

## SUPPLEMENTAL DIGITAL CONTENT

### **Assessment of 28-day in-hospital mortality in mechanically ventilated patients with COVID-19: An international cohort study**

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## **Statistical analysis**

For each patient, data collection began at the time of hospital admission, using the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC)(47) and the Short PeRiod IncideNce sTudy of Severe Acute Respiratory Infection (SPRINT-SARI)(48) 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 (18). 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, chronic pulmonary disease), selected based on previous evidence (8, 11, 12). Continuous variables (pH, PaCO<sub>2</sub>, PaO<sub>2</sub>:FiO<sub>2</sub>, lactate, creatinine and 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 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<sub>2</sub> and PaO<sub>2</sub>:FiO<sub>2</sub> 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 centred and appropriate scaled to improve interpretation of the estimated effect (Supplemental Digital Content Table 1). The baseline hazard function was modelled 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 non-proportional effects (19).

### *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) (19). 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 (15). 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).

**Table 1 Supplemental Digital Content: Definitions of independent variables considered in cause-specific Cox regression models**

<b>Variable</b>	<b>Definition including details of variable transformation</b>
<b>Time-independent variables</b>	
Age (+ 10 years)	Patient age in years; mean centered at 60 years and scaled by 10 years
Sex = Male	Male
BMI (+ 5kg/m <sup>2</sup> )	Body mass index; mean centered at 25 kg/m <sup>2</sup> and scaled by 5kg/m <sup>2</sup>
Diabetes	Diabetes reported at hospital admission (Yes)
Hypertension	Hypertension reported at hospital admission (Yes)
Chronic cardiac disease	Chronic cardiac disease (not hypertension) reported at hospital admission (Yes)
Chronic pulmonary disease	Chronic pulmonary disease (not asthma) reported at hospital admission (Yes)
Cardiac arrest prior to MV	Patient had a cardiac arrest upon commencement of mechanical ventilation (Yes)
PEEP at MV commencement (+ 5cmH <sub>2</sub> O)	Highest Positive End Expiratory Pressure within 24 hours from commencing mechanical ventilation; mean centered at 10 cmH <sub>2</sub> O and scaled by 5cmH <sub>2</sub> O
Tidal volume at MV commencement (+ 1ml/kg of ideal weight)	Highest tidal volume within 24 hours of commencing mechanical ventilation
<b>Time dependent variables</b>	
Serum creatinine (per doubling)	Measured serum creatinine within 00:00 to 24:00hr on day of assessment; log <sub>2</sub> transformed
Lactate (per doubling)	Measured lactate within 00:00 to 24:00hr on day of assessment; log <sub>2</sub> transformed
pH (per 0.1 increase)	Measured arterial pH within 00:00 to 24:00hr on day of assessment; mean centered at 7.4 and scaled by 0.1
PaCO <sub>2</sub> (per doubling)	Measured worst arterial partial pressure of carbon dioxide within 00:00 to 24:00hr on day of assessment; log <sub>2</sub> transformed
PaO <sub>2</sub> :FiO <sub>2</sub> (per doubling)	Ratio of measured arterial partial pressure of oxygen to inspiratory fraction of oxygen within 00:00 to 24:00hr on day of assessment; log <sub>2</sub> transformed
Mean Arterial Pressure (+10mmHg)	Mean arterial pressure measured within 00:00 to 24:00hr on day of assessment; mean centered at 80mmHg and scaled by 10mmHg

