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Increased mortality in patients with severe SARS-CoV-2 infection admitted within seven days of disease onset

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Abstract

Purpose: Coronavirus disease 2019 (COVID-19) is creating an unprecedented healthcare crisis. Understanding the determinants of mortality is crucial to optimise intensive care unit (ICU) resource use and to identify targets for improving survival.

Methods: In a multicentre retrospective study, we included 379 COVID-19 patients admitted to four ICUs between 20 February and 24 April 2020 and categorised according to time from disease onset to ICU admission. A Cox proportional-hazards model identified factors associated with 28-day mortality.

Results: Median age was 66 years (53–68) and 292 (77%) were men. The main comorbidities included obesity and overweight (67%), hypertension (49.6%) and diabetes (30.1%). Median time from disease onset (i.e., viral symptoms) to ICU admission was 8 (6–11) days (missing for three); 161 (42.5%) patients were admitted within a week of disease onset, 173 (45.6%) between 8 and 14 days, and 42 (11.1%) > 14 days after disease onset; day 28 mortality was 26.4% (22–31) and decreased as time from disease onset to ICU admission increased, from 37 to 21% and 12%, respectively. Patients admitted within the first week had higher SOFA scores, more often had thrombocytopenia or acute kidney injury, had more limited radiographic involvement, and had significantly higher blood IL-6 levels. Age, COPD, immunocompromised status, time from disease onset, troponin concentration, and acute kidney injury were independently associated with mortality.

Conclusion: The excess mortality in patients admitted within a week of disease onset reflected greater non-respiratory severity. Therapeutic interventions against SARS-CoV-2 might impact different clinical endpoints according to time since disease onset.

Keywords: Coronavirus, Viral infection, Acute kidney injury, Acute respiratory distress syndrome

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Introduction

The COVID-19 pandemic has created an unprecedented healthcare crisis. With more than four million confirmed cases worldwide and nearly 280,000 deaths during the first 4 months of 2020, the number of patients with severe forms requiring critical care has overwhelmed intensive care units (ICUs) in many countries. Respiratory failure is the main source of morbidity and mortality in severe cases.

The causative agent of COVID-19, SARS-CoV-2 (severe acute respiratory syndrome-related coronavirus 2) [1, 2], is the third documented spillover of an animal coronavirus to humans in only two decades [3]. After an incubation period of about 5 days [4], clinical viral symptoms such as a fever, cough, sore throat, nasal congestion, myalgia, fatigue, headaches, and/or diarrhoea occur [5, 6]. Dyspnoea is reported in up to half the patients, and 5–20% of patients require ICU admission for acute respiratory failure [7]. In the earliest descriptions of COVID-19 patients hospitalised in Wuhan, China, time from viral symptom onset to dyspnoea was 5 days and time to hospital admission was 7 days [8, 9].

Understanding the determinants of poor outcomes in COVID-19 patients would help stratify patients at baseline based on a risk assessment to both avoid admitting patients to the ICU if they are at low risk for worsening and promptly admit patients likely to require critical care. Several studies have identified factors associated with mortality in COVID-19 patients. While advanced age has been recognised as a leading determinant of death in several studies [10, 11], little attention has been paid to outcome differences according to the timing of critical illness onset. A two-step model of lung and systemic injury seems involved, with the aggressive inflammation initiated by the viral replication resulting in a cytokine storm [12, 13]. Early after infection, SARS-CoV-2 binds to angiotensin-converting enzyme 2 receptors, multiplies in the cytoplasm, and leads to type II pneumocyte apoptosis [14]. Additionally, SARS-CoV-2 RNA acts as a pathogen-associated molecular pattern that induces a chemokine surge, which causes neutrophil migration and activation [15, 16]. The result is destruction of the alveolar-capillary walls and damage to the intra-alveolar space–stroma interface, causing exudative leakage. In addition to massive epithelial apoptosis, the early onset of rapid viral replication triggers endothelial cells to release pro-inflammatory cytokines and chemokines that cause further lung damage together with a systemic insult [17].

To test the hypothesis that COVID-19-related critical illness differs according to time from viral symptom onset to ICU admission, we assessed patient characteristics and

Take-home message

Time from COVID-19 viral symptom onset to ICU admission no longer than 7 days is associated with a higher risk of death. A faster onset of critical illness may be associated with kidney and myocardial injury in addition to lung injury, as well as with higher IL-6 concentrations.
Interventions that are currently used in COVID-19 patients might impact different clinical endpoints according to time since viral symptom onset.

outcomes in a cohort of 379 critically ill patients admitted to four university-affiliated hospitals in Paris.

