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Clinical characteristics and outcomes of critically ill patients with novel coronavirus infectious disease (COVID-19) in China: a retrospective multicenter study

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Abstract

Purpose: An ongoing outbreak of coronavirus disease 2019 (COVID-19) emerged in Wuhan since December 2019 and spread globally. However, information about critically ill patients with COVID-19 is still limited. We aimed to describe the clinical characteristics and outcomes of critically ill patients with COVID-19 and figure out the risk factors of mortality.

Methods: We extracted data retrospectively regarding 733 critically ill adult patients with laboratory-confirmed COVID-19 from 19 hospitals in China through January 1 to February 29, 2020. Demographic data, symptoms, laboratory values, comorbidities, treatments, and clinical outcomes were collected. The primary outcome was 28-day mortality. Data were compared between survivors and non-survivors.

Results: Of the 733 patients included in the study, the median (IQR) age was 65 (56–73) years and 256 (34.9%) were female. Among these patients, the median (IQR) APACHE II score was 10 (7 to 14) and 28-day mortality was 53.8%. Respiratory failure was the most common organ failure (597 [81.5%]), followed by shock (20%), thrombocytopenia (18.8%), central nervous system (8.6%) and renal dysfunction (8%). Multivariate Cox regression analysis showed that

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older age, malignancies, high APACHE II score, high D-dimer level, low PaO_2/FiO_2 level, high creatinine level, high hscTnI level and low albumin level were independent risk factors of 28-day mortality in critically ill patients with COVID-19.

Conclusion: In this case series of critically ill patients with COVID-19 who were admitted into the ICU, more than half patients died at day 28. The higher percentage of organ failure in these patients indicated a significant demand for critical care resources.

Keywords: COVID-19, Critically ill, Organ failure, Mortality

Introduction

Since the first case was reported as Coronavirus Infectious Disease 2019 (COVID-19) in Wuhan in last December [1], there has been more than 14,000,000 laboratory-confirmed cases around the world, among whom more than 600,000 patients have died [2]. As a response, World Health Organization (WHO) declared that the outbreak of COVID-19 constituted a public health emergency of international concerns on January 30, 2020.

The clinical spectrum of COVID-19 ranges from mild to severe, while 5% of all symptomatic patients with COVID-19 were classified as critical cases (i.e. severe respiratory failure requiring mechanical ventilation, shock, and/or multiple organ dysfunction), with mortality of 49% [3]. Only a few studies described the characteristics and outcomes of critically ill patients with COVID-19 [">3–6]. Grasselli et al. reported baseline characteristics of 1591 patients with COVID-19 admitted to intensive care units (ICUs) of the Lombardy region, Italy [6]. However, at the time of reporting, 920 patients (58%) were still in the ICU. The others were all single-center studies enrolling a small number of ICU patients [3–5]. Yang et al. reported that, among 52 critically ill patients with COVID-19, 37 required mechanical ventilation and 32 died at 28 days [4].

The objective of this study was to describe the clinical characteristics and outcomes of critically ill patients with COVID-19, the disease progression in survivors and non-survivors, and risk factor of case fatality.

Take home message

In this large sample of 733 critically ill patients with COVID-19, more than half patients died at day 28. A high prevalence of organ dysfunction such as respiratory failure, shock and acute renal failure was found during ICU stat. In addition, older age, male sex, malignancies, high APACHE II score, high D-dimer level, high creatinine level and low albumin level were independent risk factors of mortality in critically ill patients with COVID-19. The higher percentage of organ failure in these patients indicated a significant demand for critical care resources.

Methods

Study design

This retrospective, multi-center observational study was conducted in 19 designated hospitals for COVID-19 in Wuhan (Hubei Province), Huangshi (Hubei Province), Shenzhen (Guangdong Province), and (Jiangsu Province) (Table S1). The study was approved by the ethics committee of Jin Yin-tan Hospital (KY-2020-10.02). The informed consent was waived due to the retrospective and observational nature of the study.

All adult patients with COVID-19 who were admitted to ICUs of the participating hospitals between January 1 and February 29, 2020 were included in this study, if they met the following inclusion criteria: (1) > 18 years of age; (2) laboratory-confirmed diagnosis of COVID-19 [7]; (3) severe respiratory failure requiring advanced respiratory support [i.e. high flow nasal oxygen (HFNO), noninvasive mechanical ventilation (NIV), and invasive mechanical ventilation (IMV)], circulatory shock, or multiorgan failure. There were no exclusion criteria.

