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Assessment of 28-Day In-Hospital Mortality in Mechanically Ventilated Patients With Coronavirus Disease 2019: An International Cohort Study

IMPORTANCE: Factors associated with mortality in coronavirus disease 2019 patients on invasive mechanical ventilation are still not fully elucidated.

OBJECTIVES: To identify patient-level parameters, readily available at the bedside, associated with the risk of in-hospital mortality within 28 days from commencement of invasive mechanical ventilation or coronavirus disease 2019.

DESIGN, SETTING, AND PARTICIPANTS: Prospective observational cohort study by the global Coronavirus Disease 2019 Critical Care Consortium. Patients with laboratory-confirmed coronavirus disease 2019 requiring invasive mechanical ventilation from February 2, 2020, to May 15, 2021.

MAIN OUTCOMES AND MEASURES: Patient characteristics and clinical data were assessed upon ICU admission, the commencement of invasive mechanical ventilation and for 28 days thereafter. We primarily aimed to identify time-independent and time-dependent risk factors for 28-day invasive mechanical ventilation mortality.

RESULTS: One-thousand five-hundred eighty-seven patients were included in the survival analysis; 588 patients died in hospital within 28 days of commencing invasive mechanical ventilation (37%). Cox-regression analysis identified associations between the hazard of 28-day invasive mechanical ventilation mortality with age (hazard ratio, 1.26 per 10-yr increase in age; 95% CI, 1.16–1.37; $p < 0.001$), positive end-expiratory pressure upon commencement of invasive mechanical ventilation (hazard ratio, 0.81 per 5 cm H_2O increase; 95% CI, 0.67–0.97; $p = 0.02$). Time-dependent parameters associated with 28-day invasive mechanical ventilation mortality were serum creatinine (hazard ratio, 1.28 per doubling; 95% CI, 1.15–1.41; $p < 0.001$), lactate (hazard ratio, 1.22 per doubling; 95% CI, 1.11–1.34; $p < 0.001$), $Paco_2$ (hazard ratio, 1.63 per doubling; 95% CI, 1.19–2.25; $p < 0.001$), pH (hazard ratio, 0.89 per 0.1 increase; 95% CI, 0.8–14; $p = 0.041$), Pao_2/Fio_2 (hazard ratio, 0.58 per doubling; 95% CI, 0.52–0.66; $p < 0.001$), and mean arterial pressure (hazard ratio, 0.92 per 10 mm Hg increase; 95% CI, 0.88–0.97; $p = 0.003$).

CONCLUSIONS AND RELEVANCE: This international study suggests that in patients with coronavirus disease 2019 on invasive mechanical ventilation, older age and clinically relevant variables monitored at baseline or sequentially during the course of invasive mechanical ventilation are associated with 28-day invasive mechanical ventilation mortality hazard. Further investigation is warranted to validate any causative roles these parameters might play in influencing clinical outcomes.

KEY WORDS: coronavirus disease 2019; intensive care unit; mechanical ventilation; severe acute respiratory syndrome coronavirus 2

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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). Reports on critically ill patients have been limited to small cohorts (3, 6), single-center reports (7), mixed populations with and without need of IMV (2, 4, 8, 9), and single-country studies (10). Early studies have revealed substantial variability in mortality rates—ranging from 30% (2) to 80% (2, 4, 8).

Studies (2, 10–12) that have focused on COVID-19 patients on IMV have identified a variety of demographic and clinical characteristics associated with mortality. In COVID-19 patients requiring IMV, routinely measured parameters could be of significant prognostic value. The pattern and value of their clinical trajectory have been investigated in a recent study (9) in a mixed Italian population, but corroboration of these findings in international populations on IMV remains to be elucidated. Ignoring changes in biochemical parameters over time when estimating associations with hospital outcomes is likely to produce biased estimates (13). 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-center 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-d IMV mortality).

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MATERIALS AND METHODS

Study Design and Setting

We analyzed COVID-19–CCC study (14) dataset (Trial registration: ACTRN12620000421932), which is a prospective international, multicenter, observational study in 377 hospitals spanning 53 countries. The study protocol was approved by the Alfred Hospital Ethics Committee, Melbourne, Australia (Project: 62066, Local reference: 108/20). Participating hospitals obtained 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 Research Electronic Data Capture electronic data capture tool, hosted at the University of Oxford, Oxford, United Kingdom; University College Dublin, Dublin, Ireland; and Monash University, Melbourne, Victoria, Australia.

Participants

Patients admitted to a COVID-19–CCC ICUs, from February 2, 2021, to May 15, 2021, with laboratory-confirmed (real-time polymerase chain reaction) 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 SARS-CoV-2 infection were excluded. Given our interest in examining associations between routinely tested parameters while in the ICU, we further identified the subset of patients with available longitudinal data over the course of ICU admission.

Variables, Data Sources, Measurements, and Definitions

After enrollment, 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 (14, 15). Details of respiratory and hemodynamic support, physiologic 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 article, analysis of daily data was restricted to the first 28 days following the initiation of IMV. Copies of case report forms detailing all variables can be found with the published study protocol (14).

