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# Time course of risk factors associated with mortality of 1260 critically ill patients with COVID-19 admitted to 24 Italian intensive care units

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## Abstract

**Purpose:** To evaluate the daily values and trends over time of relevant clinical, ventilatory and laboratory parameters during the intensive care unit (ICU) stay and their association with outcome in critically ill patients with coronavirus disease 19 (COVID-19).

**Methods:** In this retrospective–prospective multicentric study, we enrolled COVID-19 patients admitted to Italian ICUs from February 22 to May 31, 2020. Clinical data were daily recorded. The time course of 18 clinical parameters was evaluated by a polynomial maximum likelihood multilevel linear regression model, while a full joint modeling was fit to study the association with ICU outcome.

**Results:** 1260 consecutive critically ill patients with COVID-19 admitted in 24 ICUs were enrolled. 78% were male with a median age of 63 [55–69] years. At ICU admission, the median ratio of arterial oxygen partial pressure to fractional inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ ) was 122 [89–175] mmHg. 79% of patients underwent invasive mechanical ventilation. The overall mortality was 34%. Both the daily values and trends of respiratory system compliance,  $\text{PaO}_2/\text{FiO}_2$ , driving pressure, arterial carbon dioxide partial pressure, creatinine, C-reactive protein, ferritin, neutrophil, neutrophil–lymphocyte ratio, and platelets were associated with survival, while for lactate, pH, bilirubin, lymphocyte, and urea only the

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daily values were associated with survival. The trends of PaO<sub>2</sub>/FiO<sub>2</sub>, respiratory system compliance, driving pressure, creatinine, ferritin, and C-reactive protein showed a higher association with survival compared to the daily values.

**Conclusion:** Daily values or trends over time of parameters associated with acute organ dysfunction, acid–base derangement, coagulation impairment, or systemic inflammation were associated with patient survival.

**Keywords:** COVID-19, Intensive care unit, Mortality, Predictors, Time course, Longitudinal models

## Introduction

The coronavirus disease 2019 (COVID-19) was firstly diagnosed in December 2019 in Wuhan (China) and then quickly evolved into a pandemic.

The clinical spectrum of COVID-19 ranges from an asymptomatic condition to a severe and critical disease [1].

Multicentric case series show that between 5 and 32% of the patients hospitalized for COVID-19 need intensive care unit (ICU) admission [2–5], mainly for acute hypoxemic respiratory failure. Indeed, acute respiratory distress syndrome (ARDS) is diagnosed in 40–96% of the ICU patients [2, 3, 6–8] and 30–88% of them need invasive mechanical ventilation (IMV) [1, 4, 6, 8, 9]. Most ICU patients are males affected by obesity, hypertension, cardiovascular diseases, and diabetes [2, 4–8].

The ICU mortality reported ranges from 16 to 78% [3, 6–10] according to patient and healthcare system characteristics and the percentage of patients still in ICU at the end of the follow-up. Notably, the ICU mortality of patients receiving IMV is consistently higher, reaching values up to 88% [11].

To date, few large multicentric studies have analyzed the clinical and laboratory parameters at ICU admission as independent predictors for mortality of critically ill patients [8, 12], showing significant variability among the different series. Our group [5] showed in a large cohort of patients that older age, male gender, history of chronic pulmonary disease, and the need for IMV are independent predictors for ICU mortality.

Since critically ill patients with COVID-19 usually require prolonged IMV and ICU stay [5], we hypothesized that the temporal trends of the clinical and laboratory parameters could predict ICU outcomes even more accurately than values at the single point of admission. Indeed, a recently published study on mechanically ventilated patients with COVID-19 showed the importance of analyzing longitudinal data to assess patient prognosis more accurately [13].

Based on available data regarding the target organs of COVID-19, we analyzed the trends of clinical parameters reflecting the cardiac, pulmonary, kidney, liver, coagulation function, and inflammatory response.

## Take-home message

Reported mortality of critically ill patients suffering from COVID-19 is consistently high. The trends over the entire ICU stay of driving pressure, compliance of respiratory system, creatinine, C-reactive protein, and ferritin were more predictive of mortality compared with the single daily values.

The present large multicentric study evaluates the trends over time of relevant clinical and laboratory parameters and ventilator settings during the entire ICU stay and their association with outcome in critically ill patients with COVID-19 admitted to 24 Italian ICUs during the first three months of the pandemic.

## Materials and methods

### Study design and population

A COVID-19 retrospective–prospective multicentric registry was set up at the end of February 2020, at the beginning of the pandemic, including most ICUs in Northern Italy. The registry was approved by the institutional review board of each hospital and was registered on clinicaltrials.gov (NCT04388670).

For this study, all patients with laboratory-confirmed SARS-CoV-2 infection admitted to the ICU of the participant institutions (see Electronic Supplementary Material [ESM] for the complete list of ICUs) from February 22, 2020, to May 31, 2020, were included in the present study. The Ethics Committee waived the consent for the retrospective part of the study, while written informed consent or deferred consent was obtained according to the regulations of each participating center for the prospective part of the study.

Laboratory confirmation for SARS-CoV-2 infection was obtained by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay on nasal and pharyngeal swabs and, when clinically indicated, also on lower respiratory airway aspirate.

### Data collection

Clinical patient data were daily recorded on an electronic database (REDCap, Research Electronic Data Capture; Vanderbilt University, Nashville, TN, USA) by one or more trained investigators in each center. Demographics data (age, sex, pre-existing comorbidities, chronic medications, date of symptoms onset) were recorded at ICU admission.