Data collection

For every enrolled patient, we collected demographic data, comorbidities, presenting signs and symptoms, severity of illness, laboratory tests, pharmacological and non-pharmacological treatment during ICU stay, and patient outcome. Laboratory tests included complete blood count, electrolytes, hepatic and renal function tests, coagulation tests, arterial blood gas, biomarkers of inflammation [hypersensitive C-reactive protein (hs-CRP)], and biomarkers of cell injury [lactate dehydrogenase (LDH), hypersensitive cardiac troponin I (hsc-TnI)]. In cases when arterial blood gas analysis was not available, PaO_2/FiO_2 ratio was calculated based on Rice equation [8]. Severity of illness was assessed by Acute Physiology and Chronic Health Evaluation (APACHE) II score, based on the worst variables recorded during the first 24 h of ICU admission. Organ dysfunction was assessed by Sequential Organ Failure Assessment (SOFA) score, together with vital signs and laboratory tests, on day 1, 3, 7 and 14 after ICU admission. Individual organ failure was defined as a component SOFA score greater than 2 [9]. Cardiac injury was defined as serum level

of hsc-TnI above the upper limit of the reference range (> 28 pg/mL).

All patients included in the study were followed up to 28 days or death, which occurred earlier after enrollment. The primary outcome was 28-day mortality after ICU admission. Secondary outcomes included use of life-sustaining treatment [IMV, extracorporeal membrane pulmonary oxygenation (ECMO), and continuous renal replacement therapy (CRRT)], ICU length of stay, virus negative conversion rate and dynamic changes of laboratory tests.

Statistical analysis

Values were presented as frequency/percentage of a group from which they were derived (categorical variables), or as the mean ± standard deviation (SD) or median [interquartile range (IQR)] when appropriate (continuous variables). Categorial variables were compared with the use of Chi-square test or Fisher's exact test, while continuous variables were compared with the Student's *t* test or Mann–Whitney *U* test.

Three multivariate models were constructed to determine the risk factors of 28-day mortality. First, the multivariate Cox proportional-hazards regression model was used to explore the independent risk factors associated with 28-day mortality. Variables on ICU admission with *P* value < 0.05 in univariate analysis or determined as risk factors of mortality in previous studies were entered into the model. Variables with considerable collinearity [e.g. blood urea nitrogen (BUN) and serum creatinine] were carefully selected, and those with more clinical relevance were entered into the model. The final model was tested for proportional hazards assumptions (using Schoenfeld residuals) and nonlinearity in relationship between the log hazard and the covariates (using Martingale-residual plots). Continuous variables with nonlinearity [international normalized ratio (INR), creatinine, and hscTnI] were transformed to categorial variables according to quartiles and then included in the Cox regression model. Second, a frailty Cox model was used to test the inter-center variability based on the first approach. Last, we performed multivariate Cox regression model to adjust for both variables on ICU admission and time-dependent variables (including SOFA, PaO_2/FiO_2 ratio, lymphocyte count, albumin, creatinine, LDH, hsCRP, D-dimer, hsc-TnI, and INR) [10].

The joint longitudinal model was used to analyze the dynamic changes of laboratory tests. Missing data of key variables was summarized in Table S2. We used multiple imputation by chained equation (MICE) which generated values for all missing data using the observed data for all patients (supplements) for multivariate Cox proportional-hazards regression. Given the censored outcome, the cumulative baseline hazard was introduced in the imputation model. Kaplan–Meier survival curve was performed to analyze 28-day survival rates in all patients. All statistical analyses were performed using the RStudio (version 1.2.5019) and Stata (version 15.1), and $P < 0.05$ was considered statistically significant.

Results

Demographic and clinical characteristics

During the study period, 733 critically ill patients with COVID-19 were admitted to the ICUs of the participating hospitals and thus included in the analysis. The median age was 65 years (IQR 56–73), and 477 (65.1%) were male (Figure S1). Of these patients, 454 (61.9%) had one or more comorbidities, with hypertension (42%) as the most common comorbidity, followed by diabetes (18.8%) and coronary heart disease (12.7%). The most common presenting symptoms were fever [630 (85.9%)], dry cough [550 (75%)], and dyspnea [444 (60.7%)] (Table 1). The median duration from symptom onset to hospitalization and ICU admission were 6 days (IQR 3–10) and 13 days (IQR 9–20), respectively (Table 2).

