Risk Factors for 28-Day in-Hospital Mortality in Mechanically Ventilated Patients with COVID-19: An International Cohort Study

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Keywords: COVID-19, Mechanical Ventilation, SARS-CoV-2, Intensive Care Unit

Posted Date: August 3rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-751869/v1>

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Abstract

Background: Risk factors associated with mortality in patients with coronavirus disease 2019 (COVID-19) on mechanical ventilation are still not fully elucidated. Thus, we aimed to identify patient-level factors, readily available at the bedside, associated with the risk of in-hospital mortality within 28 days from commencement of invasive mechanical ventilation (28-day IMV mortality) in patients with COVID-19.

Methods Prospective observational cohort study in 148 intensive care units in the global COVID-19 Critical Care Consortium. Patients with clinically suspected or laboratory confirmed COVID-19 infection admitted to the intensive care unit (ICU) from February 2nd through December 29th, 2020, requiring IMV. No study-specific interventions were performed. Patient characteristics and clinical data were assessed upon ICU admission, the commencement of IMV and for 28 days thereafter. We primarily aimed to identify time-independent and time-dependent risk factors for 28-day IMV mortality.

Results: A total of 1713 patients were included in the survival analysis, 588 patients died in hospital within 28 days of commencing IMV (34.3%). Cox-regression analysis identified associations between the hazard of 28-day IMV mortality with age (HR 1.27 per 10-year increase in age, 95% CI 1.17 to 1.37, $P < 0.001$), PEEP upon commencement of IMV (HR 0.78 per 5-cmH₂O increase, 95% CI 0.66-0.93, $P = 0.005$). Time-dependent parameters associated with 28-day IMV mortality were serum creatinine (HR 1.30 per doubling, 95% CI 1.19-1.42, $P < 0.001$), lactate (HR 1.16 per doubling, 95% CI 1.06-1.27 $P = 0.001$), PaCO₂ (HR 1.31 per doubling, 95% CI 1.05-1.64, $P = 0.015$), pH (HR 0.82 per 0.1 increase, 95% CI 0.74-0.91, $P < 0.001$), PaO₂/FiO₂ (HR 0.56 per doubling, 95% CI 0.50-0.62, $P < 0.001$) and mean arterial pressure (HR 0.92 per 10 mmHg increase, 95% CI 0.88-0.97, $P = 0.002$).

Conclusions: This international study establishes that in mechanically ventilated patients with COVID-19, older age and clinically relevant variables monitored at the bedside are risk factors for 28-day IMV mortality. Further investigation is warranted to validate any causative roles these parameters might play in influencing clinical outcomes.

Background

In 2020, outbreaks due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) were reported globally [1]. Among patients with coronavirus disease-2019 (COVID-19), a subset developed critical illness, and up to 17% of those severe patients received invasive mechanical ventilation (IMV) [2–5]. Published reports on critically ill patients have been limited to small patient cohorts[6, 7], single-centre reports [8], mixed populations with and without any need of IMV[2, 4, 9], and single-country studies [10]. Early studies have revealed substantial variability in mortality rates – ranging from 30% [11] to 80% [2, 4, 9].

Studies [10–13] that have focused on COVID-19 patients on IMV have identified a variety of demographic and clinical characteristics associated with mortality risk. In COVID-19 patients requiring IMV, routinely measured biochemical parameters could be of significant prognostic value. However, the pattern and value of their clinical trajectory remain unclear. Ignoring changes in biochemical parameters over time when estimating associations with hospital outcomes are likely to produce biased estimates [14]. For clinicians wanting to use model outputs for prognostic purposes, the presence of such biases will have implications for identifying patients at high risk of mortality.

In early January 2020, the *COVID-19 Critical Care Consortium (COVID-19–CCC)* was founded to provide a global perspective on the management of critically ill COVID-19 patients and resulting outcomes to overcome many of the

limitations of single-centre and single-nation studies. In this analysis, we present an inclusive characterization of mechanically ventilated patients to identify baseline and longitudinal factors associated with in-hospital mortality assessed over the first 28 days after the commencement of IMV (28-day IMV mortality).

Materials And Methods

Study Design and Setting

We analyzed COVID-19–CCC study [15] dataset (Trial registration: ACTRN12620000421932). The study protocol was initially approved by the Alfred Hospital Ethics Committee, Melbourne, Australia (Project: 62066, Local reference: 108/20). Participating hospitals had to obtain local ethics committee approval, and a waiver of informed consent was granted in all cases. De-identified patient data were collected and stored via the REDCap electronic data capture tool, hosted at the University of Oxford, in Oxford, United Kingdom, University College Dublin, in Dublin, Ireland and Monash University, in Melbourne, Australia.

Participants

Patients admitted to a COVID-19–CCC ICU, from February 2nd through December 29th, 2020, with a clinically suspected or laboratory confirmed (by real-time PCR) diagnosis of SARS-CoV-2 infection and requiring IMV for any cause were enrolled. Patients under the age of 15 years and those admitted to the ICU for reasons not related to an acute infection with SARS-CoV-2 were excluded.

Variables, data sources, measurements and definitions

After enrolment, data on demographics, comorbidities, clinical symptoms, and laboratory results were collected by clinical/research staff in all participating ICUs and recorded in an electronic case report form [16]. Details of respiratory and hemodynamic support, physiological variables, and laboratory results were collected daily up to 28 days from commencement of IMV. When multiple results for the same test were available for a single given day, the worst daily value was recorded preferentially. The duration of IMV and ICU stay also were recorded. In this paper, analysis of daily data was restricted to the first 28 days following the initiation of IMV.