**Table 1 Patients' characteristics at ICU admission, respiratory and hemodynamic parameters, blood tests, and univariate risk factors for outcome**

	Overall (N = 1260)	Survival (N = 834, 66.19%)	Death (N = 426, 33.81%)	P value	HR (95% CI)
<b>Demographics</b>					
Age (years)	63 [55–69] (N = 1259)	60 [53–67] (N = 833)	67 [62–73] (N = 426)	<0.001	1.060 (1.048–1.071)
Male (n)	979 (77.70%)	640 (76.64%)	339 (79.58%)	0.444	1.097 (0.865–1.390)
Female (n)	281 (22.30%)	194 (23.26%)	87 (20.42%)		
BMI (kg/m <sup>2</sup> )	28 [25–31] (N = 1115)	28 [25–31] (N = 749)	28 [25–31] (N = 366)	0.308	1.009 (0.992–1.027)
<b>Clinical parameters</b>					
SOFA score	4 [3–5] (N = 1192)	4 [3, 4] (N = 794)	4 [3–5] (N = 398)	<0.001	1.206 (1.188–1.336)
Temperature (°C)	37.0 [36.3–37.7] (N = 1132)	37.0 [36.4–37.8] (N = 754)	36.9 [36.1–37.6] (N = 378)	0.008	0.874 (0.791–0.965)
FiO <sub>2</sub> (%)	70 [60–85] (N = 1203)	60 [50–80] (N = 804)	70 [60–90] (N = 399)	0.032	1.006 (1.000–1.011)
PEEP (cmH <sub>2</sub> O)	12 [10–14] (N = 1047)	12 [10–14] (N = 699)	12 [10–15] (N = 348)	0.206	1.026 (0.986–1.067)
PaO <sub>2</sub> /FiO <sub>2</sub> (mmHg)	122 [89–175] (N = 1166)	128 [93–186] (N = 780)	107 [81–152] (N = 386)	0.004	0.998 (0.996–0.999)
pH	7.41 [7.33–7.46] (N = 1181)	7.42 [7.35–7.47] (N = 791)	7.36 [7.29–7.44] (N = 390)	<0.001	0.045 (0.017–0.114)
PaO <sub>2</sub> (mmHg)	80 [66–102] (N = 1187)	81 [67–104] (N = 795)	77 [64–100] (N = 392)	0.066	0.997 (0.995–1.000)
PaCO <sub>2</sub> (mmHg)	42 [36–51] (N = 1176)	41 [35–49] (N = 788)	44 [37–55] (N = 388)	0.001	1.012 (1.005–1.019)
Lactate (mEq/L)	1.2 [0.9–1.6] (N = 865)	1.2 [0.9–1.5] (N = 566)	1.3 [1.0–1.8] (N = 299)	<0.001	1.173 (1.113–1.236)
Heart rate (bpm)	82 [71–95] (N = 1140)	80 [71–94] (N = 759)	85 [71–97] (N = 381)	0.464	1.002 (0.997–1.007)
Mean arterial pressure (mmHg)	85 [75–95] (N = 1144)	87 [77–97] (N = 759)	80 [70–93] (N = 385)	<0.001	0.988 (0.982–0.995)
Creatinine (mg/dL)	0.89 [0.70–1.11] (N = 1155)	0.84 [0.66–1.04] (N = 771)	0.97 [0.76–1.38] (N = 384)	<0.001	1.152 (1.092–1.216)
Urea (mg/dL)	45 [32–69] (N = 1076)	40 [29–60] (N = 720)	59 [41–91] (N = 356)	<0.001	1.009 (1.007–1.011)
White blood cells (10 <sup>3</sup> /μL)	8.7 [6.2–12.0] (N = 1161)	8.4 [6.1–11.6] (N = 780)	9.2 [6.4–12.9] (N = 381)	0.032	1.009 (1.001–1.017)
Neutrophils (10 <sup>3</sup> /μL)	7.1 [5.0–10.5] (N = 937)	6.9 [4.9–9.9] (N = 632)	8.0 [5.4–11.6] (N = 305)	0.172	1.018 (0.992–1.044)
Lymphocytes (10 <sup>3</sup> /μL)	0.7 [0.5–1.0] (N = 868)	0.7 [0.5–1.0] (N = 586)	0.6 [0.4–1.0] (N = 282)	0.174	0.822 (0.620–1.091)
Neutrophil–Lymphocyte Ratio	10.8 [6.6–18.2] (N = 854)	9.8 [6.5–16.6] (N = 576)	13.6 [7.2–21.7] (N = 278)	0.522	1.001 (0.998–1.004)
Platelets (10 <sup>3</sup> /mm <sup>3</sup> )	235 [177–309] (N = 1162)	246 [185–317] (N = 779)	218 [159–292] (N = 383)	<0.001	0.998 (0.997–0.999)
Bilirubin tot (mg/dL)	0.7 [0.5–1.0] (N = 1071)	0.7 [0.5–1] (N = 723)	0.7 [0.5–1.1] (N = 348)	0.009	1.157 (1.038–1.290)
C-reactive protein (mg/L)	13.4 [5.3–22.3] (N = 1033)	13.3 [5.3–20.8] (N = 693)	13.7 [5.6–24.6] (N = 340)	0.880	1.000 (0.995–1.004)
Procalcitonin (ng/mL)	0.4 [0.2–1.2] (N = 661)	0.3 [0.2–1.0] (N = 439)	0.5 [0.2–1.7] (N = 222)	0.136	1.014 (0.996–1.033)
LDH (U/L)	475 [359–639] (N = 964)	458 [348–605] (N = 651)	509 [391–710] (N = 313)	<0.001	1.001 (1.000–1.001)
AST (U/L)	44 [30–66] (N = 619)	44 [30–65] (N = 409)	45 [29–68] (N = 210)	0.008	1.003 (1.001–1.005)
ALT (U/L)	39 [25–63] (N = 763)	40 [26–66] (N = 506)	38 [24–57] (N = 257)	0.705	1.000 (0.998–1.002)
INR	1.2 [1.1–1.3] (N = 729)	1.2 [1.1–1.3] (N = 483)	1.2 [1.1–1.3] (N = 246)	0.002	1.878 (1.254–2.811)
Albumin (g/dL)	2.9 [2.6–3.1] (N = 488)	3 [2.6–3.2] (N = 337)	2.8 [2.5–3.0] (N = 151)	0.030	0.679 (0.479–0.964)
Glucose (mg/dL)	128 [108–171] (N = 694)	123 [106–162] (N = 457)	141 [112–184] (N = 237)	0.020	1.002 (1.000–1.004)
Fibrinogen (mg/dL)	631 [485–747] (N = 533)	636 [506–753] (N = 369)	607 [425–740] (N = 164)	0.022	0.999 (0.998–1.000)
D-dimer (ng/mL)	1414 [594–4527] (N = 832)	1156 [515–3545] (N = 582)	2275 [901–6900] (N = 250)	0.148	1.000 (1.000–1.000)
Ferritin (ng/mL)	1431 [809–2311] (N = 285)	1386 [744–2394] (N = 199)	1457 [1028–2234] (N = 86)	0.116	1.000 (1.000–1.000)
Troponin T (ng/mL)	8 [0–14] (N = 301)	7 [0–12] (N = 204)	8 [0–23] (N = 97)	0.005	1.000 (1.000–1.001)
Pro-BNP (ng/L)	277 [112–875] (N = 48)	211 [104–703] (N = 35)	893 [120–1759] (N = 13)	0.007	1.000 (1.000–1.000)

