0.904
Non-invasive positive pressure ventilation	50 (9.4)	48 (14.3)	1.660 (1.083–2.544)	0.020	2.132 (1.280–3.551)	0.004

a.- Doses for norepinephrine were considered according to the cardiovascular Sepsis-related Organ Failure Assessment (SOFA score) as: low doses defined as SOFA ≤ 3 points (≤ 0.1 µg/kg/min); high doses defined as SOFA > 3 points (> 0.1 µg/kg/min). Abbreviations: PEEP, positive end-expiratory pressure; OR, odds ratio; CI confidence interval.

	Survivors N = 533	Non-Survivors N = 335	Univariate OR (CI 95%)	P value	Multivariate OR (CI 95%)	P value
Non-invasive positive pressure ventilation and High flow oxygen nasal cannula	10 (1.9)	11 (3.3)	1.901 (0.796–4.545)	0.148	2.398 (0.899–6.400)	0.081
SAPS3, median [p25, p75], points	54 [48.5, 61]	58.5 [52; 68]	1.044 (1.03–1.06)	< 0.001	1.025 (1.008–0.041)	0.002
Days until intubation, median [P_{25}, P_{75}]	3 [1; 5]	3 [1; 7]	1.050 (1.021–1.079)	0.001		
Ventilatory management						
Tidal volume, mean (SD), ml/kg PBW	7.2 (1.2)	7.2 (1.6)	1.010 (0.898–1.136)	0.862		
PEEP, mean (SD, cm of water	13 (3)	13 (3)	0.984 (0.936–1.035)	0.543		
Continuous infusion of neuromuscular blockers. No (%)	396 (74.3)	236 (70.5)	0.825 (0.608–1.118)	0.215		
Prone position, No (%)	291 (46.6)	176 (52.5)	0.921 (0.699–1.211)	0.554		
Arterial blood gases						
Ratio PaO_2/FiO_2, mean (SD)	108 (47)	100 (48)	0.997 (0.994–0.999)	0.033		
Ventilatory ratio, mean (SD)	2.0 (0.8)	2.2 (0.9)	1.376 (1.138–1.665)	0.001		
Serum biomarkers						
Ratio Neutrophil/Lymphocyte, median [p25, p75]	15 [9; 26]	22 [12; 37]	1.018 (1.001–1.026)	< 0.001	1.009 (1.002–1.016)	0.013
D-Dimer, median [P_{25}, P_{75}], µg/ml,	2.9 [0.9; 12.3]	3.9 [1.4; 14.7]	1.001 (0.94–1.008)	0.702		

a.- Doses for norepinephrine were considered according to the cardiovascular Sepsis-related Organ Failure Assessment (SOFA score) as: low doses defined as SOFA ≤ 3 points (≤ 0.1 µg/kg/min); high doses defined as SOFA > 3 points (> 0.1 µg/kg/min). Abbreviations: PEEP, positive end-expiratory pressure; OR, odds ratio; CI confidence interval.

	Survivors N = 533	Non-Survivors N = 335	Univariate OR (CI 95%)	P value	Multivariate OR (CI 95%)	P value
PCR, median [P_{25}, P_{75}], mg/L	134 [30; 250]	153 [31; 253]	1.001 (0.999–1.002)	0.132		
Drug therapy						
Selective Digestive Decontamination, No (%)	301 (56.5)	149 (44.5)	0.617 (0.469–0.813)	0.001	0.587 (0.358–0.963)	0.035
Immunomodulator therapy, No (%)	210 (39.4)	137 (40.9)	1.064 (0.805–1.406)	0.661		
Steroids, No (%)						
No	276 (51.8)	173 (51.6)	*[reference]*			
Methylprednisolone ≤ 1 mg/kg	137 (25.7)	69 (20.6)	0.803 (0.568–1.136)	0.215		
Methylprednisolone > 1 mg/kg	120 (22.5)	93 (27.8)	1.236 (0.888–1.721)	0.209		
Antiviral therapy, No (%)	492 (92.3)	304 (90.8)	0.817 (0.502–1.331)	0.417		
Anticoagulation therapy, No (%)	25 (4.7)	23 (6.9)	0.936 (0.806–1.088)	0.388		
Norepinephrine, No (%) [a]						
No	203 (38.1)	103 (30.8)	*[reference]*		*[reference]*	
Low doses	44 (8.3)	61 (18.2)	2.732 (1.735–4.304)	< 0.001	1.879 (1.119–3.153)	0.017
High doses	286 (53.7)	171 (51.0)	1.178 (0.869–1.596)	0.289	0.968 (0.685–1.369)	0.855

a.- Doses for norepinephrine were considered according to the cardiovascular Sepsis-related Organ Failure Assessment (SOFA score) as: low doses defined as SOFA ≤ 3 points (≤ 0.1 µg/kg/min); high doses defined as SOFA > 3 points (> 0.1 µg/kg/min). Abbreviations: PEEP, positive end-expiratory pressure; OR, odds ratio; CI confidence interval.