Primary outcome

The primary outcome was 28-day IMV mortality. We hypothesized that time-independent factors and temporal trends of continuous parameters, frequently assessed in patients on IMV, could influence the expected risk of 28-day IMV mortality. Not all patients had a final disposition at the time of database lock. Therefore, records in which the last update indicated that the patient had not died, been discharged, or completed 28 days of follow-up after IMV initiation at the same facility were censored at their last known date of daily data collection. In particular: Patients who were discharged alive from the hospital within 28 days were censored on the date of hospital discharge; Patients transferred to another facility, from ICU or hospital within 28 days were censored on the date of transfer; Patients whose outcome was not finalized on day 28 were censored at the last known date of daily data collection.

Secondary outcomes

Variable associations with the hazard of being discharged alive from the hospital were modelled to account for the competing risk. We also describe the overall duration of IMV, hospital stay duration, tracheostomy use, and the occurrence of complications on IMV.

Statistical analysis

We appraised dataset of the COVID-19 Critical Care Consortium, which is a prospective international, multi-centre, observational study in 377 hospitals spanning 53 countries. For each patient, data collection began at the time of hospital admission, using the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) [17] and the Short PeRiod IncideNce sTudy of Severe Acute Respiratory Infection (SPRINT-SARI) [18] case report forms. Data collection for the COVID-19–CCC observational study commenced upon ICU admission. Descriptive statistics included patient demographics, comorbidities, admission signs and symptoms, clinical signs at IMV commencement, and ICU management. Continuous variables were summarised as medians with interquartile ranges. Categorical variables were summarised as frequencies with percentages. Data completeness per variable was also reported in all tables.

For the subset of patients with daily (longitudinal) data collected on clinical parameters, we first examined temporal trends over the first 28 days from commencement of IMV. Data were presented visually as unadjusted means and 95% confidence intervals (CI) and not clustered per survival or discharge outcome. The resulting outputs allowed us to assess changes in clinical parameters during IMV, to inform the formulation of time-to-event models for estimating the hazards of mortality and discharge.

We performed time-to-event analysis to examine associations between critical variables measured on or before the commencement of IMV (time-independent) and variables assessed over time on the hazards of mortality and discharge (28-day IMV discharge) up to 28 days from commencement of IMV [19]. Mortality and discharge were considered as competing events. Associations with each outcome were estimated using cause-specific Cox proportional hazard models. In comparison with logistic regression models, the time-to-event analysis allows all patients to be included when estimating the associations between patient-level factors and the outcomes of interest, regardless of whether their outcome is known by the study end date, as required by logistic regression models. This is a significant strength of the Cox proportional hazard models we applied and an essential consideration for this study. It allowed patients to be censored at their last follow-up date if their outcome was not finalised after 28 days from IMV commencement, e.g., still in the hospital. Importantly, in studies of hospitalised patients, time-to-event analysis is recommended over traditional logistic regression models since the latter introduce selection bias due to the exclusion of patients without an outcome.

Models included fixed effects for age, sex, body mass index, cardiac arrest before IMV and comorbidities reported at hospital admission (diabetes, hypertension, chronic cardiac disease), selected based on previous evidence [8, 10, 11]. Week of ICU admission was also included to account for secular trends in death and discharge hazards over the different months of the pandemic. Based on the results of hypothesis testing for the proportional hazards assumption, a linear trend was chosen. Continuous variables, namely pH, arterial partial pressure of carbon dioxide (PaCO_2), ratio between arterial partial pressure of oxygen and inspiratory fraction of oxygen ($\text{PaO}_2/\text{FiO}_2$), lactate, creatinine and mean arterial pressure (MAP) were treated as time-dependent variables in the model to appraise the impact of dynamic changes throughout the 28-day study period on estimated hazard ratios. For each patient, we included daily observations where all time-dependent variables were observed on the same day. Tidal volume and positive end expiratory pressure (PEEP), measured upon commencement of IMV, were also included. Unlike other daily parameters, we considered baseline values for tidal volume and PEEP as these variables are specific to time spent on IMV. Since patients were likely to be extubated before death or discharge, treating these variables as time-dependent may have led to spurious associations since patients were likely to have been extubated and have spent additional time in hospital before death or discharge. Log-2 transformations were applied to serum creatinine, lactate, PaCO_2 and $\text{PaO}_2:\text{FiO}_2$ to remove skewness before analysis. The remaining variables were mean centred and appropriate scaled to improve interpretation of the estimated effect. The baseline hazard function was stratified by geographic

region (Africa, Asia, Australia/New Zealand, Europe, Latin America and the Caribbean, Northern America) to account for non-proportional effects.

Handling of missing data

Missing data on time-independent covariates, excluding cardiac arrest before IMV, were assumed to be missing at random. Values were imputed with Multiple Imputation using Chained Equations (MICE) [20]. MICE is an iterative algorithm which applies a series of linked regression models to impute missing values for each covariate, conditional on values for remaining variables. Models are fitted to multiple independent runs of the MICE algorithm; results across multiple runs are combined to produce a result. For time-dependent variables, follow-up intervals were constructed using all available daily observations per patient in line with a model specification for time-to-event analyses [14]. Final model results were pooled following ten independent rounds of MICE and model fitting.