HR hazard ratio, CI confidence interval, BMI body mass index, SOFA sequential organfailure assessment, FiO<sub>2</sub> fractional inspired oxygen, PEEP positive end expiratory pressure, PaO<sub>2</sub>/FiO<sub>2</sub> ratio of arterial oxygen partial pressure, PaO<sub>2</sub> arterial oxygen partial pressure, PaCO<sub>2</sub> arterial carbon dioxide partial pressure, LDH lactate dehydrogenase, AST aspartate transaminase, ALT alaninetransaminase, INR international normalized ratio, BNP brain natriuretic peptide

At ICU admission and then daily during the ICU stay, the following information was collected: mode of respiratory support (oxygen mask, non-invasive mechanical ventilation, invasive mechanical ventilation); ventilator settings and respiratory parameters (mode of ventilation, FiO<sub>2</sub>, positive end expiratory pressure [PEEP], respiratory

rate, tidal volume, peak pressure, plateau pressure, driving pressure, compliance of respiratory system [C<sub>RS</sub>], the arterial partial pressure of oxygen [PaO<sub>2</sub>], the arterial partial pressure of carbon dioxide [PaCO<sub>2</sub>], PaO<sub>2</sub>/FiO<sub>2</sub>); medications (neuromuscular blocking agents, antibiotics, antivirals, steroids, anticoagulative drugs, immunosuppressive drugs); prone positioning,

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extracorporeal membrane oxygenation [ECMO], tracheostomy, and renal replacement therapy; clinical and laboratory parameters (see ESM for complete list).

### Statistical analysis

No statistical sample size calculation was performed a priori, and the sample size was equal to the number of patients consecutively treated in the participating ICUs during the study period. Continuous variables are presented as median and interquartile range [IQR], while categorical variables are expressed as number of patients (percentage). Raw outcome comparisons between survivors and non-survivors were performed with Pearson's  $\chi^2$  test for categorical variables.

The modeling of the impact of longitudinal parameters on the survival outcomes was performed in three steps.

First, the association of risk factors with time to death in ICU was assessed by univariable and multivariable Cox proportional hazards regression models; see supplements. Hazard ratios [HRs] were expressed per unit of change in the corresponding variable, if not differently specified. Time span was days from ICU admission to ICU discharge, with death as the event of interest and ICU discharge as censoring.

Second, the time course of physiological variables during ICU stay according to the patient's life status at discharge was evaluated by a polynomial maximum likelihood multilevel linear regression model with a random intercept at the patient level and random slope at the time level. The longitudinal model was applied, since it takes into account the within-patient repeated measurements, differently from the analyses which only average the daily values over the ICU stay. Eighteen physiological variables were evaluated:  $\text{PaO}_2/\text{FiO}_2$ ,  $C_{\text{RS}}$ , driving pressure, tidal volume on predicted body weight [TV/PBW], pH, bilirubin, creatinine, D-dimer, ferritin, lactate, C-reactive protein, urea,  $\text{PaCO}_2$ , platelets, fibrinogen, neutrophils, lymphocytes, and neutrophils-lymphocytes ratio. Each model included one of the previous parameters, as a dependent variable, while time and patient's clinical outcome were considered independent variables. The exponential power of time and interaction between time and outcome were evaluated according to model-based likelihood ratio tests.

The analysis was performed in two ways: (1) temporal trends were modeled from ICU admission (day 0) up to 30 days or ICU discharge/death; (2) the time scale started from ICU discharge/death (day 0) back to a maximum of 30 days before (e.g., -5 corresponds to 5 days before the ICU discharge/death).

Third, full joint modeling of each longitudinal parameter with the time-to-death end point was fit, with Weibull parametric regression; the covariates for the survival

components were chosen according to the result of step 1; for the longitudinal component, only time was used as potential predictor, with the same polynomial order selected in step 2 was chosen; the longitudinal component was linked to the survival component in time-dependent associations, with daily value, slope, or both (the final model choice was based on the Akaike information criterion). For daily value, we intended each single day value for each variable along the whole ICU course. We log-transformed some variables to achieve normality before fitting the corresponding model. The *stjm* routine in Stata was employed [14]. To present effect sizes in a metric familiar to clinicians, we exponentiated the coefficients (and confidence intervals) estimated by the Weibull models, obtaining hazard ratios.

*P* values < 0.05 were statistically significant. Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA), StataSE 16.0 (StataCorp LLC), and SigmaPlot 12.0 (Systat Software Inc., San Jose, CA).

See ESM for information regarding comorbidities, medications, clinical and laboratory parameters, and statistical analysis.