**Table 2 Supplemental Digital Content: Demographic and clinical characteristics upon ICU admission**

Characteristic	All mechanically ventilated patients (n=2,234)	Patients included in survival analysis (n = 1,587)
Age, years: n; Median (IQR)	2234; 59(49 to 68)	1587; 60(50 to 68)
Female: n (%)	724/2234 (32)	485/1587 (31)
Ethnicity: n (%)		
<i>Aboriginal</i>	27/2031 (1)	14/1430 (1)
<i>Arab</i>	82/2031 (4)	51/1430 (4)
<i>Black</i>	207/2031 (10)	138/1430 (10)
<i>East Asian</i>	98/2031 (5)	70/1430 (5)
<i>Latin American</i>	390/2031 (19)	271/1430 (19)
<i>South Asian</i>	198/2031 (10)	81/1430 (6)
<i>West Asian</i>	13/2031 (1)	12/1430 (1)
<i>White</i>	836/2031 (41)	690/1430 (48)
<i>Other</i>	180/2031 (9)	103/1430 (7)
Geographic region: n (%)		
<i>Africa</i>	112/2234 (5)	103/1587 (6)
<i>Asia</i>	402/2234 (18)	186/1587 (12)
<i>Australia and New Zealand</i>	37/2234 (2)	25/1587 (2)
<i>Europe</i>	650/2234 (29)	582/1587 (37)
<i>Latin America</i>	365/2234 (16)	270/1587 (17)
<i>Northern America</i>	668/2234 (30)	421/1587 (27)
Healthcare or Lab Worker: n (%)	105/2086 (5)	70/1477 (5)
Comorbidities: n (%)		
<i>Smoking</i>	534/1520 (35)	365/1080 (34)
<i>Obese</i>	782/2160 (36)	577/1554 (37)
<i>Hypertension</i>	1117/2169 (51)	831/1560 (53)
<i>Chronic Kidney Disease</i>	202/2157 (9)	125/1547 (8)
<i>Chronic Cardiac Disease</i>	322/2151 (15)	236/1544 (15)
<i>Diabetes</i>	690/2124 (32)	483/1535 (31)
<i>Malignant neoplasm</i>	100/2153 (5)	75/1548 (5)
<i>Chronic pulmonary disease</i>	196/2155 (9)	139/1548 (9)
<i>Severe liver disease</i>	108/2193 (5)	67/1577 (4)
Body Mass Index (BMI): n; Median (IQR)	1896; 28.8(25.4 to 33.6)	1393; 29.0(25.9 to 33.7)
APACHE II: n; Median (IQR)	997; 17.0(11.0 to 23.0)	791; 17.0(11.0 to 24.0)
SOFA: n; Median (IQR)	1042; 6.0(4.0 to 8.0)	855; 6.0(4.0 to 9.0)
WBC count, 10 <sup>3</sup> /μL: n; Median (IQR)	1498; 10.1(6.9 to 14.3)	1130; 10.1(6.9 to 14.2)
Lymphocyte count, 10 <sup>3</sup> /μL: n; Median (IQR)	1170; 0.8(0.5 to 1.1)	909; 0.7(0.5 to 1.1)
Neutrophils: Lymphocyte ratio: n; Median (IQR)	1085; 10.8(6.1 to 18.4)	848; 10.8(6.2 to 18.4)
Temperature, °C: n; Median (IQR)	1101; 36.9(36.0 to 37.7)	824; 36.9(36.0 to 37.7)
Creatinine, mg/dL: n; Median (IQR)	1534; 1.0(0.7 to 1.4)	1161; 1.0(0.7 to 1.4)
C-reactive protein level, mg/dL: n; Median (IQR)	1051; 87(16 to 178)	847; 88(17 to 181)
D-dimer, mcg/mL: n; Median (IQR)	676; 1(1 to 4)	526; 1(1 to 4)
Lactate, mmol/L: n; Median (IQR)	1276; 1.5(1.0 to 2.1)	1064; 1.4(1.0 to 2.0)
Ferritin, ng/mL: n; Median (IQR)	541; 2.7(1.3 to 4.5)	425; 2.8(1.5 to 5.0)
IL-6, ng/L: n; Median (IQR)	180; 90(41 to 236)	158; 91(43 to 244)