Patients and methods

This retrospective observational study was performed in four university-affiliated hospitals in Paris. Consecutive patients with laboratory-confirmed SARS-CoV-2 infection admitted to one of the ICUs between 21 February and 24 April 2020 were enrolled. The appropriate ethics committee approved the study and waived the need for informed consent in accordance with French legislation about retrospective studies.

Laboratory confirmation of SARS-Cov-2 was defined as a positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs [18].

The four participating ICUs applied local (Parisian) guidelines regarding ICU admission, the provision of standard of care (including sedation, and neuromuscular blockade), the use of non-invasive ventilation, antibiotic treatment, as well as the use of rescue therapies for refractory hypoxemia (prone positioning, ECMO, etc.). These guidelines were approved by all and shared on the Health Regional Agency website (https://www.iledefrance.ars.sante.fr/coronavirus-covid-19-information-aux-professionnels-de-sante). There were no guidelines regarding the use of anti-viral agents, steroids, or cytokine-blockade that were mostly used in RCTs, sometimes through TUA (temporary use authorisation) or upon clinician's decisions.

Data were recorded by the intensivists in each ICU. The variables reported in the tables and figures were abstracted from the medical charts and electronic reports. Chronic obstructive pulmonary disease was defined as previously reported [19] and acute kidney injury according to the operational decision [20]. Causes of immunosuppression included solid tumours, haematological malignancies, solid organ transplantation, long-term immunosuppressive therapy (i.e., high-dose steroids (>1 mg/kg whatever the duration) or any immunosuppressant for more than 3 months), and HIV infection [21]. Obesity was defined as previously reported [22]. The

SOFA score was calculated within 24 h of ICU admission [23].

Time from viral symptom onset to ICU admission was defined as the number of days between the onset of flu-like viral symptoms (fever or chills, cough, sore throat, runny nose, anosmia, muscle pain, body aches, headaches, fatigue, vomiting or diarrhoea) and the day of ICU admission. In patients who were intubated and sedated, and unable to respond, relatives were asked to provide the detailed medical history. Otherwise, data were retrieved from the medical charts from the emergency department, outpatient consults, general practitioner or medicalised ambulances. Time from viral symptom onset to hospitalisation or from hospitalisation to ICU admission was calculated as number of days between viral symptom onset or admission to the hospital, and ICU admission.

Patient status at ICU and hospital discharge was recorded on 15 May 2020. ICU length of stay was recorded.

Statistical analysis

Continuous variables are described as median (interquartile range [IQR]) and compared between groups using the non-parametric Wilcoxon rank-sum test. Categorical variables are described as frequency (percentages) and compared between groups using Fisher's exact test. Mortality was assessed using survival analysis.

The patients were categorised according to the number of days between disease onset (i.e., the number of days between viral symptoms onset) and ICU admission (< 8, 8–14, and > 14 days).

Independent risk factors for day-28 mortality were identified using a Cox model. Conditional stepwise variable selection was performed with 0.2 as the critical p value for entry into the model and 0.1 as the p value for removal. Interactions and correlations between the explanatory variables, the validity of the proportional hazards assumption, the influence of outliers, and linearity of the relationship between the log hazard and the covariates were carefully checked. For the first step of the variable selection process, age, comorbidities (asthma, diabetes, COPD, hypertension, immunosuppression), time from viral symptom onset to ICU admission, acute kidney injury, and troponin were included in the model.

Kaplan–Meier graphs were used to express the probability of death from ICU admission to day 28. Comparisons were performed using the log-rank test.

In a sensitivity analysis, a double adjustment was performed. First, patients were matched on risk factors for ICU admission within the first 7 days of COVID-19. Then, a propensity score (PS)-matched analysis was performed on the risk of ICU admission within 7 days after viral symptom onset. Variables were selected to the PS model if associated with $p < 0.2$; they included comorbidities (asthma, hypertension, heart failure), body temperature at admission, and acute kidney injury. Case-matching was with a 1:1 ratio, without replacement, and according to the nearest neighbour method. Adequacy of the matching procedure was assessed by plotting PS across groups and computing the standardised mean difference. A univariate analysis was performed, and a Cox model was then built with double adjustment on relevant variables that were associated with the outcome and poorly matched.

Centre effect was assessed by a random effects model

The missing data rate was 7.3% overall and < 5% for major outcomes or covariates. Imputation of missing data was not performed.

Statistical analyses were performed with R statistical software, version 3.4.3 (available online at https://www.r-project.org/), using the 'Survival' and 'MatchIt' packages. Values of $p < 0.05$ were considered significant.