### Results

From February 22, 2020, to May 31, 2020, a total of 1284 consecutive critically ill patients with laboratory-confirmed COVID-19 were admitted to the 24 ICUs participating in the present study. Data were not available for 24 patients; thus, data from 1260 patients were included in this report.

Table 1 shows demographic and clinical characteristics at ICU admission. Overall, about 78% were male and age was 63 [55–69] years.

At least one comorbidity was reported in 988 patients (78%); hypertension was the most common comorbidity (607 [48.2%]), followed by diabetes (228 [18.1%]), cardiovascular diseases different from hypertension (197 [15.6%]), and pulmonary diseases (100 [7.9%]) (ESM Table 1s).

The time intervals from the symptoms' onset to intubation and from hospital to ICU admission were 9 [6–12] and 3 [1–5] days, respectively (ESM Table 4s). At ICU admission,  $\text{PaO}_2/\text{FiO}_2$  was 122 [89–175] mmHg, while PEEP was 12 [10–14] cmH<sub>2</sub>O. 707 (56%) patients were invasively ventilated at admission (ESM Table 2s), while a further 287 patients underwent invasive mechanical ventilation during the ICU stay. 84% of patients received neuromuscular blocking drugs for 6 [4–10] days, while 41% was pronated for 2 [1–4] days (ESM Table 5s and Figs. 38s–39s). See ESM for demographic and clinical characteristics of intubated and non-intubated patients (ESM Tables 2s–4s) and for a list of therapies used during the ICU stay (ESM Table 5s).

The overall ICU mortality was 33.8% (426/1260), while among intubated patients it was 38.5% (272/707).

Multiple clinical and laboratory parameters reflecting cardiac, pulmonary, kidney, liver, and coagulation functions at ICU admission were associated with mortality at univariable analysis (Table 1 and ESM Tables 2s–3s).

### Multivariable Cox regression analysis

At multivariable analysis, age (HR=1.046, 95% CI 1.031–1.062,  $P<0.0001$ ), SOFA score (HR=1.257, 95% CI 1.162–1.360,  $P<0.0001$ ), pH (HR=0.074, 95% CI 0.021–0.256,  $P<0.0001$ ), and lactate (HR=1.226, 95% CI 1.123–1.337,  $P<0.0001$ ) at ICU admission were significantly associated with mortality. Among comorbidities, only diabetes (HR=1.609, 95% CI 1.189–2.178,  $P=0.002$ ) showed an association with mortality. See ESM for details.

### Parameter changes over time and association with outcome

Figures 1, 2, and 3 and ESM 36s–37s show the trends throughout the ICU stay of 18 relevant parameters, while their associations with survival are reported in Table 2. Detailed results are reported in the ESM.

After the final models' choice, the daily value of 15 parameters and the weekly slope of ten parameters were associated with survival. For five parameters ( $C_{RS}$ , driving pressure, creatinine, ferritin, C-reactive protein), the effect size (shown as hazard ratio for ease of interpretation) of the slope was higher compared to the daily value.

At ICU admission, both  $PaO_2/FiO_2$  and  $C_{RS}$  were higher in survivors than in non-survivors, while driving pressure and  $PaCO_2$  were higher in non-survivors. In survivors,  $PaO_2/FiO_2$  progressively increased throughout ICU stay and  $C_{RS}$  slightly decreased following ICU admission while it increased towards ICU discharge. Both  $PaO_2/FiO_2$  and  $C_{RS}$  decreased over the days in non-survivors. Driving pressure and  $PaCO_2$  increased in non-survivors throughout the ICU stay, while, in survivors, driving pressure remained stable and  $PaCO_2$  decreased (Fig. 1).

For  $PaO_2/FiO_2$ ,  $PaCO_2$ ,  $C_{RS}$ , and driving pressure, both the daily values and the slopes were strongly associated

with survival, with most trends showing higher effect (HRs) than daily values (Table 2).

At ICU admission, in survivors, lactate was lower, and pH was higher than in non-survivors, while pH decreased, and lactate increased in non-survivors during the ICU stay (Fig. 2). However, at the joint model analysis, only the daily values were associated with survival (Table 2).

At ICU admission, bilirubin and creatinine were higher in non-survivors and increased in non-survivors during the days (Fig. 2). The daily values of both these parameters were associated with survival, but only for creatinine the slope was strongly associated with survival (Table 2).

Ferritin and C-reactive protein at ICU admission were equally elevated in survivors and non-survivors. Both continuously decreased over the days only in survivors (Fig. 3). Strong association with survival was detected for both ferritin and C-reactive protein's daily values and slopes (Table 2).

Neutrophil–lymphocyte ratio was higher in non-survivors at ICU admission and increased in non-survivors during the ICU stay (Fig. 3). Both daily value and slope were associated with survival (Table 2).

D-Dimer at ICU admission was higher in non-survivors than in survivors, then decreased in both groups (Fig. 3), but was not shown to be associated with survival in joint modeling (Table 2).

### Discussion

The present multicentric study describes 1260 critically ill patients with COVID-19-associated acute respiratory failure consecutively admitted to 24 Italian ICUs during the first pandemic wave. This study specifically analyzes the trends of clinical, ventilatory and laboratory parameters throughout the entire ICU stay and their relationship with outcome. The daily values of 15 parameters associated with acute organ dysfunction (lung, liver, kidney), acid–base derangement, coagulation impairment, or systemic inflammation were associated with higher patient survival. Ten of these parameters showed different slopes between survivors and non-survivors, and the associations with the patient outcome of such slopes were stronger than the

(See figure on next page.)