After admission to the ICU, within the first 48 hours, hypoxemia in non-survivors was slightly worse (mean ratio PaO_2/FiO_2 99 vs. 108; p = 0.016).

Severe ARDS criteria and hypercapnia were also higher in nonsurvivors: (61% vs. 53%; p = 0.018) and (mean $PaCO_2$ 56 mmHg vs. 52 mmHg; p < 0.001), respectively.

A higher, but non-significant proportion of these patients also had a ventilatory ratio ≥ 2 (61% vs. 55% in survivors; p = 0.18). Within the first 48 hours, ventilatory management (tidal volume, PEEP) was similar in both cohorts (Additional file 1: Table S1 and Figure S2). No clinically relevant differences were observed in driving pressure [mean (SD): 15 cm H_2O (5) in non-survivors vs 14 cm H_2O (4) in survivors; p = 0.05] or in plateau pressure [mean (SD): 28 cm H_2O (5) in non-survivors vs 27 cm H_2O (4) in survivors; p = 0.07]. Early use of adjuvant therapies (prone position, ECMO, nitric oxide inhaled, steroids, and neuromuscular blockers) did not improve survival (Additional file 1: Table S6).

The neutrophil to lymphocyte ratio was the most clinically relevant and most significant difference in serum biomarkers (Additional file 1: Table S1 and Table S8).

Of the pharmacological treatments initiated in the ICU within the first 48 hours, only the implementation of selective digestive decontamination strategy was associated with a significant decrease in mortality (Additional file 1: Table S1).

Concerning survivors at hospital discharge, 426/553 patients were transferred home (77%) and 23% (129/553) were transferred to a nursing facility.

Ninety-day survival was 69% (confidence interval [CI] 95% 66% – 72%) and 180-day survival was 59% (95% CI 56% – 63%) (Fig. 1). Unadjusted Kaplan-Meier survival curves by subgroups showed that survival rates at 90 days and 180 days of follow-up were lower in patients over 70 years (52% versus 76%, log-rank test < 0.001; 40% versus 66.5%, log rank test < 0.001, respectively) (Additional file 1: Figure S4).

Adjusted analysis of ICU mortality

In the multivariable multiple imputation model, we found that age [odds ratio per 1-year increase 1.049 (95% CI 1.032–1.066)], SAPS3 [odds ratio [OR] per 1-point increase 1.025 (95% CI 1.008–1.041], ratio neutrophils to lymphocytes [OR per 1-unit increase 1.009 (95% CI 1.002–1.016)], failure of noninvasive positive pressure ventilation prior to orotracheal intubation [OR 2.131 (95% CI 1.279–3.550), administration of selective digestive decontamination [OR 0.587 (95% CI 0.358–0.963)] and need for vasopressor support [OR 1.878 (95% CI 1.119–3.152)] were independently associated with ICU mortality (Table 2). The model was internally validated by bootstrapping. The algorithm had an AUC of 0.71 (95% CI 0.68–0.75), and a calibration, CITL 0.001 (95% CI -0.30–0.30) with slope 1.02 (95% CI 0.82–1.22). The predictors were built in a nomogram to estimate the individual risk of ICU mortality (Fig. 2).

The model was consistent with models for predicting 28-day mortality, hospital mortality, and 60-day, 90-day mortality and 180-day mortality (Table 3).

Table 3
Multivariable risk-adjusted predictive model for short and long-term mortality.