**Table 2 Supplemental Digital Content caption**

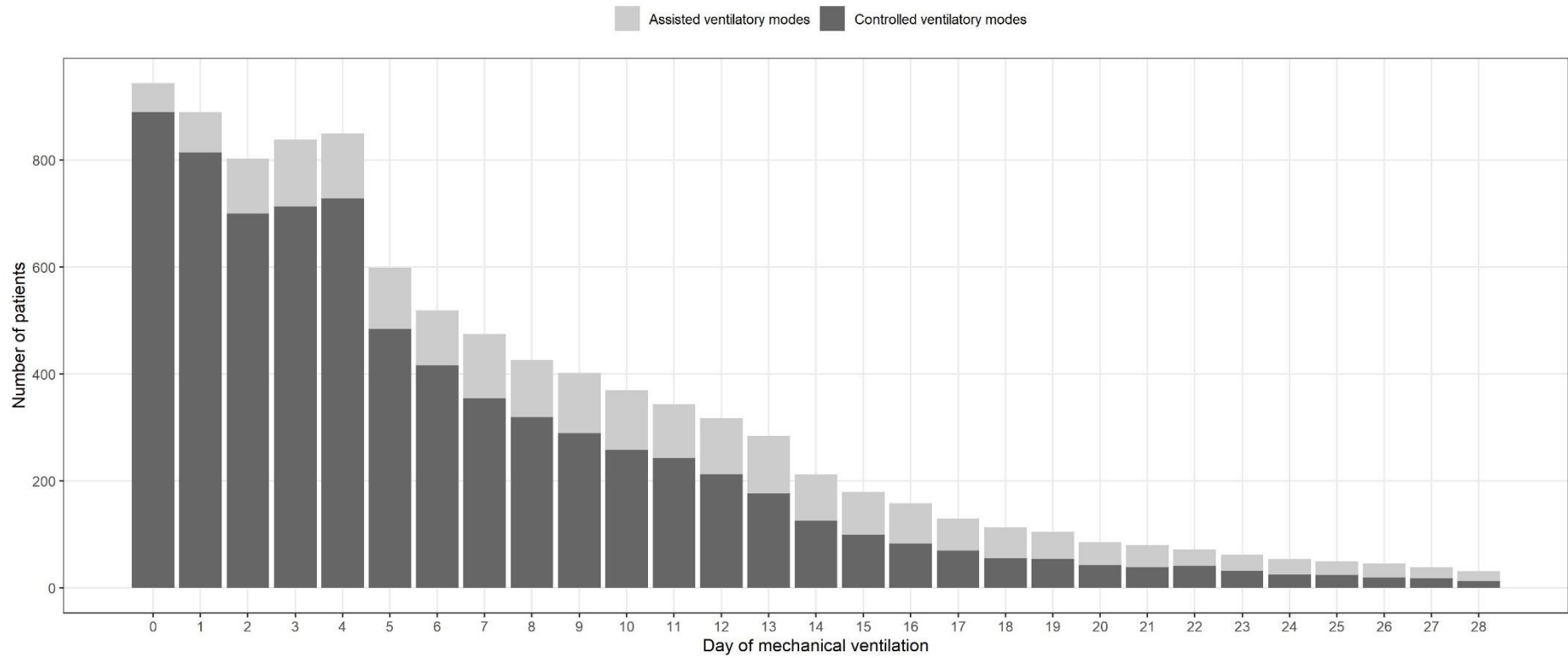
Percentages are calculated for non-missing data. BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II score; SOFA, Sequential Organ Failure Assessment Score; WBC, white blood cell count; CRP, c-reactive protein; IL-6, interleukin 6.

**Table 3 Supplemental Digital Content: Cardio-pulmonary complications**

Complication at any time during hospitalization n (%)	All mechanically ventilated patients (n=2,234)	Patients included in survival analysis (n = 1,587)
Cardiac Arrhythmia	479/2078 (23)	364/1480 (25)
Pleural Effusion	381/2054 (19)	299/1461 (20)
Cardiac Arrest	439/2090 (21)	236/1486 (16)
Deep Vein Thrombosis	39/513 (8)	31/375 (8)
Pneumothorax	212/2089 (10)	161/1485 (11)
Pulmonary Embolism	116/1828 (6)	91/1259 (7)
Heart Failure	99/2049 (5)	67/1457 (5)
Cardiac Ischemia	78/2048 (4)	52/1457 (4)
Cardiomyopathy	46/1799 (3)	35/1239 (3)
Cryptogenic organizing pneumonia	46/2028 (2)	38/1441 (3)
Myocardial Infarction	45/1805 (2)	30/1243 (2)
Bronchiolitis	28/2029 (1)	24/1442 (2)
Myocarditis/Pericarditis	44/1804 (2)	27/1243 (2)
Endocarditis	9/1803 (0)	9/1242 (1)