All analyses were conducted using R version 4.0.1 or higher (The R Foundation).

Results

A total of 3372 COVID-19 patients, enrolled at 148 collaborating sites across 33 countries, were screened for final analysis (Fig. 1). Among those patients, 2379 (70%) received IMV and were included in the analysis, while 993 (29%) patients who never received IMV were excluded.

Patient characteristics

In the studied cohort, the median age (IQR) was 59 years (50–68), and patients were predominantly white (46%) and from Europe (36%) (Table 1). Hypertension, obesity, smoking and diabetes were the most common comorbidities. The median time from onset of symptom to ICU admission was eight days (IQR: 5–11 days), as was time from symptom onset to commencement of IMV (median 8 days, IQR 5–12 days). IMV was initiated upon ICU admission for 67% of the patients. At the time of IMV commencement (Table 2), median (IQR) creatinine and lactate were 0.9 mg/dL (0.7–1.4) and 1.4 mmol/L (1.0–2.0), respectively. Patients were severely hypoxemic, and their median (IQR) $\text{PaO}_2/\text{FiO}_2$ was 106mmHg (75–155), pH was 7.35 (7.28–7.42), and PaCO_2 was 44.8mmHg (37.0–53.7). Patients presented with respiratory system compliance of 33 mL/cmH₂O (25–43) and were ventilated using PEEP of 12 cmH₂O (10–14). Vasopressors were required in 54% of the patients. Common treatment strategies over the first 28 days included antibiotics (96%), neuromuscular blocking agents(81%), prone positioning(55%), corticosteroids(52%), and antivirals(49%) (Table 3).

Table 1
Demographic and clinical characteristics upon ICU admission

Characteristic	All mechanically ventilated patients (n = 2,379)	Patients included in survival analysis (n = 1,713)
Age, years: n; Median (IQR)	2379; 59(49 to 68)	1713; 59(50 to 68)
Female: n (%)	785/2378 (33)	530/1712 (31)
Ethnicity: n (%)		
<i>Aboriginal</i>	24/2180 (1)	11/1561 (1)
<i>Arab</i>	56/2180 (3)	47/1561 (3)
<i>Black</i>	265/2180 (12)	188/1561 (12)
<i>East Asian</i>	119/2180 (5)	87/1561 (6)
<i>Latin American</i>	119/2180 (5)	274/1561 (18)
<i>South Asian</i>	172/2180 (8)	71/1561 (5)
<i>West Asian</i>	18/2180 (1)	14/1561 (1)
<i>White</i>	890/2180 (41)	721/1561 (46)
<i>Other</i>	267/2180 (12)	148/1561 (9)
Geographic region: n (%)		
<i>Africa</i>	186/2379 (8)	170/1713 (10)
<i>Asia</i>	420/2379 (18)	204/1713 (12)
<i>Australia and New Zealand</i>	36/2379 (2)	24/1713 (1)
<i>Europe</i>	686/2379 (29)	609/1713 (36)
<i>Latin America</i>	322/2379 (14)	258/1713 (15)
<i>Northern America</i>	729/2379 (31)	448/1713 (26)
Healthcare or Lab Worker: n (%)	109/2223 (5)	76/1603 (5)
Comorbidities: n (%)		
<i>Smoking</i>	586/1659 (35)	391/1179 (33)
<i>Obese</i>	875/2335 (37)	644/1683 (38)
<i>Hypertension</i>	1166/2351 (50)	869/1692 (51)
<i>Chronic Kidney Disease</i>	220/2333 (9)	140/1675 (8)
<i>Chronic Cardiac Disease</i>	362/2328 (16)	261/1671 (16)
<i>Diabetes</i>	762/2315 (33)	536/1664 (32)
<i>Malignant neoplasm</i>	106/2331 (5)	75/1676 (4)
<i>Chronic pulmonary disease</i>	222/2335 (10)	150/1677 (9)

Characteristic	All mechanically ventilated patients (n = 2,379)	Patients included in survival analysis (n = 1,713)
<i>Severe liver disease</i>	112/2366 (5)	68/1701 (4)
Body Mass Index (BMI): n; Median (IQR)	2083; 28.6(25.3 to 33.6)	1521; 28.7(25.5 to 33.6)
APACHE II: n; Median (IQR)	1054; 16.0(11.0 to 22.8)	821; 17.0(11.0 to 23.0)
SOFA: n; Median (IQR)	1186; 5.0(3.0 to 8.0)	962; 6.0(4.0 to 8.0)
WBC count, 10 ³ /μL: n; Median (IQR)	1621; 10.0(6.8 to 14.1)	1226; 10.0(6.9 to 14.1)
Lymphocyte count, 10 ³ /μL: n; Median (IQR)	1213; 0.8(0.5 to 1.2)	944; 0.8(0.5 to 1.2)
Neutrophils: Lymphocyte ratio: n; Median (IQR)	1108; 10.8(6.0 to 18.2)	868; 10.8(6.1 to 18.0)
Temperature, °C: n; Median (IQR)	1114; 37.0(36.2 to 37.9)	844; 37.0(36.3 to 37.9)
Creatinine, mg/dL: n; Median (IQR)	1661; 1.0(0.7 to 1.4)	1263; 1.0(0.7 to 1.4)
C-reactive protein level, mg/dL: n; Median (IQR)	1144; 88(16 to 185)	917; 92(17 to 191)
D-dimer, mcg/mL: n; Median (IQR)	691; 2(1 to 4)	527; 2(1 to 5)
Lactate, mmol/L: n; Median (IQR)	1394; 1.4(1.0 to 2.1)	1166; 1.4(1.0 to 2.0)
Ferritin, ng/mL: n; Median (IQR)	554; 2.7(1.3 to 4.5)	420; 2.7(1.4 to 4.5)
IL-6; ng/L: n; Median (IQR)	179; 90(38 to 238)	152; 92(44 to 247)

Table 1 caption

Percentages are calculated for non-missing data. BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II score; SOFA, Sequential Organ Failure Assessment Score; WBC, white blood cell count; CRP, c-reactive protein; IL-6, interleukin 6.