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. Given that some patients did not have final disposition at the time of database lock, those who were discharged alive from the hospital within 28 days were censored on the date of hospital discharge; patients transferred within 28 days to another healthcare facility 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 modeled 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

Further details about the statistical analysis are reported in the **Supplementary Digital Content** (http://links.lww.com/CCX/A834). In addition, variable transformations are detailed in **Table 1** (Supplementary Digital Content, http://links.lww.com/CCX/A852). Descriptive statistics included patient demographics, comorbidities, admission signs and symptoms, clinical signs at IMV commencement, and ICU management. Continuous variables were summarized as medians with interquartile ranges. Categorical variables were summarized 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% CIs 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-d IMV discharge) up to 28 days from commencement of IMV (13). Mortality and discharge were considered as competing events. Associations with each outcome were estimated using cause-specific Cox proportional hazard models. 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, chronic pulmonary disease), selected based on previous evidence approximately (2, 7, 10). 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. Log-2 transformations were applied to serum creatinine, lactate, $Paco_2$, and $Pao_2:Fio_2$ to resolve right-skewness in variables prior to inclusion as independent variables in each Cox model; a 1 unit increase in transformed variables therefore corresponded to a doubling in value on the original scale. The remaining variables were mean centered and appropriate scaled to improve interpretation of the estimated effect (Table 1, Supplementary Digital Content, http://links.lww.com/CCX/A852). The baseline hazard function was modeled on the calendar time scale stratified by geographic region (Africa, Asia, Australia/New Zealand, Europe, Latin America and the Caribbean, Northern America) to account for nonproportional effects (16).

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) (16). MICE is an iterative algorithm that 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 (13). 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 for Statistical Computing, Institute for Statistics and Mathematics, Vienna, Austria).

RESULTS

A total of 3,244 COVID-19 patients, enrolled at 132 collaborating sites across 32 countries, were screened for final analysis (**Fig. 1**). Among those patients, 2,234 (69%) received IMV and were included in the analysis, while 1,010 patients (31%) who never received IMV were excluded.

Patient Characteristics

In the studied cohort, the median age (IQR) was 59 years (49–68 yr), and patients were predominantly White (41%) and from Northern America (30%) (**Table 2**, Supplementary Digital Content, http://links.lww.com/CCX/A852). Hypertension, obesity, smoking, and diabetes were the most common comorbidities. The median time from onset of symptom to ICU admission was 8 days (IQR, 5–12 d), as was time from symptom onset to commencement of IMV (median, 8 d; IQR, 5–12 d). IMV was initiated upon ICU admission for 63% of the patients. At the time of IMV commencement (**Table 1**), median (IQR) creatinine and lactate were 1.0 mg/dL (0.7–1.4 mg/dL) and 1.4 mmol/L (1.0–2.1 mmol/L), respectively. Patients were severely hypoxemic, and their median (IQR) Pao_2/Fio_2 was 107 mm Hg (74–148 mm Hg), pH was 7.35 (7.28–7.42), and $Paco_2$ was 43.8 mm Hg (36.0–53.2 mm Hg). Patients presented with respiratory
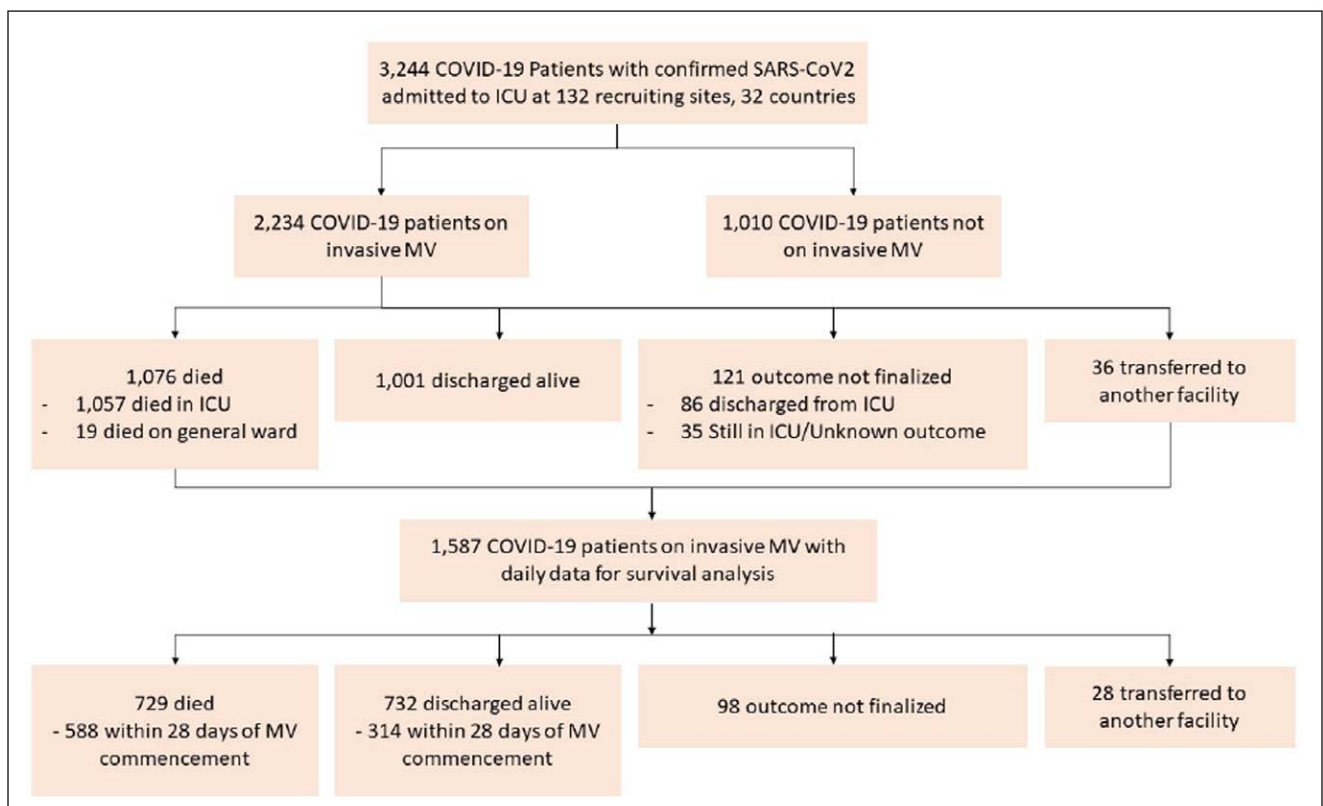