Results

We included 379 patients admitted between February 21 and April 24 2020. Table 1 reports their main features. All but 35 (9.2%) patients had at least one comorbidity, and the main comorbidities were obesity and overweight (31.2 and 36%, respectively), hypertension (49.6%), and diabetes (30.1%). Time from viral symptom onset to ICU admission had a median of 8 [6–11] days overall and was ≤ 7 days in 161 (42.5%) patients, 8–14 days in 173 (45.6%) patients, and more than 14 days in 42 (11.1%) patients. The information was missing for three patients. At ICU admission, digestive viral symptoms were present in 99 (26.1%) patients.

At ICU admission, temperature was 38 °C [37–38.7], oxygen flow was 15 [9–15] L/min, and the SOFA score was 5 [3–8]. The number of quadrants involved on the chest radiograph was 4 [2–4]. Initial computed tomography angiography disclosed pulmonary embolism in 42 (14%) patients. Initial oxygenation management included continuous positive airway pressure in six (1.6%) patients, noninvasive ventilation in 27 (7.1%) patients, high-flow nasal oxygen in 146 (38.5%) patients, and standard oxygen in the remaining 200 patients. Overall, 257 (67.8%) patients were intubated (at a median time from ICU admission of 0 days [0–1]). The median PaO_2/FiO_2 ratio on day 1 was 127 [89–193]. Extracorporeal membrane oxygenation was needed in 25 (6.6%) patients. Clinically or microbiologically documented bacterial infection developed in 63 (19.8%) patients. Vasopressors were used in 165 (43.8%) patients. Among the 195 (51.5%) patients with acute

Table 1 Main characteristics at ICU admission of patients with severe SARS-CoV-2 infection

Medical (IQR) or N (%)	<7 days N = 161	8–14 days N = 173	>14 days N = 42	p value
Age	61 (54–69)	62 (53–68)	62 (52–67)	0.84
Female sex	34 (21.1)	43 (24.9)	10 (23.8)	0.72
Comorbidities				
Asthma	6 (3.7)	11 (6.4)	6 (14.3)	0.01
COPD	10 (6.2)	8 (4.6)	2 (4.8)	0.80
Chronic heart failure	19 (11.8)	12 (6.9)	1 (2.4)	0.09
Immunocompromised ¥	32 (20.1)	27 (15.6)	9 (21.4)	0.48
Chronic kidney disease	34 (21.1)	24 (13.9)	6 (14.3)	0.18
Diabetes	54 (33.5)	50 (28.9)	10 (23.8)	0.40
Hypertension	93 (57.8)	71 (41)	22 (52.4)	0.009
Body mass index	28 (25–32)	28 (25–31)	28 (24–31)	0.70
Time since viral symptom onset	5 (4–7)	10 (9–11)	17 (16–22)	< 0.0001
Time from hospital to ICU admission	0 (0–1)	0 (0–1)	1 (0–7)	< 0.0001
Temperature at ICU admission	38 (37.3–38.9)	38 (37.2–38.7)	37.5 (37–38.1)	0.01
Oxygen flow at ICU admission (L/min)	12 (9–15)	15 (9–15)	15 (7–15)	0.23
Number of quadrants involved on Chest X Ray	3 (2–4)	4 (2–4)	4 (3–4)	0.007
Digestive viral symptoms at ICU admission £	39 (24.2)	49 (28.3)	11 (26.2)	0.69

The total number of patients is 376 as the time between viral symptom onset and ICU admission was unavailable for three patients

¥immunocompromised patients included patients with solid tumours, haematological malignancies, solid organ transplantation, or long-term or high-dose steroid therapy

£Digestive viral symptoms included diarrhoea, abdominal pain, vomiting, and/or occlusion

kidney injury, 74 (19.5%) required renal replacement therapy. ICU stay length was 10 [5–21] days. ICU, hospital, and day-28 mortality rates were 31% (n = 98), 39% (n = 103), and 26% (n = 100), respectively. On 15 May 2020, 103 (27%) patients were still hospitalised.

As shown in Fig. 1, day-28 mortality decreased with increasing time from viral symptom onset to ICU admission. Patients admitted within a week after viral symptom onset had a higher day-28 mortality rate than did those admitted in the second or third week after viral symptom onset (Figs. 2 and 3). Tables 1 and 2 compare patient characteristics across the three groups. Patients admitted within the first week were more often treated for hypertension and more often febrile at ICU admission; also, their radiographic lung involvement was more limited compared to that in the other two groups. Patients admitted in the first week less often received high-flow nasal oxygen; they had a higher prevalence of acute kidney injury and more often required renal replacement therapy during the ICU stay.