**Fig. 1** Time course of physiological variables during ICU stay according to the patient's outcome life status at discharge obtained by a polynomial maximum likelihood multilevel model with a random intercept at the patient level and random slope at the time level (see text for description of the model). **a** and **b**  $PaO_2/FiO_2$ ; **c** and **d** respiratory system compliance; **e** and **f** driving pressure; **g** and **h**  $PaCO_2$ . Dots represent data from the overall models, error bars represent 95% confidence interval of the model. Blue color represents patients discharged from ICU, while red color represents patients died in ICU. The analysis was performed in two ways: (1) temporal trends were modeled from ICU admission (day 0) up to 30 days or ICU discharge/death (left panels **a, c, e, g**); (2) the time scale was adjusted by subtracting each patient's ICU discharge/death time (day 0) back to a maximum of 30 days (right panels **b, d, f, h**)

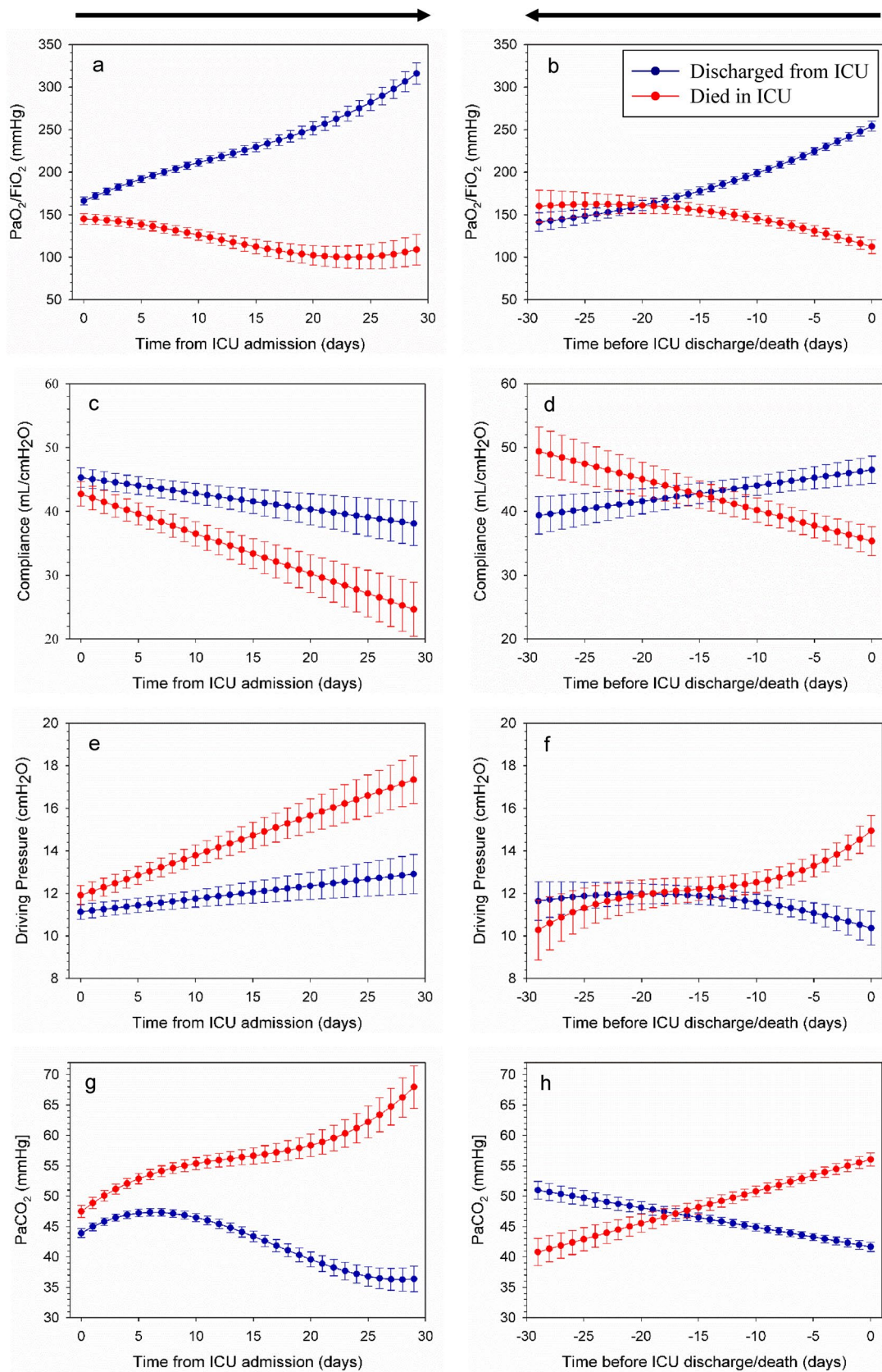


Fig. 1 (See legend on previous page.)

daily value of the same parameters. This finding supports the common clinical knowledge that the time course of relevant variables is more relevant than the single daily value.

The majority of the patients included in the study were elderly men with hypertension; four out of five received mechanical ventilation, about half were treated with rescue strategies for refractory hypoxemia, primary prone position, and 98% received inotropic or vasoactive drugs at least once during ICU stay.

The overall ICU mortality rate was 34%, but increased to 38% if considering only the patients undergoing mechanical ventilation at ICU admission. These findings are consistent with similar European multicenter studies [5, 15–20].

In the present study, the factors showing independent association with worse ICU outcome were older age, acid–base derangement (low pH and high lactate), and SOFA at ICU admission and diabetes.

We developed a polynomial maximum likelihood multilevel regression model and a joint model to compute the association between ICU outcome and the daily value and trends of main clinical parameters. Joint modeling has the advantage over simpler methods to take into account differential missing data of the longitudinal parameter in surviving vs. dead patients (differential dropout bias). Few authors showed, in critically ill patients, that changes in clinical parameters throughout the first few days of ICU stay are different between survivors and non-survivors [21–24]. However, differently from a joint model, these studies generally do not take into account the within-patient repeated measurement. Moreover, we included time backward from ICU discharge to clearly show the parameter trends over the last part of the ICU stay.

Furthermore, none of the previously cited studies compared trends to single daily values, to the best of our knowledge.