Figure 1. Flow of patient enrollment by the censor date of December 29, 2020. COVID-19 = coronavirus disease 2019, MV = mechanical ventilation, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

TABLE 1.
Clinical Characteristics Upon Commencement of Invasive Mechanical Ventilation

Characteristic	All Mechanically Ventilated Patients (*n* = 2,234)	Patients Included in Survival Analysis (*n* = 1,587)
Clinical signs and laboratory findings within 24 hr from commencement of IMV		
WBC count, $10^3/\mu L$: *n*; median (IQR)	1,504; 10.7 (7.2–14.9)	1,167; 10.6 (7.1–14.7)
Lymphocyte count, $10^3/\mu L$: *n*; median (IQR)	1,114; 0.8 (0.5–1.2)	890; 0.8 (0.5–1.1)
Neutrophils: lymphocyte ratio: *n*; median (IQR)	1,037; 11 (6–19)	832; 11 (6–19)
Temperature, °C: *n*; median (IQR)	1,096; 37 (36–38)	855; 37 (36–38)
Creatinine, mg/dL: *n*; median (IQR)	1,536; 1.0 (0.7–1.4)	1,205; 0.9 (0.7–1.4)
C-reactive protein level, mg/dL: *n*; median (IQR)	967; 86 (16–178)	819; 90 (18–183)
D-dimer, µg/mL: *n*; median (IQR)	623; 1.6 (0.8–3.9)	495; 1.4 (0.7–3.7)
Lactate, mmol/L: *n*; median (IQR)	1,286; 1.4 (1.0–2.1)	1,143; 1.4 (1.0–2.1)
Ferritin; ng/mL: *n*; median (IQR)	492; 2.7 (1.4–4.5)	398; 2.7 (1.5–5.4)
Interleukin-6; ng/L: *n*; median (IQR)	167; 95 (32–295)	156; 103 (33–313)
Gas exchange and level of support within 24 hr from commencement of IMV		
pH: *n*; median (IQR)	1,593; 7.35 (7.28–7.42)	1,260; 7.35 (7.28–7.43)
F_{IO_2}, mm Hg: *n*; median (IQR)	1,581; 0.80 (0.60–1.00)	1,254; 0.80 (0.60–1.00)
Pa_{O_2}/F_{IO_2}, mm Hg: *n*; median (IQR)	1,460; 107.07 (74.00–158.05)	1,211; 108.33 (74.85–157.50)
Pa_{CO_2}, mm Hg: *n*; median (IQR)	1,577; 43.80 (36.00–53.20)	1,245; 44.20 (36.90–53.60)
Static respiratory system compliance, mL/cm H_2O: *n*; median (IQR)	663; 33 (25–42)	571; 33 (26–42)
Plateau pressure, cm H_2O: *n*; median (IQR)	875; 25 (21–28)	755; 25 (21–28)
Driving pressure, cm H_2O: *n*; median (IQR)	872; 12 (10–15)	753; 12 (10–15)
Respiratory rate, breaths/min: *n*; median (IQR)	1,364; 22 (19–28)	1,023; 22 (18–27)
Positive end-expiratory pressure level, cm H_2O: *n*; median (IQR)	1,392; 12 (10–14)	1,066; 12 (10–14)
Minute ventilation, L/min: *n*; median (IQR)	1,033; 9 (8–11)	797; 9 (8–11)
Ventilatory ratio: *n*; median (IQR)	836; 0.73 (0.59–0.92)	675; 0.74 (0.60–0.93)
Heart rate, beats/min: *n*; median (IQR)	1,384; 98 (78–116)	1,019; 96 (76–114)
Mean arterial pressure, mm Hg: *n*; median (IQR)	1,679; 75 (64–89)	1,279; 74 (64–88)
Vasopressor/inotropic support, *n* (%)	939/1,726 (54)	732/1,300 (56)
Tracheostomy, *n* (%)	27/1,745 (2)	22/1,316 (2)

IMV = invasive mechanical ventilation, IQR = interquartile range.

Twenty-eight-day ventilator-free day (VFD) was calculated as following: VFDs = 0 if subject dies within 28 d of mechanical ventilation; VFDs = of −x if successfully liberated from ventilation × days after initiation; VFDs = 0 if the subject is mechanically ventilated for > 28 d.

Static respiratory system compliance was calculated as: tidal volume (mL)/(static airway plateau pressure−positive end-expiratory pressure [cm H_2O]).

Percentages are calculated for nonmissing data.

system compliance of 33 mL/cm H_2O (17–33) and were ventilated using PEEP of 12 cm H_2O (2, 9–12). Vasopressors were required in 54% of the patients. Common treatment strategies over the first 28 days included antibiotics (95%), neuromuscular blocking agents (74%), prone positioning (51%), corticosteroids (52%), and antivirals (49%) (**Table 2**).