Among the 379 patients, 30% had an associate bacterial infection, including 9.4% with a SARS-CoV-2 superinfection and 20% with hospital acquired infections. Superinfections were diagnosed at the time of SARS-CoV-2 diagnosis in 50 patients and were related to S aureus (n = 16), other Staphylococcus sp. (n = 5), H. influenzae (n = 5), E Coli (n = 4), K. pneumonia (n = 5), P. aeruginosa (n = 3), Enterobacter sp. (n = 2), Citrobacter sp. (n = 3), Serratia sp. (n = 3), and M. catarrhalis (n = 4).

Factors associated with day-28 mortality included time since viral symptom onset: 36.7% vs. 20.8% vs. 11.9% patients died in the groups admitted within 0–7 days, 8–14 days, or >14 days after viral symptom onset, respectively (p < 0.0001); other factors were older age (66 y [57–72] in patients who died vs. 60 y [52–67] in patients who survived, p < 0.0001), COPD (12% vs. 2.9%, p = 0.001), hypertension (65% vs. 44%, p = 0.001), diabetes (45% vs. 25%, p < 0.0001), immunodeficiency (29% vs. 14%, p = 0.001), heart failure (14% vs. 6%, p = 0.03), chronic kidney disease (30% vs. 12%, p < 0.0001), SOFA score at ICU admission (7 [5–10] vs. 4 [3–7], p < 