Variables	Multivariable Odds Ratio (95% Confidence interval [CI])					
	ICU Mortality	Hospital Mortality	28-day Mortality	60-day Mortality	90-day Mortality	180-day mortality
Age, (per 1-year increase)	1.049 (1.032–1.066)	1.050 (1.033–1.068)	1.058 (1.035–1.081)	1.065 (1.046–1.086)	1.052 (1.033–1.071)	1.051 (1.033–1.068)
Male					1.475 (1.017–2.140)	
Diabetes mellitus		1.546 (1.084–2.203)	1.·626 (1.093–2.420)	1.760 (1.224–2.531)	1.434 (1.001–2.055)	1.546 (1.085–2.204)
Chronic steroids			3.697 (1.633–8.371)	2.401 (1.084–5.315)	2.453 (1.105–5.444)	
SAPS3, (per 1-point increase)	1.025 (1.008–1.041)	1.027 (1.011–1.044)			1.017 (1.000-1.034)	1.027 (1.011–1.044)
N:L ratio (per 1-unit increase)	1.009 (1.002–1.016)	1.008 (1.000-1.016)				1.008 (1.001–1.016)
Failed attempt of noninvasive ventilation prior to ICU stay	2.131 (1.279–3.550)	1.878 (1.123–3.39)			1.815 (1.064–3.096)	1.878 (1.124–3.140)
Selective Digestive Decontamination strategy	0.587 (0.358–0.963)	0.591 (0.358–0.972)				0.590 (0.358–0.972)
Need of vasopressor support	1.878 (1.119–3.152)	2.042 (1.205–3.460)	2.158 (1.197–3.891)	1.983 (1.155–3.406)	1.010 (1.257–3.625)	
Methylprednisolone ≤ 1 mg/kg			0.500 (0.302–0.828)			2.042 (1.205–3.460)
Methylprednisolone > 1 mg/kg			0.479 (0.283–0.811)	0.575 (0.363–0.912)	0.629 (0.403–0.980)	0.958 (0.677–1.355)
AUC (95% CI)	0.712 (0.677; 0.746)	0.728 (0.694; 0.761)	0.746 (0.705; 0.787)	0.720 (0.683; 0.757)	0.715 (0.678; 0.751)	0.716 (0.682–0.749)
Calibration, CITL (95% CI)	0.001 (-0.306; 0.308)	0.0007 (-0.312;0.313)	< 0.001 (-0.398; 0.398)	< 0.001 (-0.338; 0.338);	< 0.001 (-0.318; 0.318)	0.001 (-0.318-0.307)

Abbreviations: SAPS, Simplified Acute Physiology Score; N: L, neutrophil to lymphocyte ratio.

Variables	Multivariable Odds Ratio (95% Confidence interval [CI])					
Slope	1.025	1.018	1.000	1.000	1.000	0.925
(95% CI)	(0.822; 1.228)	(0.827; 1.209)	(0.788; 1.214)	(0.788; 1.214).	(0.794; 1.206).	(0.734–1.116)
Abbreviations: SAPS, Simplified Acute Physiology Score; N: L, neutrophil to lymphocyte ratio.						

The adjusted predictive variables associated with 180-day survival were: age [OR per 1-year increase 1.051, 95% CI 1.033–1.068)], SAPS3 [OR per 1-point increase 1.027, 95% CI 1.011–1.044], diabetes [OR 1.546, 95% CI 1.085–2.204], neutrophils to lymphocytes ratio [OR per 1-unit increase 1.008, 95% CI 1.001–1.016], failure of noninvasive positive pressure ventilation prior to orotracheal intubation [OR 1.878 (95% CI 1.124–3.140), use of selective digestive decontamination strategy during ICU stay [OR 0.590 (95% CI 0.358–0.972] and administration of low dosage of corticosteroids (methylprednisolone 1 mg/kg) [OR 2.042 (95% CI 1.205–3.460).

The results of the mixed-effect analysis (Additional file 1: Table S9) showed that center had an effect associated with ICU mortality (median odds ratio [MOR] = 1.856). Sensitivity analysis also showed effects when comparing centers that included more than 50 patients (N = 7; MOR = 1.667) with those with less than 50 patients (N = 9, MOR = 1.756).

Discussion

This multicenter cohort study in 868 adult patients with severe COVID-19 undergoing invasive mechanical ventilation in Spain provides follow-up data concerning long-term survival after ICU admission. Independent predictors associated with ICU mortality were older age, higher SAPS3, the need for norepinephrine, an increased neutrophil-to-lymphocyte ratio, a failed attempt of noninvasive positive pressure ventilation, and the lack of use of a selective digestive decontamination strategy. The proportion of patients who died varied widely between centers.