In 1,587 patients with complete daily assessment, 588 patients died in hospital within 28 days of commencing IMV (37%), 28 patients (1.8%) were transferred to another hospital. At the study end date, outcomes of 98 patients (6.2%) 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

TABLE 2.
ICU Clinical Management Within the First 28 Days of ICU Admission

Characteristic	All Mechanically Ventilated Patients (*n* = 2,234)	Patients Included in Survival Analysis (*n* = 1,587)
Antibiotics, *n* (%)	2,098/2,203 (95)	1,514/1,565 (97)
Any antiviral, *n* (%)	890/1,822 (49)	591/1,286 (46)
Remdesivir, *n* (%)	281/1,205 (23)	177/867 (20)
Corticosteroids, *n* (%)	816/1,573 (52)	596/1,138 (52)
Continuous renal replacement therapy, *n* (%)	329/2,148 (15)	231/1,545 (15)
Vasoactive drugs, *n* (%)	1,263/2,118 (60)	913/1,527 (60)
Cardiac assist devices, *n* (%)	111/2,141 (5)	91/1,532 (6)
Extracorporeal membrane oxygenation, *n* (%)	499/2,202 (23)	350/1,577 (22)
Prone positioning, *n* (%)	1,129/2,204 (51)	927/1,577 (59)
Use of inhaled nitric oxide, *n* (%)	251/2,203 (11)	198/1,576 (13)
Use of neuromuscular blockade, *n* (%)	1,627/2,198 (74)	1,275/1,575 (81)
Recruitment maneuvers, *n* (%)	541/2,042 (26)	483/1,472 (33)
Tracheostomy inserted, *n* (%)	366/2,166 (17)	304/1,576 (19)
28-d ventilator-free day, d: *n*; median (IQR)	2,082; 0 (0–13)	1,471; 0 (0–13)
Days from ICU admission to death: *n*; median (IQR)	1,076; 13 (5–23)	729; 14 (7–24)
Days from IMV commencement to death: *n*; median (IQR)	1,076; 12 (6–23)	729; 13 (7–24)
Duration of ICU stay (died), d: *n*; median (IQR)	1,076; 13 (5–23)	729; 14 (6–23)
Duration of ICU stay (discharged), d: *n*; median (IQR)	1,001; 20 (12–34)	732; 20 (13–34)
Days from hospital admission to IMV commencement: *n*; median (IQR)	2,231; 0 (0–3)	1,585; 0 (0–3)
Days from ICU admission to IMV commencement: *n*; median (IQR)	2,234; 0 (0–0)	1,587; 0 (0–0)
Days from first reported symptom to IMV commencement: *n*; median (IQR)	2,169; 8 (5–12)	1,545; 8 (5–12)
Commenced IMV on ICU admission, *n* (%)	1,413/2,234 (63)	1,039/1,587 (65)

IMV = invasive mechanical ventilation, IQR = interquartile range.
Twenty-eight-day ventilator-free day (VFD) was calculated as following: VFDs = 0 if subject dies within 28 d of mechanical ventilation; VFDs = of −x if successfully liberated from ventilation × days after initiation; VFDs = 0 if the subject is mechanically ventilated for > 28 d. Percentages are calculated for nonmissing data.

death was 14 days (IQR, 6–23 d) from ICU admission. For patients with a reported cause of death (*n* = 675), respiratory failure was the most common (*n* = 268; 40%), while other causes included multiple organ failure (*n* = 233; 35%), septic shock (*n* = 65; 10%), cardiac failure (*n* = 37; 5%), cerebrovascular accident (*n* = 19; 3%), hemorrhagic shock (*n* = 6; 1%), or other causes (*n* = 47; 7%).