0.0001), acute kidney injury (73% vs. 44%, p = 0.001), platelet count (166 × 109/L [135–236] vs. 221 × 109/L [168–284], p < 0.0001), procalcitonin (0.72 ng/mL [0.40–1.57] vs. 0.42 ng/mL [0.18–1.06], p = 0.001), normal troponin concentration at admission (41% vs. 68%, p < 0.0001), need for invasive mechanical ventilation (80% vs. 61%, p < 0.0001), need for vasopressors (69% vs. 34%, p = 0.001), and need for renal replacement therapy (39% vs. 12%, p = 0.001).

By multivariable Cox proportional analysis, factors independently associated with day-28 mortality were age, COPD, immunocompromised status, time from viral symptom onset to ICU admission, normal troponin at ICU admission, and acute kidney injury (Table S1).

Fig. 1 Predicted mortality according to time from viral symptom onset to ICU admission
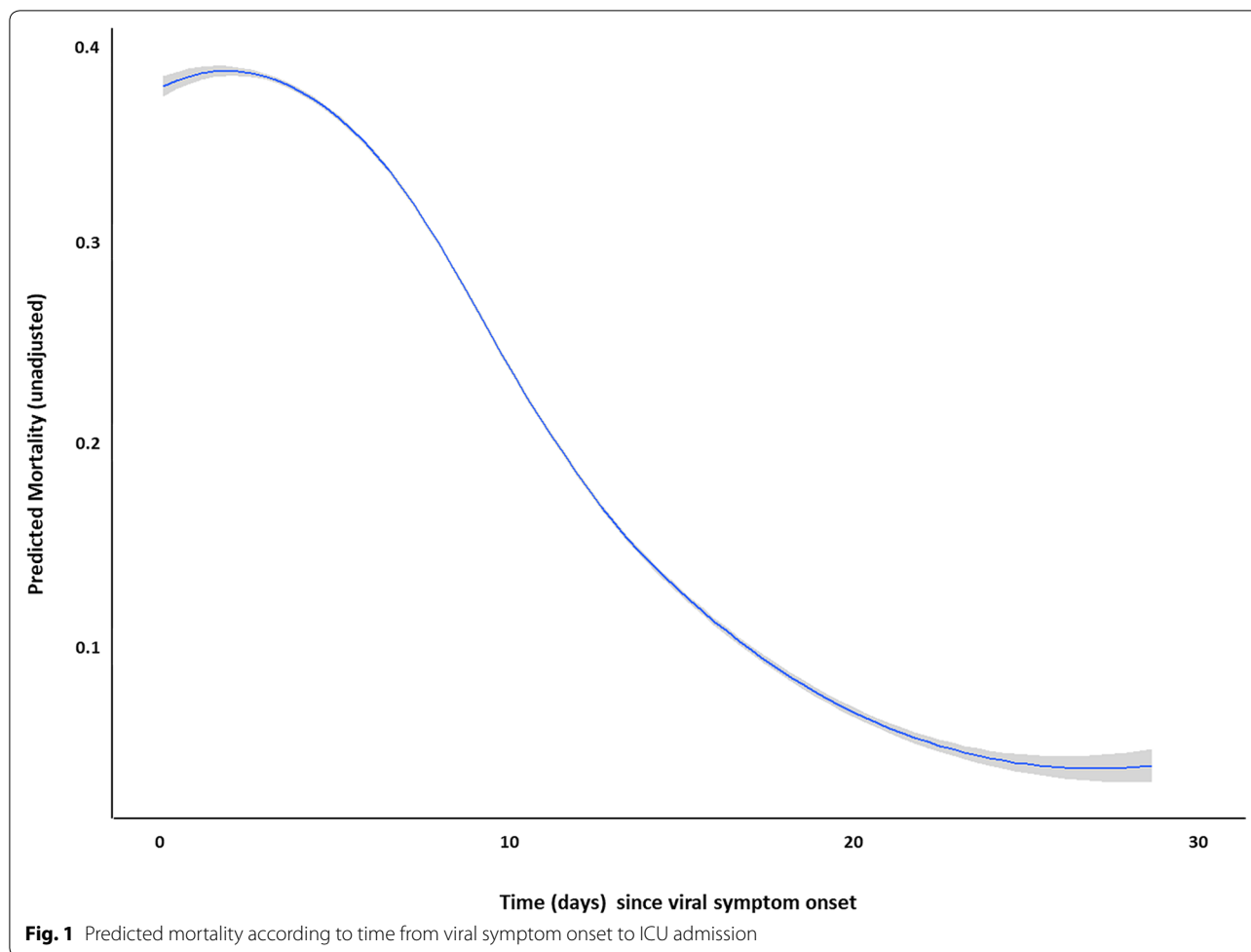
There was no centre effect in this study. For instance, when adding to our final model in the whole population a random effects model for the centre effect, our results were unchanged (HR for time since viral symptom onset 8–14 days: 0.51; 95% CI 0.32–0.80; HR for time > 14 days: 0.39; 95% CI 0.15–0.98).