To the best of our knowledge, this is the first report dealing with and long-term outcomes in a large cohort of mechanically ventilated patients with severe COVID-19. Overall, in-hospital mortality was 40.5%, which is considerably lower than that in other high-income countries (18–24). However, the age distribution and comorbidities of patients on mechanical ventilation was similar to that in these cited national studies. ICU mortality in our cohort was also similar (38%) to that in a large cohort of critically ill patients with COVID-19 in the Netherlands (24). It is of note that patients in our study were followed for up to 180-days and survival rate was 59%.

Age has been one of the most controversial aspects during the outbreak of the COVID-19 pandemic. In our study, the unadjusted 90-day and 180-day survival curves in severely ill patients over 70 years of age was above 50%, representing a better clinical outcome than in previous studies in older patients undergoing mechanical ventilation (26). Despite being considered clinically relevant, this difference in survival implies that age cannot be used as a clinical criterion to determine initiation of invasive mechanical ventilation. The availability of complementary clinical tools could aid decision-making with respect to initiating mechanical ventilation. In this sense, assessment of frailty has shown to be a robust guide to resource allocation in severely ill older patients with COVID-19 (27).

The use of non-invasive positive pressure ventilation for respiratory management of patients with severe acute respiratory distress is controversial (28). Studies related to non-invasive positive pressure ventilation failure have shown that the delay in interrupting this ventilation may be associated with increased mortality (29–31). Specifically, in a retrospective chart review study of patients with COVID-19 in Italy, mortality was 76% (32) in those who received noninvasive ventilation. In our study, the application of NPPV was not protocolized, and therefore patients received any modality of NPPV (CPAP and BiPAP), and any kind of interfaces were used. Unfortunately, monitoring of respiratory parameters during sessions was not performed due to the overwhelmed healthcare resources consumption during the pandemic. Helmet noninvasive ventilation has been evaluated as an alternative for the noninvasive respiratory support of patients with hypoxemia with promising results in severe patients with COVID-19, but not found significant difference in the number of days free of respiratory support (33). Hence, monitoring of patients receiving noninvasive respiratory support during AHRF remains of paramount importance not to delay endotracheal intubation.

The beneficial effect of the SDD strategy in mechanically ventilated critically ill patients has been widely studied, and meta-analysis based on individual patient data have consistently shown improved patient outcomes with this approach (34–36).

Indeed, the similarity in ICU mortality between our findings and Dutch study (24) may be explained because SDD are currently widely used in the Spanish participating ICU and Dutch ICU (37). This is the first study to report that SDD has the beneficial effect of decreasing ICU mortality in mechanically ventilated patients with severe COVID-19. We did not, however, analyze the relationship between SDD-nosocomial infections in patients with severe COVID-19 and mortality, an objective for post-hoc analysis.

A hematological dysfunction defined as an increased neutrophil to absolute lymphocyte ratio (NLR) was recently described. The NLR has been identified as biomarker of higher in-hospital mortality (38). Another study showed that NLR was significantly higher in hospitalized patients with severe forms of COVID-19 (39) and a higher NLR at hospital admission was associated with worse outcome (40, 41). In our predictive model, an NLR higher than 15 on day 1 was significantly associated with increased mortality. Our data also confirm that NLR is a useful independent prognostic factor in COVID19 patients under mechanical ventilation.

We did not find that adjunctive therapies such as prone positioning or the use of neuromuscular blocking agents or glucocorticosteroids had a beneficial effect on mortality. It is important to highlight that the predictive model described here is based on the first 48 hours of mechanical ventilation. One can therefore argue that these measures would not have been implemented for long enough to have a positive clinical impact on patients with severe COVID-19. Furthermore, this observational study collected the local clinical practice from centers during the pandemic outbreak. Most of the patients therefore received all these measures, thus limiting the possibility to extrapolate conclusions in the absence of adjusted and reliable comparisons.

According to recent evidence, treatment with systemic corticosteroids is associated with reduced mortality for critically ill patients with COVID-19 (42). The clinical management of corticosteroids during the outbreak, nevertheless, was very heterogeneous. Indeed, in this recent meta-analysis, the effect of glucocorticoids on mortality at 28 days showed a marked heterogeneity (I^2 44%), suggesting that different populations or different associated treatment effects may play a role. On the other hand, the multivariate model for long term outcomes (90-day and 180-day mortality) showed that the administration of corticosteroids had a beneficial effect on mortality.