Organ failure and life-sustaining treatment in ICU

Of the 733 patients, respiratory failure was the most common organ failure [597 (81.5%)], as suggested by PaO_2/FiO_2 ratio of 100 mmHg (IQR 40–191). shock was the second most common organ dysfunction [147 (20%)], followed by thrombocytopenia [138 (18.8%)], central nervous system [63 (8.6%)] and renal failure [59 (8.0%)] (Figure S2). In particular, 357 (59.2%) out of 603 patients had evidence of cardiac injury. As a result, HFNO, NIV, and IMV were used in 397 (54.2%), 388 (52.9%), and 307 (41.9%) patients, respectively. In patients treated with IMV, duration of HFNO and NIV before IMV was much shorter in survivors than non-survivors [2 days (IQR 0–8) vs. 4 days (IQR 1–7), $P = 0.039$]. Moreover, 297 (40.4%) and 95 (13%) patients received vasopressors and CRRT, respectively. Other pharmacological treatments, such as antivirals, corticosteroids, and immunomodulatory therapy, were reported in Table S2.

Clinical outcome and risk factors for case fatality

Three hundred and ninety-four patients died at day 28 after ICU admission, corresponding to mortality of 53.8% [95% confidence interval (CI) 50.1–57.4%] (Fig. 1). The length of ICU stay was 12 (6–25) days and viral negative conversion rate was 66.3%. Compared with survivors, non-survivors were more likely to be older [68 (IQR 62–75.5) vs. 61 (IQR 51–69), $P < 0.001$], male (69% vs. 60.5%, $P = 0.015$), and having comorbidities (67.5% vs. 55.5%, $P = 0.001$). The length of ICU stay was significantly longer and the viral negative conversion rate

Table 1 Characteristics of critically ill patients with COVID-19

Characteristic	All (*N* = 733)	Survivor (*N* = 339)	Non-survivor (*N* = 394)	*P* value
Age, median (IQR)	65 (56–73)	61 (51–69)	68 (62–75.5)	< 0.001
Female, *n* (%)	256 (34.9)	134 (39.5)	122 (31)	0.015
APACHE II score on the first day of ICU admission-median (IQR)	10 (7–14)	7 (5–11)	13 (10–16)	< 0.001
SOFA score on the first day of ICU admission-median (IQR)	4 (1–5)	2 (0–4)	5 (4–7)	< 0.001
No. of comorbidities-median (IQR)	1(0–2)	1(0–2)	1(0–2)	0.022
Any comorbidity, *n* (%)	454 (61.9)	188 (55.5)	266 (67.5)	0.001
Hypertension, *n* (%)	308 (42)	122 (36)	186 (47.2)	0.002
Diabetes, *n* (%)	138 (18.8)	60 (17.8)	78 (19.8)	0.469
Coronary heart disease, *n* (%)	93 (12.7)	38 (11.2)	55 (14)	0.265
Chronic lung disease, *n* (%)	37 (5)	13 (3.8)	24 (6.1)	0.164
Congestive heart failure, *n* (%)	15 (2)	6 (1.8)	9 (2.3)	0.624
Stroke, *n* (%)	34 (4.6)	14 (4.1)	20 (5.1)	0.544
Chronic renal failure, *n* (%)	13 (1.8)	5 (1.5)	8 (2)	0.570
Malignancies, *n* (%)	24 (3.3)	7 (2.1)	17 (4.3)	0.088
Cirrhosis, *n* (%)	11 (1.5)	4 (1.2)	7 (1.8)	0.508
Immune suppression, *n* (%)	8 (1.1)	2 (0.6)	6 (1.5)	0.297
Connective tissue disease, *n* (%)	5 (0.7)	1 (0.3)	4 (1)	0.380
Ever smoker, *n* (%)	45 (6.1)	12 (3.5)	33 (8.4)	0.007
Ever drinker, *n* (%)	36 (4.9)	11 (3.2)	25 (6.3)	0.053
Symptoms, *n* (%)				
Fever	630 (85.9)	287 (84.7)	343 (87.1)	0.352
Cough	550 (75)	254 (74.9)	296 (75.1)	0.950
Dyspnea	444 (60.7)	163 (48.1)	281 (71.3)	< 0.001
Diarrhea	90 (12.3)	44 (13)	46 (11.8)	0.592
Fatigue	402 (54.8)	165 (48.7)	237 (60.2)	0.002
HFNO[a]	397 (54.2) (50.5–57.8)	185 (54.6) (49.2–59.9)	212 (53.8) (48.9–58.8)	0.836
Non-invasive ventilation[a]	388 (52.9) (49.3–56.6)	136 (40.1) (34.9 –45.4)	252 (64) (59.2–68.7)	< 0.001
PEEP, cmH_2O, median (IQR)	8 (6–10)	6 (5–8)	8 (6–10)	< 0.001
FiO_2, %, median (IQR)	80 (55–100)	60 (45–80)	90 (75–100)	< 0.001