Dynamics of Daily Clinical Parameters

Daily averages for clinical variables, including arterial blood gases, are depicted in **Figure 2**. There was a clear improvement in the dynamics of Pao_2/Fio_2 (from 131.1 ± 2.5 mm Hg upon start IMV to 173.9 ± 9.1 mm Hg at 28 d), pH (from 7.34 ± 0.003 to 7.40 ± 0.01), serum creatinine (from 1.38 ± 0.04 to 1.17 ± 0.01 mg/dL), and lactate (from 2.03 ± 0.07 to 1.18 ± 0.09 mmol/L). Differently, trajectories of $Paco_2$ and mean arterial pressure (MAP) were more convoluted, with early worsening during the first days of IMV and delayed improvement. **Figure 1** (Supplementary Digital Content, http://links.lww.com/CCX/A852) 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
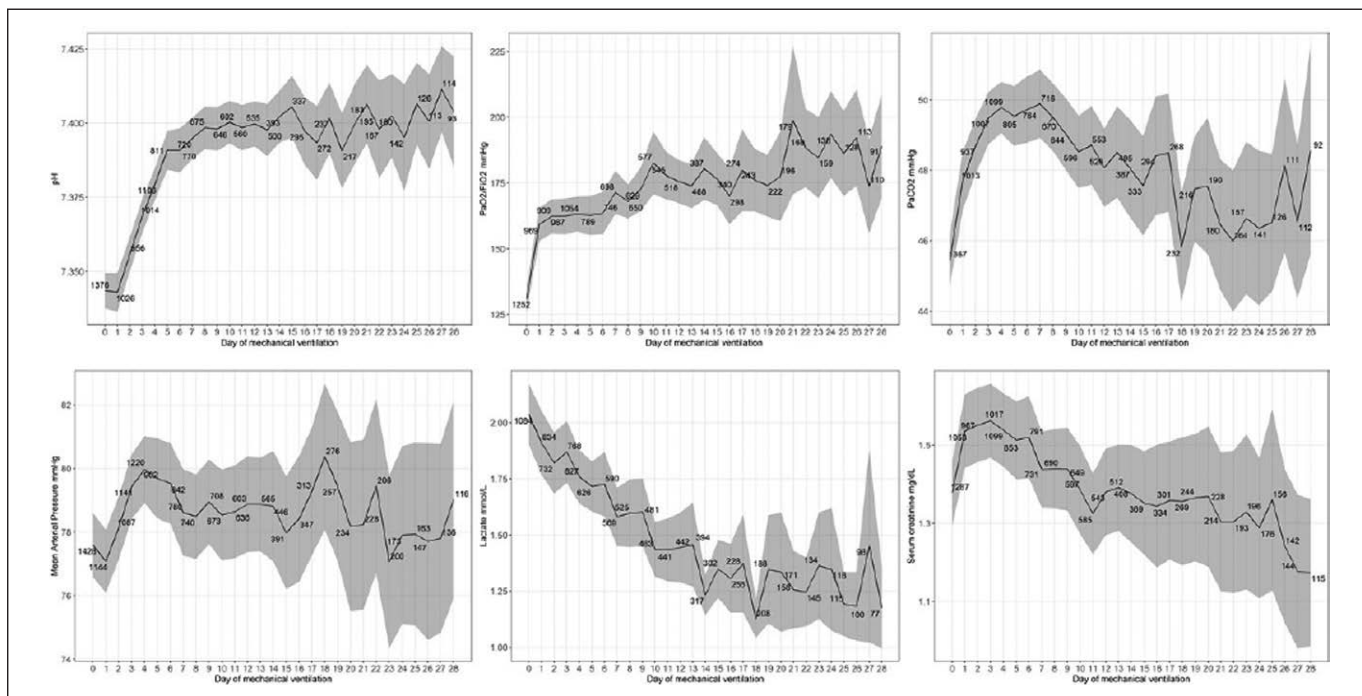
Figure 2. Dynamics of time-dependent parameters included in survival analysis. Average daily parameters collected during the first 28 d following commencement of mechanical ventilation. Data are reported as unadjusted means and 95% CIs.

separately in **Figures 2** and **3** (Supplementary Digital Content, http://links.lww.com/CCX/A852). There was an apparent discrepancy between survivors and nonsurvivors in the applied FIO_2, while tidal volume and PEEP were similar throughout the assessment period.

Primary Outcome

Time-to-event analysis (**Fig. 3A**) identified age (hazard ratio [HR], 1.26 per 10-yr increase in age; 95% CI, 1.16–1.37; $p < 0.001$) and PEEP upon commencement of IMV (HR, 0.81 per 5 cm H_2O increase; 95% CI, 0.67–0.97; $p = 0.02$) as statistically significant associations with of the hazard of 28-day IMV mortality. Among time-dependent variables, an increase in serum creatinine (HR, 1.28 per doubling; 95% CI, 1.15–1.41; $p < 0.001$), lactate (HR, 1.22 per doubling; 95% CI, 1.11–1.34; $p < 0.001$), and $Paco_2$ (HR, 1.63 per doubling; 95% CI, 1.19–2.25; $p = 0.003$) increased the hazards of 28-day IMV mortality. Conversely, an increase in pH (HR, 0.89 per 0.1 increase; 95% CI, 0.78–1; $p = 0.041$), Pao_2/FIO_2 (HR, 0.58 per doubling; 95% CI, 0.52–0.66; $p < 0.001$), and MAP (HR, 0.92 per 10 mm Hg increase; 95% CI, 0.88–0.97; $p < 0.003$) decreased the hazards of 28-day IMV mortality. **Figure 4A** depicts variability in the stratified baseline survival function for the death, by geographic regions.

Secondary Outcomes

Estimated HRs for the variables as mentioned above and the hazard of discharge are reported in **Figure 3B**. Results indicated that older age (HR, 0.87 per 10-yr increase in age; 95% CI, 0.79–0.96; $p = 0.004$), increased creatinine (HR, 0.84 per doubling; 95% CI, 0.73–0.96; $p = 0.01$), and $Paco_2$ (HR, 0.6 per doubling; 95% CI, 0.38–0.94; $p = 0.027$) decreased the hazards of 28-day IMV discharge, while higher Pao_2/FIO_2 (HR, 1.69 per doubling; 95% CI, 1.45–1.96; $p < 0.001$) increased the hazard. Similar to mortality, stratification of the baseline survival function for the hazards of discharge revealed nonproportional effects between geographic regions (**Fig. 4B**).