Our data indicate that 60% of all deaths among ventilated patients occurred in the first 30 days of ICU stay. These deaths were due to refractory hypoxemia and multiorgan failure, and were probably related to the development of progressive, fibrotic lung disease.

Although the virus is eradicated in the most severe COVID-19 patients, the cause of lung damage is not. Linked to the inflammatory response, lung fibrosis emerges as a secondary event related to the progression of the pathology and worse outcomes (43–45).

We acknowledge a number of limitations. First, due to the fact that most participating centers rapidly reached ICU saturation at the critical moment of the COVID-19 outbreak, and as intensivists were facing difficult decisions, not all patients admitted to the participating ICUs during the study period were collected. Nevertheless, we calculated a predefined sample size according to the protocol in order to reach significant power to detect clinical differences in outcomes. Second, it is plausible that differences in clinical outcomes may be explained by variability in clinical practice. Such an increased risk for ICU mortality can be explained by differences in practice between centers (46). Lastly, the predictive model could be affected by unmeasured confounders in patient populations in ICUs, explaining some of the variation observed in treatments and outcomes. Accordingly, our findings should be interpreted cautiously.

Conclusions

Overall survival was slightly more than 50% of patients at 90 and 180 days but this varied considerably between centers. Among the clinical factors that were predictors of death, our findings suggest that the most relevant of these could be avoidance of noninvasive positive pressure ventilation as respiratory support in patients with severe acute respiratory hypoxemic failure due to COVID-19.

Abbreviations

Acute hypoxemic respiratory failure

AHRF; Acute respiratory distress syndrome:ARDS; Area under the receiver operating curve:AUROC; Calibration-in-the-large:CITL Coronavirus disease 2019:COVID-19; Intensive care units:ICU; Median odds ratio:MOR; Multivariate imputation by chained equations:MICE; Noninvasive positive pressure ventilation:NPPV; Positive end-expiratory pressure:PEEP; Real-time reverse-transcriptase polymerase chain reaction:RT-PCR; Simplified Acute Physiology Score:SAPS; Standard deviation:SD; Selective digestive decontamination:SDD.

Declarations

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Author Contributions: OP, LCA, FFV and AM had full access to all of the data of the study and take responsibility for the integrity of the data and the accuracy of data analysis. OP and FFV contributed equally to this work. *Concept and design*: OP, FFV, AE. *Data Acquisition and quality control and aslocal investigator of each site*: OP, ALGA, JMA, CRS, JM, PV, DB, JJ, EM, JCF, NF, AA, EG, JPA, RD, BA, AC, AA, FG, JG, JGS, JC, BMP, EM, OM, RB, TB, DP, AE, JAL. *Oversaw recruitment and data collection:* OP, ALGA, JMA, CRS, JM, PV, DB, JJ, EM, JCF, NF, AA, EG, JPA, RD, BA, AC, AA, FG, JG, JGS, JC, BMP, EM, OM, RB, TB, DP. *Analysis and interpretation of data*. OP, LCA, FFV and AM. *Drafting of the manuscript*: OP, LCA, FFV, AE, JM and AM. *Critical revision of the manuscript for important intellectual content*: OP, LCA, FFV, JM, AE, JAL and AM. *Statistical analysis*: LCA, AM, OP, FFV. *Administrative, technical or material support*: OP.

Competing interests

The authors declare that they have no competing interests.

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Ethical Approval and Consent to participate

This study was conducted following approval from the ethics committee of each study site. A waiver of consent was obtained from all participants or their representative (*Hospital Universitario de Getafe CEIm*, registry number#20/06, April 15 2020).

Consent for publication

Not applicable.

Availability of supporting data

The datasets generated and/or analyzed during the current study are publicly available due to ethics guidelines, but are available from the corresponding author on reasonable request.