Table 2
Clinical characteristics upon commencement of invasive mechanical ventilation

Characteristic	All mechanically ventilated patients (n = 2,379)	Patients included in survival analysis (n = 1,713)
Clinical signs and laboratory findings within 24h from commencement of IMV		
WBC count, 10 ³ /μL: n; Median (IQR)	1654; 10.5(7.2 to 14.7)	1293; 10.4(7.2 to 14.5)
Lymphocyte count, 10 ³ /μL: n; Median (IQR)	1153; 0.8(0.5 to 1.2)	928; 0.8(0.5 to 1.2)
Neutrophils: Lymphocyte ratio: n; Median (IQR)	1055; 11(6 to 18)	851; 11(6 to 18)
Temperature, °C: n; Median (IQR)	1122; 37(36 to 38)	882; 37(36 to 38)
Creatinine, mg/dL: n; Median (IQR)	1690; 1.0(0.7 to 1.4)	1341; 0.9(0.7 to 1.4)
C-reactive protein level, mg/dL: n; Median (IQR)	1065; 87(16 to 183)	904; 93(18 to 189)
D-dimer, mcg/mL: n; Median (IQR)	642; 1.7(0.8 to 4.7)	510; 1.5(0.8 to 4.5)
Lactate, mmol/L: n; Median (IQR)	1427; 1.4(1.0 to 2.1)	1274; 1.4(1.0 to 2.0)
Ferritin, ng/mL: n; Median (IQR)	507; 2.7(1.4 to 4.5)	406; 2.7(1.5 to 4.8)
IL-6; ng/L: n; Median (IQR)	156; 98(31 to 287)	144; 102(33 to 313)
Gas exchange and level of support within 24h from commencement of IMV		
pH: n; Median (IQR)	1741; 7.35(7.28 to 7.42)	1390; 7.35(7.28 to 7.42)
FiO ₂ , mmHg: n; Median (IQR)	1745; 0.80(0.60 to 1.00)	1386; 0.80(0.60 to 1.00)
PaO ₂ /FiO ₂ , mmHg: n; Median (IQR)	1611; 105.20(74.00 to 156.00)	1344; 106.65(75.00 to 155.12)
PaCO ₂ , mmHg: n; Median (IQR)	1726; 44.00(36.50 to 53.20)	1378; 44.80(37.00 to 53.70)
Static respiratory system compliance, mL/cmH ₂ O: n; Median (IQR)	714; 33(25 to 42)	616; 33(25 to 42)
Plateau Pressure, cmH ₂ O: n; Median (IQR)	934; 25(21 to 28)	804; 25(21 to 28)
Driving Pressure, cmH ₂ O: n; Median (IQR)	931; 12(10 to 15)	802; 12(10 to 15)
Respiratory rate, breaths/min: n; Median (IQR)	1388; 22(18 to 27)	1053; 22(18 to 26)
PEEP level, cmH ₂ O: n; Median (IQR)	1440; 12(10 to 14)	1114; 12(10 to 14)
Minute ventilation, L/min: n; Median (IQR)	1080; 9(8 to 11)	839; 9(8 to 11)
Ventilatory ratio: n; Median (IQR)	875; 0.74(0.59 to 0.92)	719; 0.76(0.61 to 0.92)
Heart rate, beats/min: n; Median (IQR)	1449; 98(79 to 116)	1064; 98(78 to 114)
Mean Arterial Pressure, mmHg: n; Median (IQR)	1835; 74(64 to 90)	1408; 74(64 to 89)
Vasopressor/Inotropic Support N. (%)	999/1893 (53)	775/1432 (54)

Characteristic	All mechanically ventilated patients (n = 2,379)	Patients included in survival analysis (n = 1,713)
Tracheostomy (N, %)	26/1907 (1)	21/1444 (1)

Table 2 Caption: Percentages are calculated for non-missing data. IQR, interquartile range; WBC, white blood cell count; IL-6, interleukin 6. PaO₂, arterial partial pressure of oxygen; FiO₂, inspiratory fraction of oxygen; PaCO₂, arterial partial pressure of carbon dioxide; PEEP, positive end expiratory pressure; 28-day ventilator free day (VFD) was calculated as following: VFDs = 0 if subject dies within 28 days of mechanical ventilation; VFDs = 28 – x if successfully liberated from ventilation x days after initiation; VFDs = 0 if the subject is mechanically ventilated for >28 days; IMV, invasive mechanical ventilation. Static respiratory system compliance was calculated as: tidal volume (mL)/(static airway plateau pressure-PEEP (cmH₂O)).