In the paired matched analysis, 140 patients admitted within the first week after viral symptom onset were matched to 140 controls. Day-28 mortality was 36.4% in the group admitted within a week after disease onset and 21.4% in the group of patients admitted later (Fig. S1, $p = 0.001$). The multivariable Cox proportional model in the 280 paired patients showed that determinants of day-28 mortality were age (hazard ratio [HR], 1.04/year; 95% confidence interval [95% CI] 1.01–1.06, $p = 0.0004$), ICU admission more than 7 days after disease onset (HR 0.53; 95% CI 0.34–0.84; $p = 0.007$), SOFA score at ICU admission (HR, 1.11/point; 95% CI, 1.03–1.19; $p = 0.006$), and normal troponin (HR 0.64; 95% CI 0.39–1.06; $p = 0.05$).

In an exploratory analysis in 100 patients from our cohort (Table S2), concentrations of cytokines including IL6 and IL8 varied significantly across the three patient groups.

Discussion

Identifying the determinants of outcomes of critically ill patients with severe COVID-19 is vital to optimise the use of ICU and other hospital resources. This study collecting data from 379 COVID-19 patients showed that mortality decreased with increasing time from viral symptom onset to ICU admission. Mortality was significantly higher in patients admitted to the ICU within a week after viral symptom onset, independently from acute illness severity at ICU admission. These findings may help to guide the clinical management. They may also be useful for the identification and rational design of effective therapies.
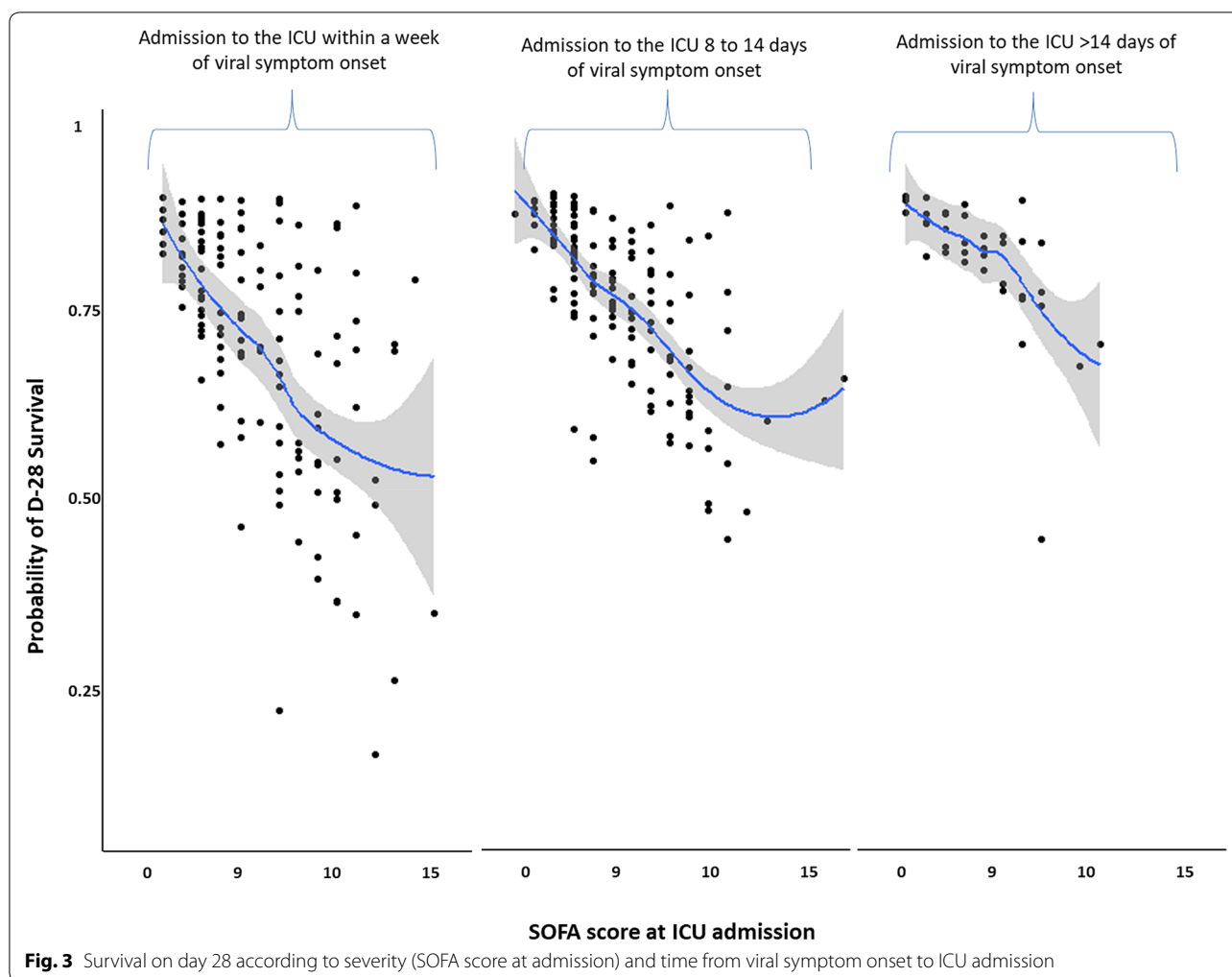
Interestingly, apart from the prevalence of hypertension, the baseline patient characteristics (age, sex, body mass index, hypoxaemia severity at admission, and inflammation) were mostly similar across the three patient groups defined by viral symptom duration at ICU