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Figures

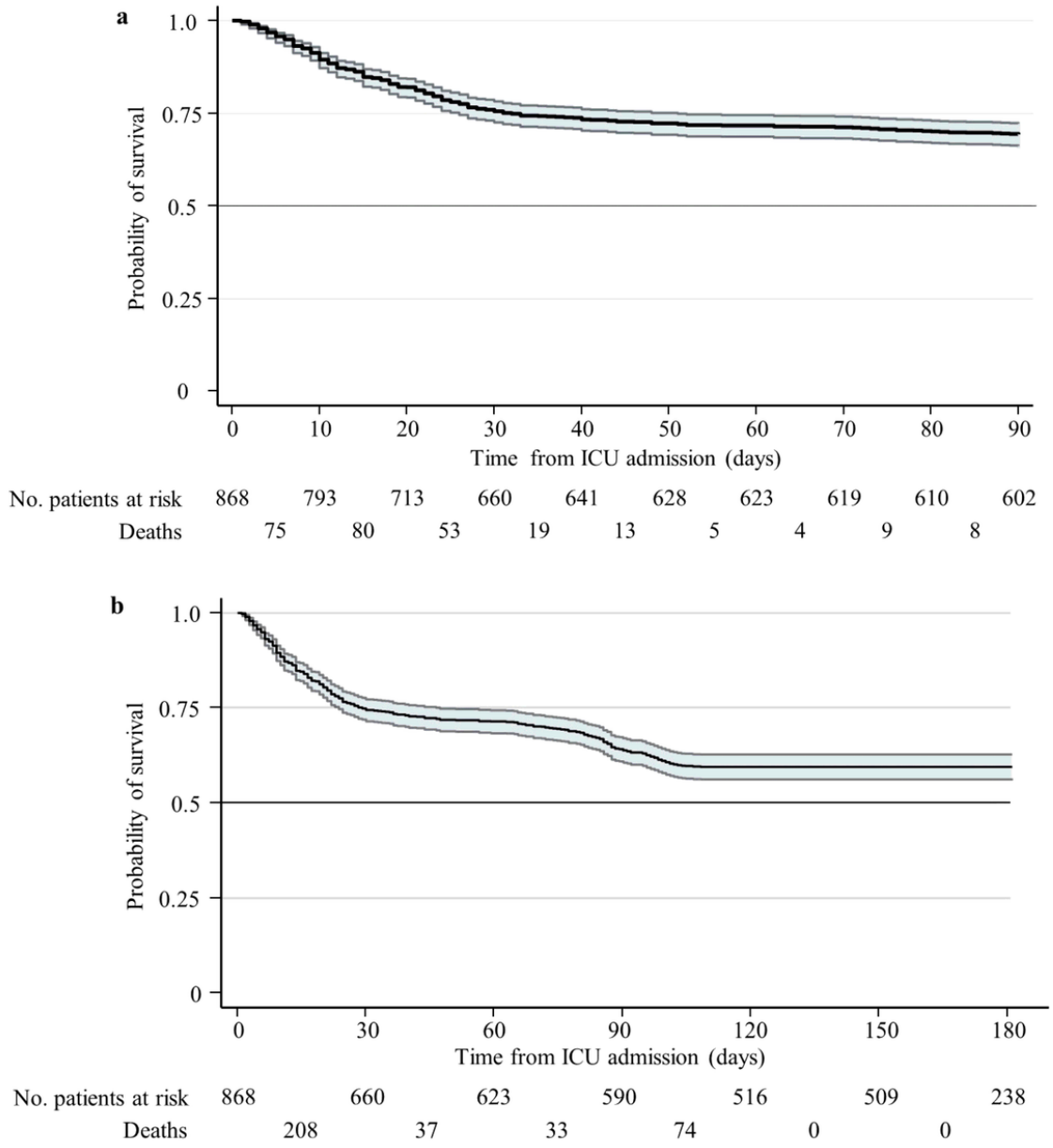

Figure 1

Kaplan-Meier Survival Curves. A. Overall survival at 90-days; B. Overall survival at 180 days. Grey lines represent the 95% confidence interval.