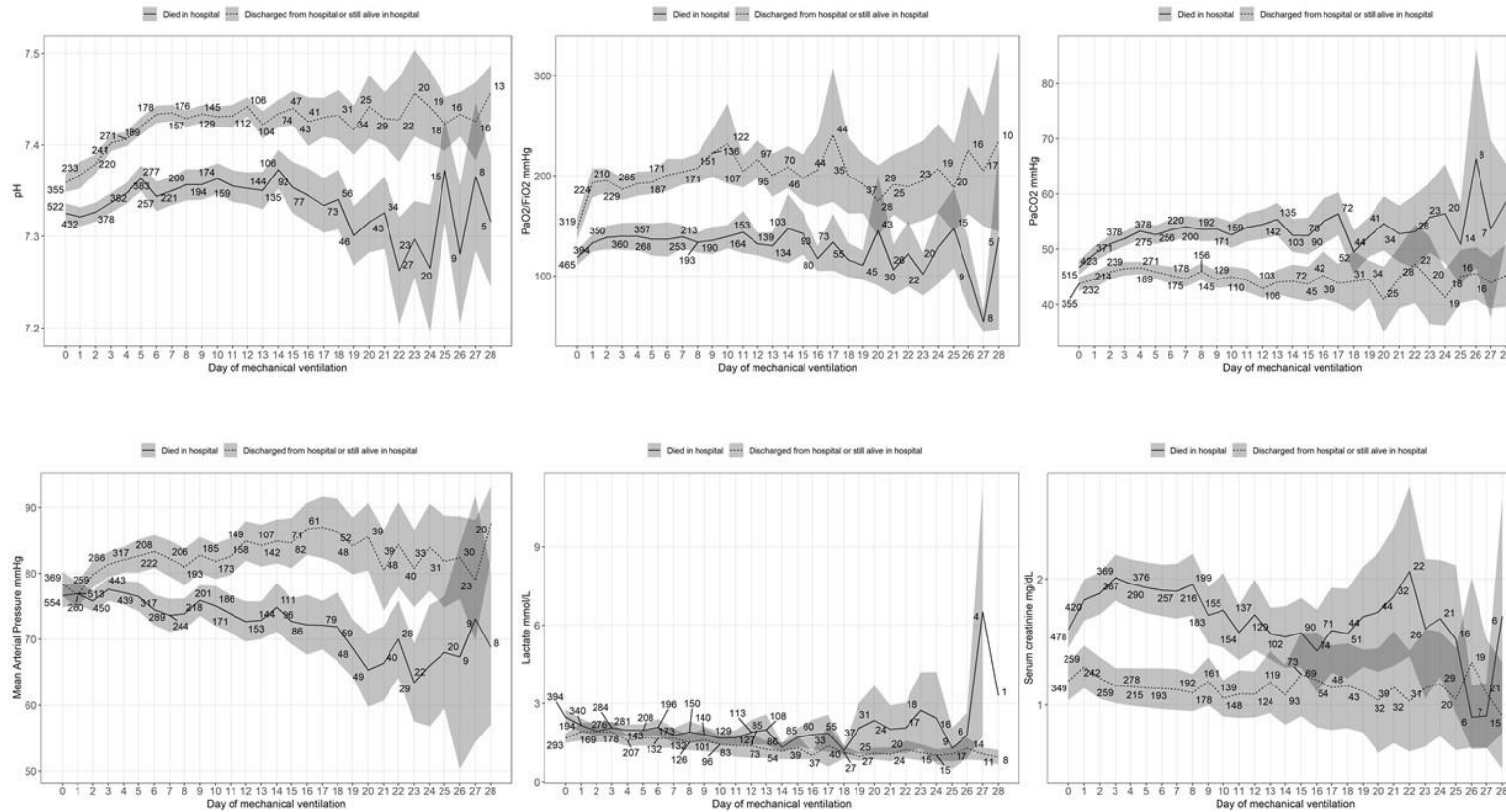
**Figure 1 Supplemental Digital Content**



**Figure 1 Supplemental Digital Content Caption**

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.