Fig. 2 Survival probability according to time (in weeks) from viral symptom onset to ICU admission
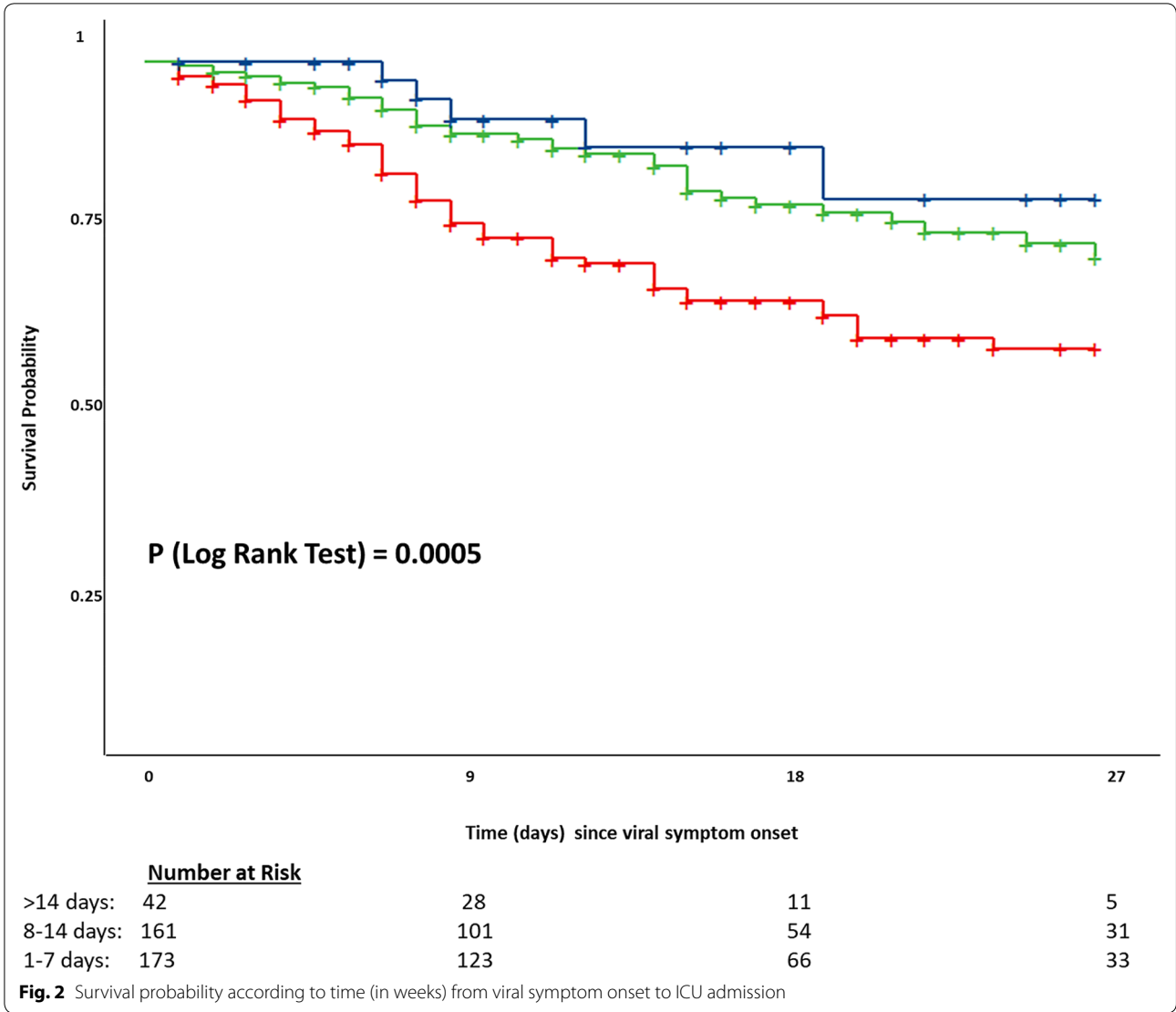
admission. The severity of respiratory failure as assessed by the PaO_2/FiO_2 ratio at admission was not significantly different across the three groups. In contrast, the group with early ICU admission had a worse SOFA score value and a higher prevalence of acute kidney injury, suggesting that the increased mortality was related to early multi-organ dysfunction, as opposed to only severe lung involvement. The significantly smaller number of lung quadrants involved in the early admission group supports this possibility. SARS-CoV-2 can bind to many target organs via the angiotensin-converting enzyme 2 receptor. The virus predominantly infects airway and alveolar epithelial cells, but can also infect vascular endothelial cells and macrophages [24]. SARS-CoV-2 viral particles and genome have been detected in monocytes and lymphocytes [25]. The aggressive inflammation induced by viral replication not only generates type II pneumocyte

apoptosis and severe respiratory distress related to cytokine-induced fluid leakage, but also induces a cytokine storm with multi-organ failure.

Three lines of evidence seem to support a two-hit model in which an initial insult related to viral replication and responsible for inflammation and injury to multiple organs is followed by a second insult related to exaggerated cytokine production by both epithelial and endothelial cells. First, in a study of 476 patients admitted in Wuhan, Shanghai, and Anhui, the time from viral symptom onset to the first positive RT-PCR test was shorter in the group with critical illness than in the groups with moderate or severe illness [9]. Second, virus-induced alveolar cell death and the accumulation of apoptotic and necrotic cellular debris have been reported to first elicit a pro-inflammatory response from the macrophages then to result in the production of large

Fig. 3 Survival on day 28 according to severity (SOFA score at admission) and time from viral symptom onset to ICU admission

amounts of eicosanoids, which in turn stimulate the production of pro-inflammatory cytokines by immune cells such as macrophages [26]. Thus, the eicosanoid storm induces a cytokine storm, which promotes further leucocytosis and immune-cell infiltration. Last, a study of 150 patients from Wuhan showed that the survival time from viral symptom onset to death had two peaks, at about 14 and 22 days, respectively, in keeping with our findings in patients having a length of stay of about 10 days [27]. Strikingly, 40% of the patients who died had myocardial damage [27], a finding consistent with the higher troponin levels in the patients who died compared to survivors in our study. The contribution of fulminant myocarditis to increased mortality in patients admitted within a week of disease viral symptoms deserves further investigation.