Table 3
Intensive Care Unit Clinical management within the first 28 days of ICU admission

Characteristic	All mechanically ventilated patients (n = 2,379)	Patients included in survival analysis (n = 1,713)
Antibiotics, n (%)	2196/2299 (96)	1587/1660 (96)
Any antiviral: n (%)	874/1691 (52)	596/1214 (49)
Ramdesivir: n (%)	261/1069 (24)	166/778 (21)
Corticosteroids: n (%)	873/1697 (51)	645/1245 (52)
Continuous renal replacement therapy: n (%)	339/2271 (15)	236/1656 (14)
Vasoactive drugs: n (%)	1291/2240 (58)	926/1636 (57)
Cardiac-assist devices: n (%)	118/2261 (5)	96/1639 (6)
ECMO: n (%)	449/2339 (19)	343/1702 (20)
Prone positioning: n (%)	1174/2340 (50)	944/1702 (55)
Use of Inhaled Nitric Oxide: n (%)	259/2340 (11)	196/1701 (12)
Use of neuromuscular blockade: n (%)	1767/2341 (75)	1383/1701 (81)
Recruitment maneuvers: n (%)	655/2143 (31)	577/1565 (37)
Tracheostomy inserted	338/2326 (15)	289/1698 (17)
28-day VFD, days: n; Median (IQR)	2023; 0(0 to 15)	1468; 0(0 to 14)
Days from ICU admission to death: n; Median (IQR)	1031; 11(5 to 21)	718; 12(6 to 23)
Days from IMV commencement to death: n; Median (IQR)	1031; 11(5 to 21)	718; 12(6 to 22)
Duration of ICU stay (died), days: n; Median (IQR)	1031; 11(5 to 21)	718; 12(6 to 22)
Duration of ICU stay (discharged), days: n; Median (IQR)	981; 19(12 to 33)	739; 19(12 to 33)
Days from hospital admission to IMV commencement: n; Median (IQR)	2376; 0(0 to 3)	1710; 0(0 to 2)
Days from ICU admission to IMV commencement: n; Median (IQR)	2379; 0(0 to 0)	1713; 0(0 to 0)
Days from first reported symptom to IMV commencement: n; Median (IQR)	2310; 8(5 to 12)	1664; 8(5 to 12)
Commenced IMV on ICU admission: n (%)	1554/2379 (65)	1152/1713 (67)

Table 3 Caption: Percentages are calculated for non-missing data. ECMO, extracorporeal membrane oxygenation; iNO, inhaled nitric oxide; IMV, invasive mechanical ventilation; ICU, intensive care unit. 28-day ventilator free day (VFD) was calculated as following: VFDs = 0 if subject dies within 28 days of mechanical ventilation; VFDs = 28 - x if

successfully liberated from ventilation x days after initiation; VFDs = 0 if the subject is mechanically ventilated for >28 days

In 1713 patients with complete daily assessment, 588 patients died in hospital within 28 days of commencing IMV (34.3%), 26 patients (1.5%) were transferred to another hospital. At the study end date, outcomes of 230 patients (13.4%) who were censored at their last known follow-up date were unknown, based on daily data collection. Among patients who died, the median time to death was 12 days (IQR 6–23 days) from ICU admission. For patients with a reported cause of death (n = 648), respiratory failure was the most common (n = 189;45%), while other causes included multi-organ failure (n = 231;36%), septic shock (n = 49; 8%), cardiac failure (n = 38;6%), cerebrovascular accident (n = 13;2%), hemorrhagic shock (n = 6;1%) or other causes (n = 46;7%).

Dynamics of daily clinical parameters

Daily averages for clinical variables, including arterial blood gases, are depicted in Fig. 2. There was a clear improvement in the dynamics of $\text{PaO}_2/\text{FiO}_2$ (from 132.7 ± 2.9 mmHg upon start IMV to 198.8 ± 9.2 mmHg at 28 days), pH (from 7.34 ± 0.00 to 7.40 ± 0.00), serum creatine (from 1.39 ± 0.04 mg/dL to 1.18 ± 0.09) and lactate (from 1.98 ± 0.06 mmol/L to 1.15 ± 0.07). Differently, trajectories of PaCO_2 and MAP were more convoluted, with early worsening during the first days of IMV and delayed improvement. Figure 3 shows ventilatory modes throughout the study period. Controlled modes were predominantly used during the first 2 weeks of IMV. Stratification of clinical variables and ventilatory settings for patients with known final outcome within the first 28 days of IMV are reported separately in Figs. 4 and 5. There was an apparent discrepancy between survivors and non-survivors in the applied FiO_2 , while tidal volume and PEEP were similar throughout the assessment period.

Primary Outcome

Time-to-event analysis (Fig. 6A) identified older age (HR 1.27 per 10-year increase in age, 95% CI 1.17 to 1.37, $P < 0.001$) and lower values of PEEP, upon commencement of IMV (HR 0.78 per 5-cmH₂O increase, 95% CI 0.66–0.93, $P = 0.005$) as statistically significant associations with of the hazard of 28-day IMV mortality. Among time-dependent variables, an increase in serum creatinine (HR 1.3 per doubling, 95% CI 1.19–1.42, $P < 0.001$), lactate (HR 1.16 per doubling, 95% CI 1.06–1.27, $P = 0.001$) and PaCO_2 (HR 1.31 per doubling, 95% CI 1.05–1.64, $P = 0.015$) increased the hazards of 28-day IMV mortality. Conversely, an increase in pH (HR 0.82 per 0.1 increase, 95% CI 0.74–0.91, $P < 0.001$), $\text{PaO}_2/\text{FiO}_2$ (HR 0.56 per doubling, 95% CI 0.50–0.62, $P < 0.001$) and MAP (HR 0.92 per 10 mmHg increase, 95% CI 0.88–0.97, $P = 0.002$), decreased the hazards of 28-day IMV mortality. Figure 7A depicts variability in the baseline survival function for 28-day IMV mortality among geographic regions.