Tracheostomy was carried out in 304 of 1,576 patients (19%) included in the survival analysis (Table 2). During hospitalization, the most common complications in the mechanically ventilated population were cardiac arrhythmia (23%), pleural effusion (19%), and cardiac arrest (21%) (**Table 3**, Supplementary Digital Content, http://links.lww.com/CCX/A852). The median duration of IMV was 14 days (IQR, 7–25 d). Among patients in whom final disposition was available within 28 days of IMV, the median time from ICU to death was 14 days (IQR, 7–22 d). Among patients known to be discharged alive from the hospital, the median duration of ICU admission was 20 days (IQR, 13–34 d).
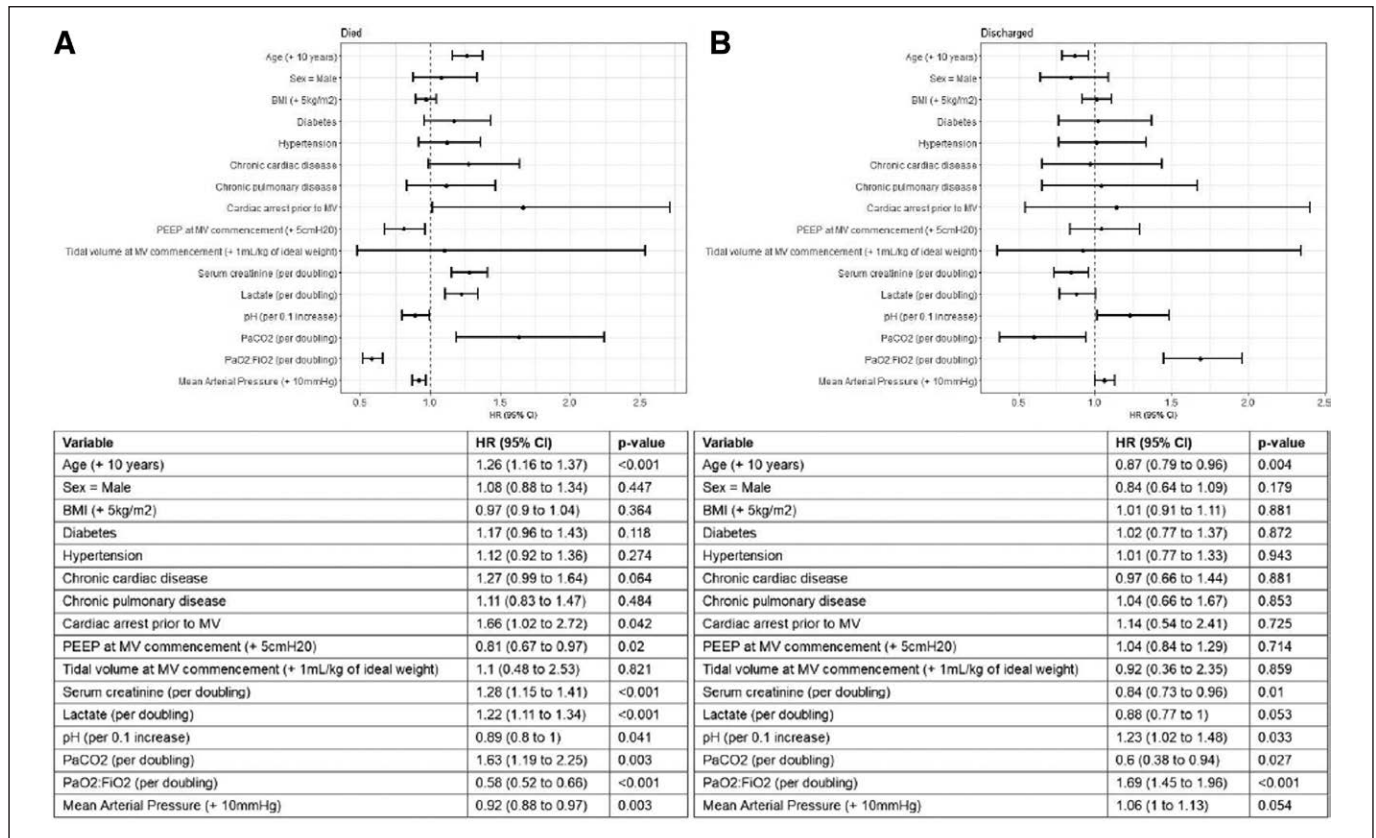
Variable	HR (95% CI)	p-value
Age (+ 10 years)	1.26 (1.16 to 1.37)	<0.001
Sex = Male	1.08 (0.88 to 1.34)	0.447
BMI (+ 5kg/m2)	0.97 (0.9 to 1.04)	0.364
Diabetes	1.17 (0.96 to 1.43)	0.118
Hypertension	1.12 (0.92 to 1.36)	0.274
Chronic cardiac disease	1.27 (0.99 to 1.64)	0.064
Chronic pulmonary disease	1.11 (0.83 to 1.47)	0.484
Cardiac arrest prior to MV	1.66 (1.02 to 2.72)	0.042
PEEP at MV commencement (+ 5cmH20)	0.81 (0.67 to 0.97)	0.02
Tidal volume at MV commencement (+ 1mL/kg of ideal weight)	1.1 (0.48 to 2.53)	0.821
Serum creatinine (per doubling)	1.28 (1.15 to 1.41)	<0.001
Lactate (per doubling)	1.22 (1.11 to 1.34)	<0.001
pH (per 0.1 increase)	0.89 (0.8 to 1)	0.041
PaCO2 (per doubling)	1.63 (1.19 to 2.25)	0.003
PaO2:FiO2 (per doubling)	0.58 (0.52 to 0.66)	<0.001
Mean Arterial Pressure (+ 10mmHg)	0.92 (0.88 to 0.97)	0.003

Variable	HR (95% CI)	p-value
Age (+ 10 years)	0.87 (0.79 to 0.96)	0.004
Sex = Male	0.84 (0.64 to 1.09)	0.179
BMI (+ 5kg/m2)	1.01 (0.91 to 1.11)	0.881
Diabetes	1.02 (0.77 to 1.37)	0.872
Hypertension	1.01 (0.77 to 1.33)	0.943
Chronic cardiac disease	0.97 (0.66 to 1.44)	0.881
Chronic pulmonary disease	1.04 (0.66 to 1.67)	0.853
Cardiac arrest prior to MV	1.14 (0.54 to 2.41)	0.725
PEEP at MV commencement (+ 5cmH20)	1.04 (0.84 to 1.29)	0.714
Tidal volume at MV commencement (+ 1mL/kg of ideal weight)	0.92 (0.36 to 2.35)	0.859
Serum creatinine (per doubling)	0.84 (0.73 to 0.96)	0.01
Lactate (per doubling)	0.88 (0.77 to 1)	0.053
pH (per 0.1 increase)	1.23 (1.02 to 1.48)	0.033
PaCO2 (per doubling)	0.6 (0.38 to 0.94)	0.027
PaO2:FiO2 (per doubling)	1.69 (1.45 to 1.96)	<0.001
Mean Arterial Pressure (+ 10mmHg)	1.06 (1 to 1.13)	0.054