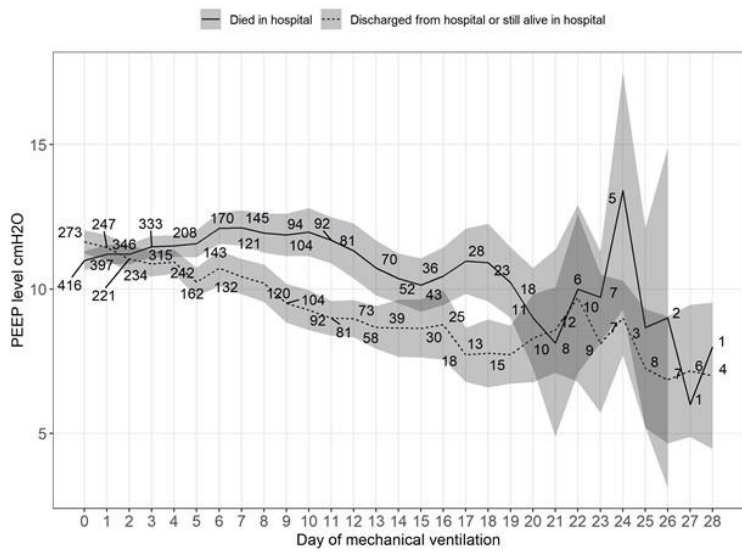
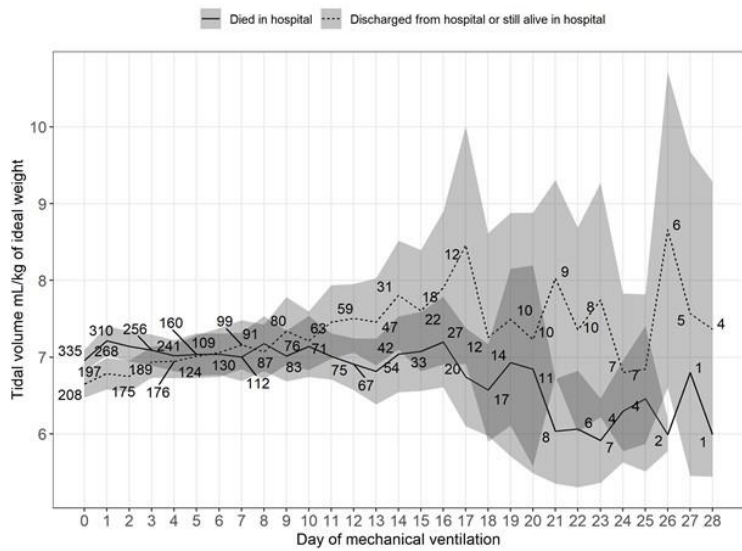
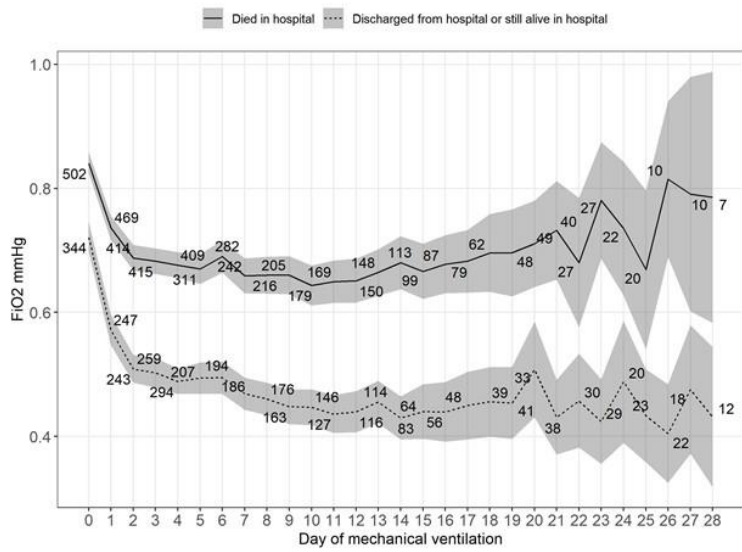
## Figure 2 Supplemental Digital Content



## Figure 2 Supplemental Digital Content Caption

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 3 Supplemental Digital Content**



### **Figure 3 Supplemental Digital Content Caption**

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. Of note, inspiratory fraction of oxygen and tidal volume data from patient while on extracorporeal membrane oxygenation were excluded. FiO<sub>2</sub> or the inspiratory fraction of oxygen; PEEP or the positive end-expiratory pressure.