Secondary Outcomes

Estimated hazard ratios for the variables as mentioned above and the hazard of discharge are reported in Fig. 6B. Results indicated that older age (HR 0.85 per 10-year increase in age, 95% CI 0.78 to 0.93, $P < 0.001$), increased creatinine (HR 0.81 per doubling, 95% CI 0.71–0.92, $P = 0.001$) and PaCO_2 (HR 0.52 per doubling, 95% CI 0.36–0.77, $P < 0.001$) decreased the hazards of 28-day IMV discharge, while higher $\text{PaO}_2/\text{FiO}_2$ (HR 1.54 per doubling, 95% CI 1.33–1.79, $P < 0.001$) increased the hazard. Similar to IMV 28-day mortality, baseline survival function of 28-day IMV discharge varied between geographic regions (Fig. 7B).

Tracheostomy was carried out in 289/1698 patients (17%) included in the survival analysis (Table 3). During hospitalization, the most common complications in the mechanically ventilated population were cardiac arrhythmia (26%), pleural effusion (20%) and cardiac arrest (17%) (Table 4). The median duration of IMV was 13 days (IQR:7–24

days). Among patients in whom final disposition was available within 28 days of IMV, the median time from ICU to death was 12 days (IQR:6–22 days). Among patients known to be discharged alive from the hospital, the median time from ICU admission to hospital discharge was 19 days (IQR:12–33 days).

Table 4
Cardio-pulmonary complications

Complication at any time during hospitalization	All mechanically ventilated patients	Patients included in survival analysis
n (%)	(n = 2,379)	(n = 1,713)
Cardiac Arrhythmia	471/1955 (24)	356/1393 (26)
Pleural Effusion	359/1932 (19)	280/1377 (20)
Cardiac Arrest	415/1966 (21)	232/1400 (17)
Deep Vein Thrombosis	7/67 (10)	6/45 (13)
Pneumothorax	170/1966 (9)	135/1400 (10)
Pulmonary Embolism	104/1635 (6)	83/1108 (7)
Heart Failure	105/1926 (5)	70/1373 (5)
Cardiac Ischemia	79/1922 (4)	55/1369 (4)
Cardiomyopathy	46/1602 (3)	34/1087 (3)
Cryptogenic organizing pneumonia	50/1906 (3)	38/1357 (3)
Myocardial Infarction	45/1612 (3)	28/1094 (3)
Bronchiolitis	26/1904 (1)	22/1356 (2)
Myocarditis/Pericarditis	44/1610 (3)	25/1094 (2)
Endocarditis	7/1610 (0)	7/1094 (1)

Discussion

The present international multicentre cohort study from six continents constitutes the most extensive epidemiological investigation of mechanically ventilated patients with severe COVID-19. The study enabled delineation of the clinical course during the first 28 days of IMV, corroborating age and accounting for longitudinal changes in pH, PaO₂/FiO₂, MAP, PaCO₂, lactate and creatinine when assessing associations with 28-day IMV mortality.

Reported average mortality rates in mechanical ventilated COVID-19 patients have varied [2, 4, 9, 13, 21]. Those findings have been potentially biased by highly variable censor dates to define death, and substantial percentages of patients still requiring ICU care at the chosen censor date [2, 4, 6, 8, 9, 22–26]. In our study, among 1713 ventilated patients, we reported an overall 28-day IMV mortality of 34.3%, similar to rates in ventilated patients from the Netherlands [10] and Spain [8] and lower than figures from United Kingdom [27]. Given the observational nature of our study, extrapolations on the mortality figures of our population can only be speculative. Nevertheless, the mortality rate should be interpreted in the context of the enrollment period of February-December 2020, since early dismal survival from outbreak epicenters might have been counterbalanced by lower mortality rates later in the year. In addition, in comparison with previous single-country observational studies [28, 29], corticosteroids were used in fewer

patients, due to either differences in practice among geographical regions or inclusion of data acquired early in the pandemic. Nevertheless, we found that period of admission to ICU was not significantly associated with major outcomes, implying consistent burden of the disease throughout periods of the pandemic.

In line with previous reports [9, 10, 13, 30, 31] that found older populations at the highest risk of mortality, age shared a strong positive association with the hazard of 28-day IMV mortality. Of note, we report a slightly younger population than previous investigations [8, 30, 32, 33], possibly because, in 2020, IMV was primarily reserved for younger patients in some of the geographical regions comprising our study network. Irrespective, it is still not fully elucidated why SARS-CoV-2 infection is more lethal in older adults and several theories that detail potential risks associated with age-related changes to the immune cells, inflammasome activity, epigenome, and characteristic comorbidities have emerged [34]. Among the other time-independent factors, only PEEP was found to reduce mortality hazards in our analyses, in contrast with previous evidence associating higher PEEP with mortality [30]. These findings emphasize the challenges in setting the optimal PEEP in COVID-19 patients [35], particularly in light of early controversial reports on heterogeneous static respiratory system compliance in infected patients [36].