Figure 3. Association of clinical variables with major outcomes. Cause-specific Cox proportional hazards modeling to estimate the hazards of death (**A**) or discharge (**B**), up to 28 d following commencement of mechanical ventilation (MV). The model considered time-independent variables: age, sex, body mass index (BMI), diabetes, hypertension, chronic cardiac disease, chronic pulmonary disease, cardiac arrest before invasive MV, highest positive end-expiratory pressure (PEEP) within 24 hr from commencing of MV (mean centered at 10 cm H_2O and scaled by 5 cm H_2O), and tidal volume upon commencement of MV. The model also included time-dependent covariates: serum creatinine, serum lactate, pH, $Paco_2$, Pao_2/Fio_2, and mean arterial pressure. Covariate effects are presented as hazard ratios (HRs) and 95% CI.

DISCUSSION

The present international multicenter cohort study from six continents constitutes the most extensive epidemiological investigation of IMV patients with COVID-19. The study enabled delineation of the clinical course during the first 28 days, corroborating age and accounting for longitudinal changes in pH, Pao_2/Fio_2, MAP, $Paco_2$, lactate, and creatinine when assessing associations with mortality.

Reported mortality rates in mechanical ventilated COVID-19 patients have varied (2, 4, 8, 12, 34). 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, 17, 24, 35–37). In our study, among 1,587 ventilated patients, we reported an overall 28-day IMV mortality of 37%, similar to rates from the Netherlands (10) and Spain (7) and lower than figures from United Kingdom (18). Given the observational nature of our study, extrapolations on the mortality figures can only be speculative. Nevertheless, our findings should be interpreted in the context of the enrollment period since early dismal survival might have been counterbalanced by lower mortality rates later in the pandemic. In addition, in comparison with previous single-country observational studies (19, 20), corticosteroids were used in fewer patients, due to either differences in practice among geographical regions or inclusion of data acquired early in the pandemic.

In line with previous reports (8, 10, 12, 21, 22) that found older populations at the highest risk of mortality, age shared a positive association with the hazard of 28-day IMV mortality. Of note, we report a slightly younger population than previous investigations (7, 21, 23, 24), possibly because, in 2020, IMV was
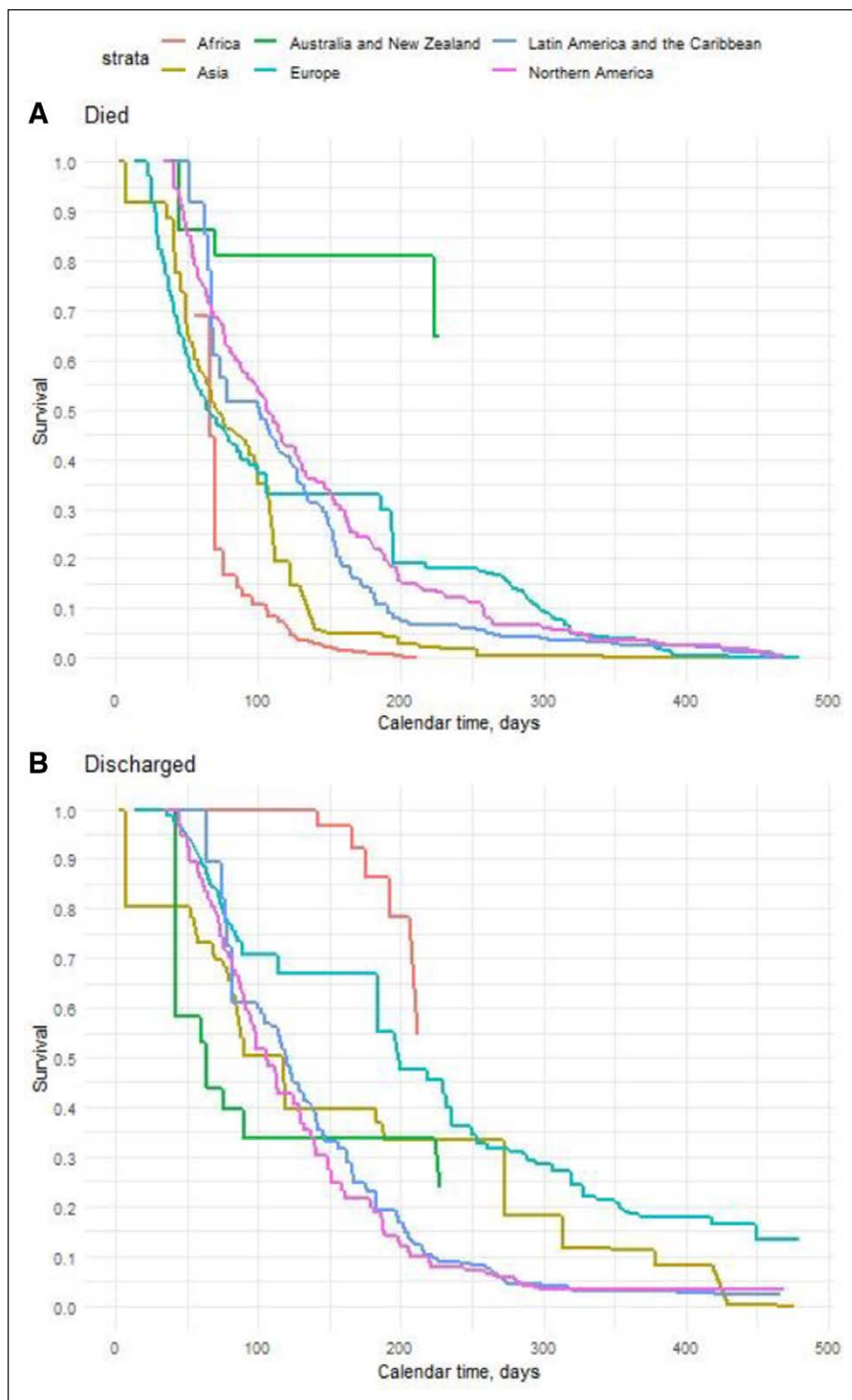
Figure 4. Geographical differences of major outcomes. Baseline survival curves by region (Africa, Asia, Australia/New Zealand, Europe, Latin America, and the Caribbean, Northern America) for in-hospital mortality (**A**) and discharge alive from the hospital (**B**). Baseline stratification in cause-specific Cox models accounted for nonproportional effects attributable to geographic region. Baseline hazards were modeling on the calendar time scale, with independent right-censoring applied to outcomes censored up to 28 d from commencement of mechanical ventilation.