This study has several limitations. First, the retrospective design limits the interpretation of the findings. However, few data were missing (7.3%). Moreover, with 379 critically ill patients managed in four centres, this study is among the largest to date. The largest study to date of critically ill COVID-19 patients [10] emphasised the association of older age with short-term mortality, but did not separate outcomes according to time since viral symptom onset. Second, the excess mortality in patients admitted to the ICU within 7 days after viral symptom onset was associated with an increased prevalence of non-respiratory injury and, more specifically, of acute kidney and myocardial injury. However, we did not specifically assess causes of death. Third, although markers for inflammation were available for all 379 patients, cytokine and lymphocyte typing data were obtained in only 100 patients. Our results suggest that targeting IL-6 might be most effective in patients admitted earlier after viral symptom onset. However, this possibility requires further assessment. Moreover, sensitivity analyses of the results of ongoing anti-IL6 trials should also explore whether IL6 blockade is most beneficial in those patients admitted to the ICU within a week after viral symptom onset.

Table 2 Organ dysfunction and outcomes in patients with severe SARS-CoV-2 infection

Median (IQR) or N (%)	≤ 7 days N = 161	8–14 days N = 173	> 14 days N = 42	p value
Oxygenation/ventilation strategy				
Non-invasive ventilation (pressure support)	11 (6.8)	9 (5.2)	7 (16.7)	0.03
Continuous positive airway pressure (CPAP)	2 (1.2)	4 (2.3)	0	0.50
High-flow nasal oxygen	48 (29.8)	81 (46.8)	16 (38.1)	0.006
Mechanical ventilation on day 1	91 (56.5)	87 (50.3)	26 (61.9)	0.29
Mechanical ventilation throughout the ICU stay	114 (70.8)	111 (64.2)	30 (71.4)	0.37
PaO$_2$/FiO$_2$ ratio on day 1 (worst value)	124 (89–202)	123 (86–185)	143 (90–194)	0.76
Leucocytes (10^9/L)	7.93 (5.32–11.05)	8.34 (5.90–11.00°)	7.57 (5.41–10.84)	0.75
Lymphocytes	0.76 (0.58–1.10)	0.77 (0.54–1.08)	0.90 (0.55–1.05)	0.75
Platelet count (G/L)	178 (140–240)	226 (176–285)	248 (175–320)	< 0.001
C-reactive protein	169 (97–263)	185 (119–248)	141 (96–206)	0.20
Procalcitonin	0.52 (0.21–1.34)	0.46 (0.23–1.17)	0.35 (0.16–0.71)	0.11
Ferritin	1441 (740–2354)	1172 (821–2000)	739 (491–1433)	0.20
D-dimers (IU)	1557 (796–3120)	1715 (919–3764)	2090 (1350–1764)	0.41
Fibrinogen (g/L)	6.70 (5.60–7.60)	6.90 (5.96–7.60)	7.19 (6.50–8.22)	0.01
Troponin in the normal range	83 (57)	103 (64)	22 (61)	0.37
Associated bacterial infection				
Clinically/microbiologically documented	8 (5.0) / 21 (13.0)	4 (2.3) / 25 (14.4)	1 (2.4) / 4 (9.5)	0.73
SOFA score on day 1	5 (3–8)	4 (3–7)	4 (2–7)	0.05
Need for vasopressors	69 (42.9)	76 (44.2)	20 (48.8)	0.06
Creatinine at admission (µmol/L)	89 (69–133)	76 (62–100)	74 (64–97)	0.002
Acute kidney injury	96 (59.6)	76 (43.9)	21 (50)	0.01
Renal replacement therapy	39 (24.2)	30 (17.3)	4 (9.5)	0.05
Documented pulmonary embolism	15 (11.1)	25 (18.1)	2 (6.2)	0.10
ICU mortality	56 (41%)	36 (27%)	5 (18)	0.01
Day-28 mortality	59 (36.6)	36 (20.8)	5 (11.9)	< 0.0001

The total number of patients is 376 as the time between viral symptom onset and ICU admission was unavailable for three patients.

IQR interquartile range; *ICU* intensive care unit; *SOFA score* Sequential Organ Failure Assessment score

In summary, excess mortality occurred in patients admitted to the ICU within a week after COVID-19 onset. This excess mortality was not related to more severe respiratory disease but, instead, to worse dysfunction of other organs and, more specifically, to acute kidney and myocardial injury. Studies to investigate the extent of organ injuries at each stage of the disease are warranted. Interventions including antiviral, anti-inflammatory, or targeted therapies that are currently used in patients with SARS-CoV-2 might impact different clinical endpoints according to time since viral symptom onset.

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