We found that several clinical variables increased the risk of 28-day IMV mortality. To the best of our knowledge, our report is the first that applied Cox proportional hazards modelling of 28-day IMV mortality to assess the impact of time-dependent clinical variables, taking into account the competing risk of ICU discharge. Indeed, previous investigations [8–10, 30, 37, 38] focused on risk factors for mortality appraised at a fixed time point, limiting inferences on variables that dynamically change during IMV. By incorporating baseline stratification by geographic region in modelling, we found substantial differences in survival, in line with the most recent reports from low-middle income countries [39]. As expected, the severity of hypoxemia during IMV was strongly associated with both mortality and delayed discharge. In this cohort, patients presented a considerable improvement in $\text{PaO}_2/\text{FiO}_2$ during the first 24h of IMV, similarly to previous evidence [8], and potentially related to the prompt pronation, NMBAs and high PEEP after commencement of IMV. However, the data also emphasizes potential long-term respiratory derangement since moderate hypoxemia persisted throughout the assessment period. The study also identified the association of PaCO_2 with the hazard of death, which was not reported in previous studies. Furthermore, an increase in PaCO_2 during the initial days of IMV was evident in this cohort, which could have been related to the initial hypercatabolic state, inadequate ventilatory management, micro or macrovascular pulmonary thrombosis [40–42] or simply to respiratory fatigue, given that on average, patients were intubated eight days from symptom onset. Previous extensive studies [9, 10, 30, 37] failed to corroborate serum lactate and MAP as risk factors for mortality in COVID-19 patients on IMV. In a large critically ill population from the United Kingdom, lactate within 24-h from ICU admission was an early predictor of mortality [37]. However, the evolution of such parameter in this population was unknown, and only 59% required IMV. Cytokine storm and septic shock in COVID-19 are linked with haemodynamic instability and lactic acidosis, and multi-organ failure in the most severe cases. Thus, our original findings imply that haemodynamic impairment could be valuable in risk stratification. Similar to the findings of the PROVENT-COVID study [10], changes in pH were associated with mortality risk. On average, pH normalization was achieved within one week. It is uncertain whether low pH was driven by refractory hypercapnia, metabolic disturbance or a mixed acid-base disorder. Importantly, interdependence of aforementioned variables should also be considered. Indeed, pH and PaCO_2 coupling may have been present during refractory hypercapnia, and similarly pH and lactate correlation could have been the result of sustained acidemia during severe hypotensive states or other metabolic disturbances. Finally, the association of serum creatinine with the hazards of death is important, because most patients in our cohort did not have chronic kidney disease before hospitalization. Further investigation of the multifactorial etiology of renal impairment in COVID-19 is urgently needed, as the angiotensin converting enzyme-two receptor is critical for SARS-CoV-2 cell entry

and widely expressed in the kidneys [43, 44], but IMV and septic shock might have also contributed to the development of kidney injury.

Strengths and limitations

In efforts to inform the field as to characteristics of COVID-19 infection, many early publications limited to small patient series or single-country experiences have appeared. These papers reported conflicting findings related to centre-specific patient populations, resource availability differences, and patient management strategy variations. The current study overcomes some of these limitations by providing a detailed global analysis of demographics and comorbidities associated with mortality and, for the first time, account for the dynamics of a clinically relevant subset of commonly tested variables associated with hazards of 28-day IMV. Limitations of the current report include that our model should not be used for prediction at an individual level, due to the lack of validation in different and larger cohorts. Admission to ICU, indication for IMV were not standardized across countries and could have depended on local practices. In this cohort, patients received IMV in 2020; thus, they may not reflect the current scenarios of ICU ventilatory management across the globe – to which subsequent reports can be compared. Further, many of the early pandemic centers were resource-limited, which may have adversely impacted the noted outcomes. Approximately 50% of the patients received corticosteroids. Consequently, any extrapolation of our findings to patients receiving dexamethasone treatment must be performed with caution [45, 46]. Given that the analyses selectively focused on demographics and comorbidities associated with increased mortality, and time-dependent parameters routinely measurable at the bedside of IMV patients, other unmeasured factors could have biased our inferences about mortality risks. The 28-day timeline could have biased results toward early mortality. Irrespective, we precisely aimed at identifying key associations affecting mortality during the period of IMV, which in COVID-19 patients is approximately ten days [10, 21, 47]. Lastly, information on SARS-CoV-2 variants and patient vaccination status is not accessible from our analyses.

Conclusions

This study represents the most extensive and comprehensive international cohort analyses of patient characteristics associated with mortality, in COVID-19 patients requiring mechanical ventilation. Age and commonly tested parameters in COVID-19 patients on IMV, including pH, blood gases, MAP, serum lactate, and serum creatinine, were associated with the increased hazards 28-day IMV mortality. These original findings offer new avenues for research efforts for the early identification of the patients most at risk and in need of altering clinical management strategies.

List Of Abbreviations

- Coronavirus disease 2019 (COVID-19)
- In-hospital mortality within 28 days from commencement of invasive mechanical ventilation (28-day IMV mortality)
- Intensive care unit (ICU)
- Hazard Ratio (HR)
- Confidence Interval (CI)
- Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)
- Invasive mechanical ventilation (IMV)
- COVID-19 Critical Care Consortium (COVID-19–CCC)

- International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC)
- Short PeRIod IncideNce sTudy of Severe Acute Respiratory Infection (SPRINT-SARI)
- Multiple Imputation using Chained Equations (MICE)
- Arterial partial pressure of carbon dioxide (PaCO_2)
- Ratio between arterial partial pressure of oxygen and inspiratory fraction of oxygen ($\text{PaO}_2/\text{FiO}_2$)
- Mean arterial pressure (MAP)
- Positive end expiratory pressure (PEEP)

Declarations

Ethics approval and consent to participate

Participating hospitals obtained local ethics committee approval and a waiver of informed consent was granted in all cases.