primarily reserved for younger patients in some of the geographical regions comprising our network. Irrespectively, it is still not fully elucidated why COVID-19 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 (25). Among the other time-independent factors, only baseline PEEP was found to reduce mortality hazards in our analyses, in contrast with previous evidence associating higher PEEP with mortality (21). These findings emphasize the challenges in setting the optimal PEEP in COVID-19 patients (26), particularly in light of early controversial reports on heterogeneous static respiratory system compliance in infected patients (27). Nevertheless, potential dissimilarities in ventilatory management across different geographical regions should be considered to cautiously infer from these results.

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 modeling of 28-day IMV mortality to assess the impact of time-dependent clinical variables, considering the competing risk of ICU discharge. Indeed, previous investigations (7, 8, 10, 18, 21, 28) focused on risk factors for mortality appraised at a fixed time point,

limiting inferences on variables that dynamically change during IMV. Zanella et al (9) specifically focused on temporal trends of clinical parameters and mortality, but in a mixed Italian population of COVID-19 patients, requiring in 21% of the cases noninvasive ventilation. Conversely, our investigation focused on patients on IMV and by incorporating geographic region stratification in modeling, we found substantial differences in survival across the globe, in line with the most recent reports from low-middle-income countries (29). 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 Pao_2/Fio_2 during the first 24 hours of IMV, similarly to previous evidence (7, 9), and potentially related to the prompt pronation, neuromuscular blocking agents, and high PEEP after commencement of IMV. However, the data also emphasize potential long-term respiratory dysfunction since moderate hypoxemia persisted throughout the assessment period. The study also identified the association of $Paco_2$ with the hazard of death, which could be related to higher lung disease severity, resulting dead space, and variations in ventilatory strategies. Furthermore, an increase in $Paco_2$ during the initial days of IMV was evident in this cohort, possibly related to the initial hypercatabolic state, inadequate ventilatory management, micro or macrovascular pulmonary thrombosis (30–32), or simply to respiratory fatigue, given that on average, patients were intubated 8 days from symptom onset. Previous studies (8–10, 18, 21) 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 hours from ICU admission was an early predictor of mortality (18). 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 hemodynamic instability and lactic acidosis, and multiple organ failure in the most severe cases. Thus, our findings imply that trends in hemodynamic impairment could be valuable in risk stratification. However, heterogeneities in local management of vasopressors, which were administered in 56% of our studied population, could have also played a role in mortality risk. In contrast with previous findings (9, 10), temporal change in pH was associated

with mortality risk. On average, pH normalization was achieved within 1 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 studied patients 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 2 receptor is critical for SARS-CoV-2 cell entry and widely expressed in the kidneys (33, 38), but IMV and septic shock might have also contributed to kidney injury.

In efforts to inform the field as to characteristics of COVID-19 infection, early publications limited to small-patient-series or single-country experiences have appeared. These articles reported conflicting findings related to center-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. Further analyses of the COVID-19–CCC dataset are focusing on the impact of treatments on mortality, specifically in subpopulations admitted to ICUs after the early phase of the pandemic. 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, several 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 corticosteroids must be performed with caution (39, 40). Given that the analyses selectively focused on a subset of variables, other unmeasured factors could have biased our inferences about mortality risks. In addition, the 28-day follow-up could have biased results toward early mortality. Irrespectively, we precisely aimed at identifying key associations affecting mortality during the period of IMV, which in COVID-19 patients is approximately 10 days (10, 34, 41). Last, approximately 20% of the analyzed patients received extracorporeal membrane oxygenation, which could have interfered on the association between arterial blood gas analysis parameters and mortality risk.

CONCLUSIONS

This study represents the most extensive and comprehensive international cohort analyses of patient characteristics associated with mortality in COVID-19 patients requiring IMV. Age and commonly tested parameters in COVID-19 patients on IMV, including pH, blood gases, MAP, serum lactate, and creatinine, were associated with increased mortality hazard. 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.

ACKNOWLEDGMENTS

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