We detected a strong association between mortality and acute kidney and respiratory impairment and activation of systemic inflammation. The effect size of creatinine slope on mortality was almost twice that of daily value. Similarly, the association between the slope

of systemic inflammation parameters (i.e., ferritin and C-reactive protein) and mortality were also stronger than the daily value. The association of neutrophil–lymphocyte ratio daily value with survival was instead higher than the trend. The slopes of both compliance of the respiratory system and  $\text{PaO}_2/\text{FiO}_2$  are associated more strongly with mortality than the daily values, although a possible effect of therapeutic interventions should be taken into account (e.g., neuromuscular blockade and prone positioning).

Even more impressive is the role of driving pressure trend as a predictor of mortality. Multiple studies identified the driving pressure as one of the strongest predictive variables of mortality, but none of them showed the superiority of the driving pressure trend compared with the single value. In the present study, the driving pressure slope had an effect almost four times stronger than the single daily value.

We observed an early multiorgan impairment due to the COVID-19 disease already at ICU admission, which subsequently worsened during the ICU stay, mainly in non-survivors. Particularly, most of the parameters, but inflammatory markers, were already different between survivors and non-survivors at ICU admission. Such differences increase throughout the ICU stay, since the parameter time courses show different, or even opposite, slopes. Therefore, the daily analysis of parameter trends, especially the most divergent, could assist the clinician in daily patient management.

Indeed, previous studies reported early differences in the temporal changes of laboratory parameters between survivors and non-survivors [8, 10] among hospitalized not-critically-ill patients with COVID-19.

Therefore, we can speculate that early and timely detection, possibly before ICU admission, of the more susceptible patients could limit organ injury and anticipate, if possible, optimization of the treatments.

Our study has several limitations. First, this is a retrospective–prospective study performed in 24 Italian hospitals in 12 different regions during the first wave of the COVID-19 pandemic. We cannot exclude high heterogeneity among viral load, admission policies and care management, also related to differences in the

(See figure on next page.)

**Fig. 2** Time course of physiological variables during ICU stay according to the patient's outcome life status at discharge obtained by a polynomial maximum likelihood multilevel model with a random intercept at the patient level and random slope at the time level (see text for description of the model). **a** and **b** Lactate; **c** and **d** pH; **e** and **f** bilirubin; **g** and **h** creatinine. Dots represent data from the overall models, error bars represent 95% confidence interval of the model. Blue color represents patients discharged from ICU while red color represents patients died in ICU. The analysis was performed in two ways: (1) temporal trends were modeled from ICU admission (day 0) up to 30 days or ICU discharge/death (left panels **a, c, e, g**); (2) the time scale was adjusted by subtracting each patient's ICU discharge/death time (day 0) back to a maximum of 30 days (right panels **b, d, f, h**)

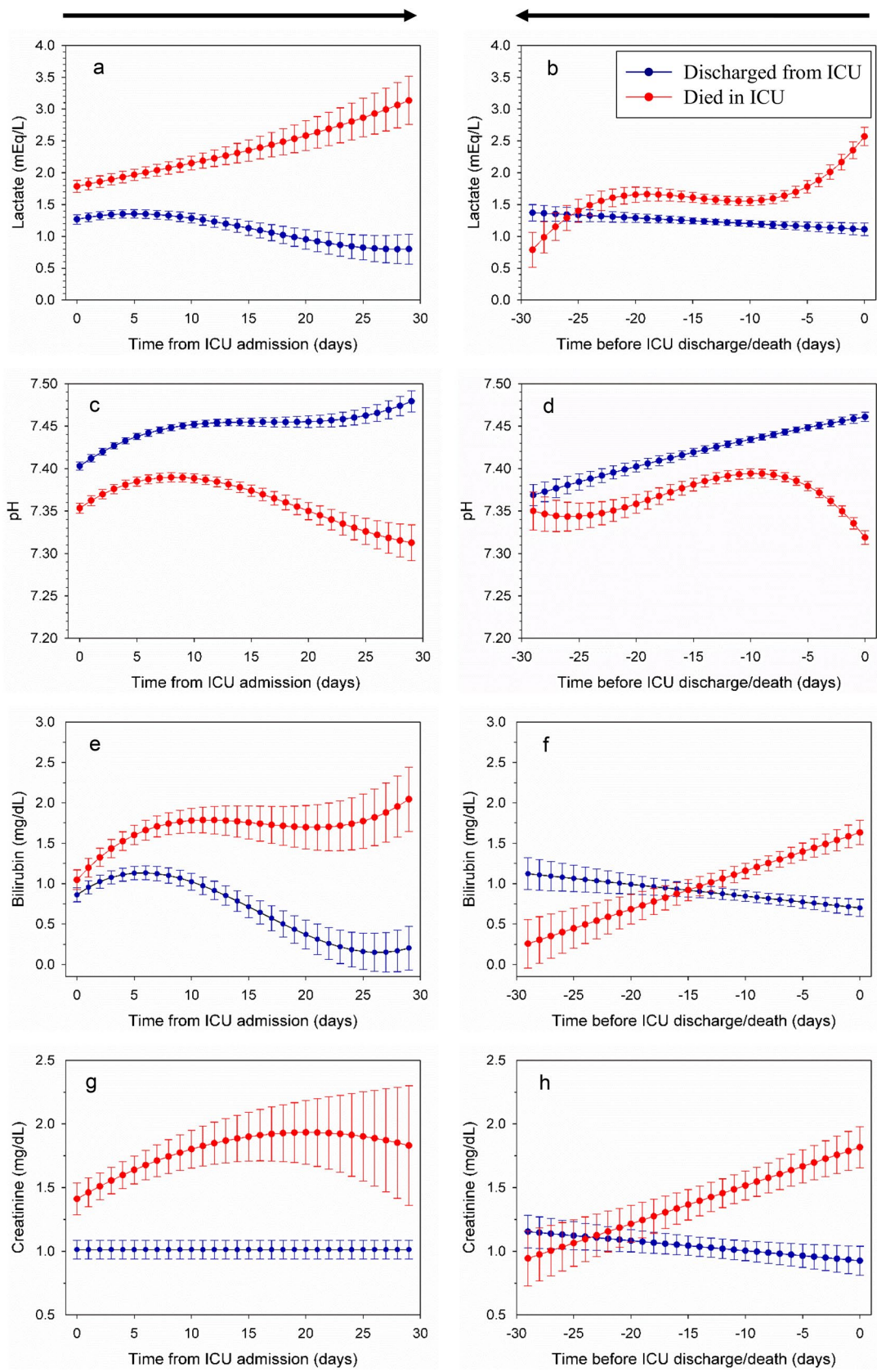


Fig. 2 (See legend on previous page.)