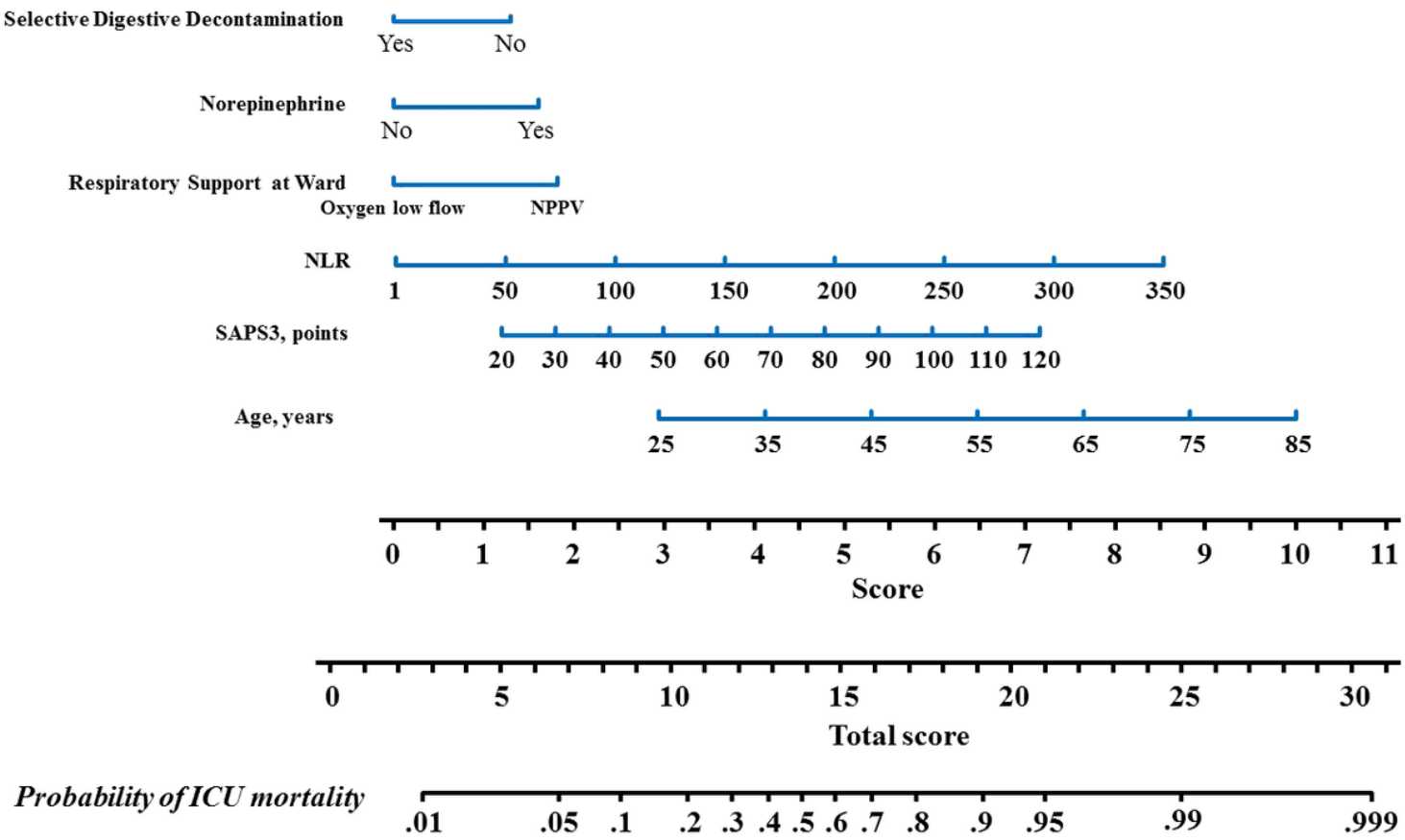

Figure 2

Nomogram for predicting ICU mortality. To obtain the predicted probability for ICU-mortality, locate the patient values on each axis. Draw a vertical line upward to the “Points” axis to determine the points of the variable. Sum up the points for all variables and locate the sum on the “Total points” axis. Draw a vertical line down to the “Risk of ICU-mortality” axis to find the probability of death. For example, for a patient undergoing mechanical ventilation and not receiving selective digestive decontamination (1.3 points), with no need for norephinephrine (0 points), with a prior attempt of NPPV (1.8 points), a neutrophil to lymphocyte ratio 110 (2.5 points), a SAPS3 score 60 points (3.6 points) and age of 72 years (8.5 points) the total score would be 17.8 points which corresponds to a predicted ICU mortality of 80.3%. On the other hand, for a patient undergoing mechanical ventilation and not receiving selective digestive decontamination (1.3 points), with no need for norephinephrine (0 points), a conventional oxygen mask (0 points), a neutrophil to lymphocyte ratio 100 (2.5 points), a SAPS3 score 60 points (3.6 points) and 67 years of age (8 points) the total score would be 14.1 points which corresponds to a predicted ICU mortality of 50%. Abbreviations: SAPS, Simplified Acute Physiologic Score; NLR ratio, neutrophil to lymphocyte ratio; NPPV, noninvasive positive pressure ventilation.

Supplementary Files

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