Consent for publication

Not applicable

Availability of data materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

A/Prof Li Bassi received research support from Fisher & Paykel outside the submitted work. Prof Dalton consults with Innovative ECMO Concepts, Abiomed and Instrumentation Labs, which does not affect the current work. Prof Brodie receives research support from ALung Technologies, and he has been on the medical advisory boards for Baxter, Abiomed, Xenios and Hemovent. A/Prof Fan reports personal fees from ALung Technologies, Baxter, Fresenius Medical Care, Getinge, and MC3 Cardiopulmonary outside the submitted work. Prof Laffey reports consulting fees from Baxter and Cala Medical, both outside the submitted work. Prof Nichol is supported by a Health Research Board of Ireland Award (CTN-2014-012). Prof Fraser receives research support from Fisher & Paykel outside the submitted work. Prof. Grasselli reports personal fees from Draeger Medical, Biotest, Getinge, Fisher & Paykel and MSD outside the submitted work.

Funding: The University of Queensland, The Wesley Medical Research, The Prince Charles Hospital Foundation, The Health Research Board of Ireland; Biomedicine International Training Research Programme for Excellent Clinician-Scientists; The European Union Research and Innovation Programme (Horizon 2020); la Caixa Foundation. Finally, Carol Hodgson is funded by the National Health and Medical Research Council Grant.

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GLB conceived of the study, participated in its design and coordination and helped to draft the manuscript; **JYS** conceived of the study, participated in its design and coordination and helped to draft the manuscript; **NW** performed

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Acknowledgments

We recognize the crucial importance of the ISARIC and SPRINT-SARI networks in developing and expanding the global COVID-19 Critical Care Consortium. We thank the generous support we received from the Extracorporeal Life Support Organization (ELSO) and the International ECMO Network (ECMONet). We greatly acknowledge Adrian Barnett for his invaluable contribution to the analysis plan and statistical insights. We greatly acknowledge Bailey Schneider (University of Michigan and University of Queensland) for her input and contribution to the critical revision of the manuscript. We owe Li Wenliang, MD from the Wuhan Central Hospital, an eternal debt of gratitude for reminding the world that doctors should never be censored during a pandemic. Finally, we acknowledge all members of the COVID-19 Critical Care Consortium and various collaborators.

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Figures

Figure 1

Flow of Patient Enrolment by the censor date of December 29th, 2020. ICU, intensive care unit; MV, mechanical ventilation.

Figure 2

Dynamics of time-dependent parameters included in survival analysis. Average daily parameters collected during the first 28 days following commencement of mechanical ventilation. Data are reported as unadjusted means and 95% confidence intervals.

Figure 3

Control and assist-control ventilatory modes during the first 28-day of invasive mechanical ventilation. Number of patients on control and assisted modes of ventilation, throughout the 28-day follow up period, are depicted.

Figure 4

Dynamics of time-dependent parameters included in survival analysis stratified per known disposition at 28 days of invasive mechanical ventilation. Average daily parameters collected during the first 28 days following commencement of invasive mechanical ventilation, stratified for patients who died in hospital within 28 days (continuous) or had been discharged from hospital or were still alive in hospital at 28 days (dashed). Data are reported as unadjusted means and 95% confidence intervals.

Figure 5

Dynamics of ventilatory settings stratified per patient disposition. Average daily ventilatory settings (inspiratory fraction of oxygen, tidal volume and PEEP) among patients discharged alive from the hospital or still alive at 28 days (dashed line) vs. patients who died in hospital within 28 days (solid line). Data are reported as unadjusted means and 95% confidence intervals for patients who had died in hospital within 28 days (continuous) or have been discharged from hospital or were still alive in hospital at 28 days (dashed). Total daily observations contributing to summary statistics are reported. FiO2 or the inspiratory fraction of oxygen; PEEP or the positive end-expiratory pressure.

Figure 6

Cause-specific Cox proportional hazards modelling to estimate the hazards of death (A) or discharge (B), up to 28 days following commencement of mechanical ventilation. The model considered both time-independent (age, sex, BMI, diabetes, hypertension, chronic cardiac disease, cardiac arrest before invasive mechanical ventilation, PEEP and tidal volume upon commencement of MV) and time-dependent covariates (serum creatinine, serum lactate, pH, PaCO₂ and PaO₂/FiO₂, MAP). Covariate effects are presented as hazard ratios (HR) and 95% confidence interval. BMI, body mass index; MV, mechanical ventilation; PaCO₂, arterial partial pressure of carbon dioxide; PaO₂/FiO₂ ratio between arterial partial pressure of oxygen and the inspiratory fraction of oxygen. MAP, mean arterial pressure.

Figure 7

Baseline survival curves by region (Africa, Asia, Australia/New Zealand, Europe, Latin America and the Caribbean, Northern America) for in-hospital mortality (A) and discharge alive from the hospital (B) up to 28 days following commencement of mechanical ventilation. Baseline stratification in cause-specific Cox models accounted for non-proportional effects attributable to geographic region.