(See figure on next page.)

**Fig. 3** Time course of physiological variables during ICU stay according to the patient's outcome life status at discharge obtained by a polynomial maximum likelihood multilevel model with a random intercept at the patient level and random slope at the time level (see text for description of the model). **a** and **b** Ferritin; **c** and **d** neutrophil-lymphocyte ratio; **e** and **f** C-reactive protein; **g** and **h** D-Dimer. Dots represent data from the overall models, and error bars represent 95% confidence interval of the model. Blue color represents patients discharged from ICU, while red color represents patients died in ICU. The analysis was performed in two ways: (1) temporal trends were modeled from ICU admission (day 0) up to 30 days or ICU discharge/death (left panels **a, c, e, g**); (2) the time scale was adjusted by subtracting each patient's ICU discharge/death time (day 0) back to a maximum of 30 days (right panels **b, d, f, h**)

characteristics, and strain on the healthcare systems and in the socioeconomic patient's status [25]. Second, only ICUs interested in this research project joined the study, promoting a possible selection bias. Third, many patients were treated, during the hospital stay, with several investigational drugs (hydroxychloroquine, antivirals, steroids, tocilizumab, and others) whose effect, in a study of this nature, is difficult to evaluate without running into interpretative errors such as survivor bias. Fourth, the daily collected data represent the last available data and not the average or the worst value of the previous 24 h.

Fifth, although we have established a sound data collection and quality control (see ESM) and maximal efforts have been employed to minimize the amount of missing data and promote data quality, being a retrospective, real-data study, no tests were made specifically for the study purposes only; thus, some parameters show some missing data. Finally, joint modeling requires several assumptions, many of which are untestable, as to the best association structure, the best covariable selection, the fit of the model, and other. Therefore, the choice of the model parameters might be considered somewhat

arbitrary. Besides, model fitting is computationally complex, and not all models could mathematically converge. Finally, the interpretation of the coefficient is not immediately evident and is difficult to convey, given the complex shape of the relationship with time involving polynomials. However, we devised our analysis strategy before fitting any models, and we caution against an overconfident interpretation of results.

### Conclusion

In this population of 1260 critically ill patients with laboratory-confirmed COVID-19 admitted to 24 Italian ICUs during the first pandemic wave, the overall mortality was 34%. The daily values throughout the entire ICU stay of clinical and biochemical parameters reflecting acute lung, liver, and kidney dysfunction, acid-base derangement, coagulation impairment, and systemic inflammation were indicative of subsequent patient survival. The temporal trends of driving pressure, compliance of respiratory system, creatinine, C-reactive protein and ferritin were more predictive of mortality compared with the single daily values.

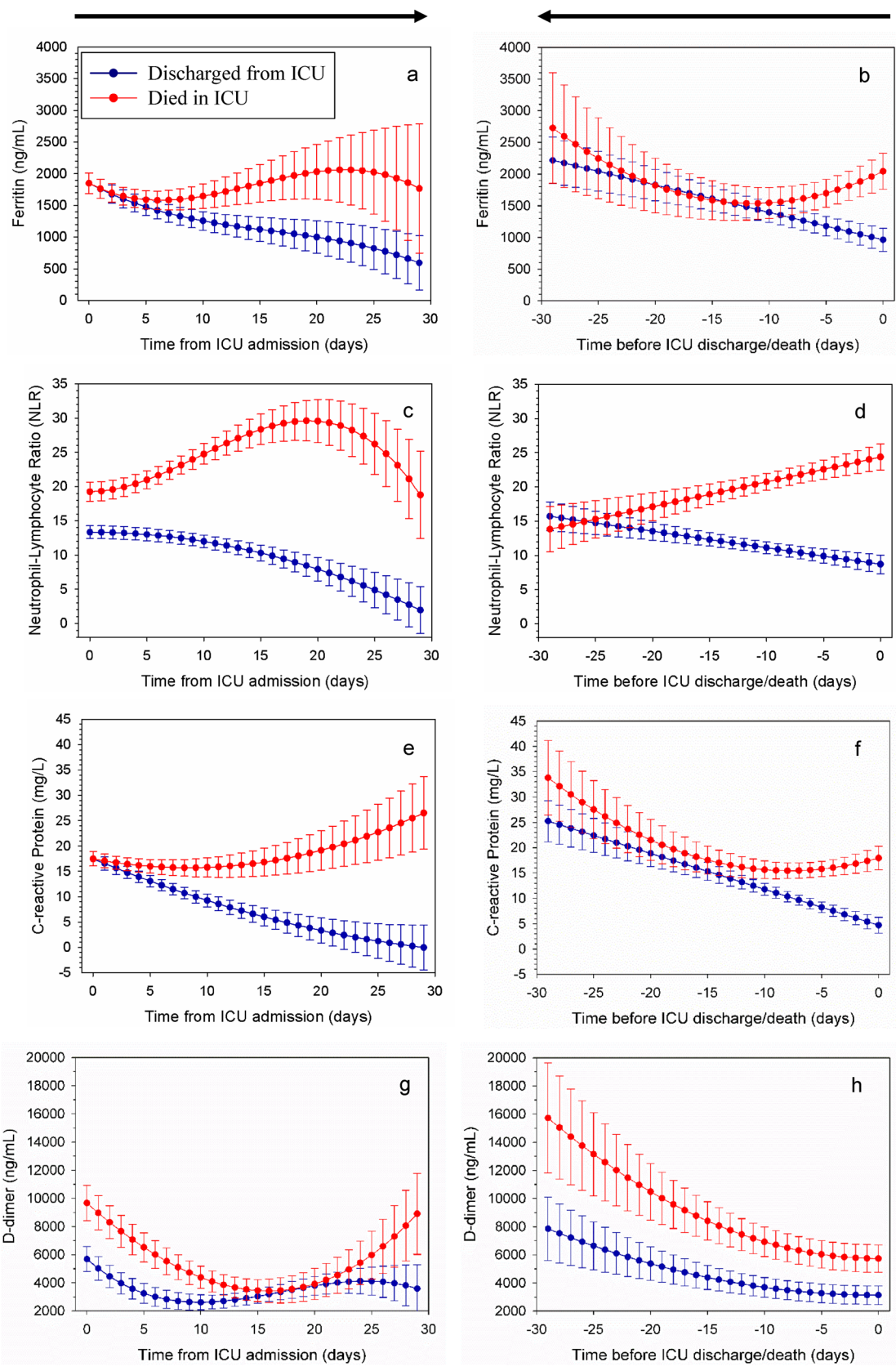


Fig. 3 (See legend on previous page.)

**Table 2 Parameter daily and trend associations with survival as assessed by joint models**

Parameter	Association with daily value			Association with trend		
	P value	HR	HR 95%CI	P value	HR	HR 95%CI
<b>Respiratory function</b>						
$C_{RS}$ (mL/cmH <sub>2</sub> O)	<0.001	0.97	0.95–0.98	<0.001	0.80	0.74–0.88
PaO <sub>2</sub> /FiO <sub>2</sub> (100 unit change)	<0.001	0.08	0.05–0.11	<0.001	0.12	0.03–0.53
Driving pressure (cmH <sub>2</sub> O)	0.001	1.11	0.05–0.05	<0.001	4.24	0.10–0.34
PaCO <sub>2</sub> (mmHg)	<0.001	1.07	1.06–1.09	0.006	1.07	1.02–1.12
TV/PBW (mL/kg)	0.656	1.01	0.97–1.05			
<b>Acid–base</b>						
Lactate (mEq/L)	<0.001	2.51	2.18–2.89	0.117	0.65	0.39–1.11
pH (0.1 unit change)	<0.001	0.28	0.23–0.34	0.537	0.76	0.31–1.84
<b>Kidney function</b>						
Creatinine (log scale mg/dL)	<0.001	1.78	1.50–2.11	0.032	2.72	1.09–6.79
Urea (mg/dL)	<0.001	1.04	1.04–1.05			
<b>Systemic inflammation</b>						
CRP (log scale mg/L)	<0.001	1.32	1.18–1.46	0.040	1.41	1.02–1.94
Ferritin (log scale ng/L)	0.001	1.61	1.23–2.10	<0.001	3.96	1.93–8.15
Neutrophils (10 <sup>3</sup> /μL)	<0.001	1.14	1.11–1.18	0.007	1.09	1.02–1.16
Lymphocytes (10 <sup>3</sup> /μL)	<0.001	0.19	0.13–0.28			
Neutrophils- Lymphocytes ratio	<0.001	2.84	2.34–3.45	0.023	1.68	1.07–2.62
<b>Liver function</b>						
Bilirubin (log scale mg/dL)	<0.001	1.58	1.35–1.84			
<b>Coagulation</b>						
D-Dimer (log scale ng/mL)	0.126	1.05	0.99–1.12			
Fibrinogen (mg/dL)	0.175	1.03	0.99–1.08			
Platelets (100 unit change 10 <sup>3</sup> /mm <sup>3</sup> )	0.006	0.93	0.89–0.98	0.02	1.43	1.07–1.92

Abbreviations: HR hazard ratio, CI confidence interval,  $C_{RS}$  compliance of respiratory system, PaO<sub>2</sub>/FiO<sub>2</sub> ratio of arterial oxygen tension and fraction of inspired oxygen, PaCO<sub>2</sub> arterial partial pressure of carbon dioxide, TV/PBW tidal volume based on predicted body weight, CRP C-reactive protein. See text and ESM for details on joint models

### Supplementary Information

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AZ, GF, EC, GC, AP, and GG conceived the study and drafted the work. AZ, GF, MA, GB, AB, TB, LC, GPC, MC, IC, DC, EDR, FDC, GF, RF, MG, RG, LG, TL, LM, DP, AP, MVR, RR, PS, SS, NS, and MV performed data collection. Data were analyzed by AZ, GF, EC, and LS and interpreted by AZ, GF, GB, EC, MC, GC, AP, LS, AP, and GG. All the authors revised the work, commented on previous versions of the manuscript, approved the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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#### Availability of data and material (data transparency)

The dataset used and/or analyzed during the current study is available from the corresponding author on reasonable request.

#### Code availability (software application or custom code)

Not applicable.

#### Declarations

#### Conflicts of interest

GG reported personal fees and non-financial support from Getinge and from Biotest, personal fees from ThermoFisher, grants and personal fees from Fisher&Paykel, and personal fees from Draeger Medical outside the submitted work. AP reported personal fees from Maquet, from Novalung/Xenios, from Baxter, and from Boehringer Ingelheim outside the submitted work. The authors certify that they have no affiliations with, or involvement in, any organization or entity with any financial or non-financial interest in the subject matter discussed in this manuscript.

#### Ethics approval

This study was approved by the Ethical Committees of all participating centers (Promoting Center's Ethical Committee: Comitato Etico Milano Area 2; protocol: 0008489; date of approval: March 20, 2020).

#### Consent to participate

The Ethics Committee waived the consent for the retrospective part of the study, while written informed consent or deferred consent was obtained according to the regulations of each participating center for the prospective part of the study.

#### Consent for publication

Not applicable.

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