IQR interquartile range, *CI* confidence interval, *APACHE* acute physiological and chronic health evaluation, *HFNO* high flow nasal oxygen, *PEEP* positive end expiratory pressure, *SOFA* sequential organ failure assessment

[a] Use before invasive mechanical ventilation

was significantly higher in survivors. Laboratory tests suggested that white blood cell count, hs-CRP, LDH, hsc-TnI, and D-dimer were higher in non-survivors, suggesting more severe systemic inflammation, cell injury, and coagulopathy (Table S4). Therefore, non-survivors were more severely ill, as suggested by higher APACHE II and SOFA score, more organ dysfunction (Figure S2), more life-sustaining treatments, and lower virus negative conversion rate (26.2% vs. 89.8%, $P < 0.001$) (Table 2 and Figure S3).

No violation against the proportional hazard assumption was detected in the test for 28-day mortality (Table S5). Older age, malignancies, high APACHE II score, high D-dimer level, high creatinine level, high hscTnI level, low P/F ratio and low albumin level were independent risk factors of mortality in critically ill patients with COVID-19 (Table 3). Similar results were found in the multivariate frailty Cox model and the Cox regression model accounting for the time-varying variables (Tables S6 and S7).

Dynamic changes of laboratory tests and life-sustaining treatment during ICU stay

From day 1 to day 14 in ICU, PaO_2/FiO_2 ratio and lymphocyte count steadily improved in survivors and remained low in non-survivors (Table S4). In comparison, hs-CRP and LDH levels significantly decreased in survivors but remained higher in non-survivors, whereas

Table 2 Clinical course and outcome of critically ill patients with COVID-19

	All (*N* = 733)	Survivor (*N* = 339)	Non-survivor (*N* = 394)	*P* value
Time course of illness-day, median (IQR)				
Symptoms to hospital admission	6 (3–10)	5 (2–9.5)	7 (3–10)	0.276
Symptom onset to ICU admission	13 (9–20)	13 (9–20)	14 (10–19)	0.309
Respiratory support at ICU admission				
Nasal and mask oxygen therapy	149 (20.3) (17.4–23.2)	81 (23.9) (19.3–28.5)	68 (17.3) (13.5–21)	0.026
HFNO	320 (43.7) (40.1–47.3)	176 (51.9) (46.6–57.3)	144 (36.5) (31.8–41.3)	< 0.001
Non-invasive ventilation	164 (22.3) (19.3–25.4)	57 (16.8) (12.8–20.8)	107 (27.2) (22.7–31.2)	0.001
Invasive machinal ventilation	100 (13.6) (11.2–16.1)	25 (7.4) (4.6–10.2)	75 (19) (15.1–22.9)	< 0.001
Life sustaining treatment during ICU stay				
Invasive mechanical ventilation, *n* (%) (95%CI)	307 (41.9) (38.3–45.5)	59 (17.4) (13.5–21.9)	248 (62.9) (58–67.7)	< 0.001
Duration of IMV, day, median (IQR)	7 (3–12)	9 (5–15)	6 (3–11)	< 0.001
PEEP, cmH_2O, median (IQR)	10 (9–12)	10 (8–12)	10 (9–12)	0.355
FiO_2, %, median (IQR)	90 (70–100)	80 (70–100)	100 (75–100)	< 0.001
Tidal volume, ml, median (IQR)	400 (370–450)	420 (400–450)	400 (360–450)	0.497
Vasopressor, *n* (%) (95%CI)	297 (40.4) (36.8–44)	41 (12.1) (8.8–16)	255 (64.7) (59.8–69.4)	< 0.001
CRRT, *n* (%) (95%CI)	95 (13) (10.6–15.6)	18 (5.3) (3.2–8.3)	77 (19.5) (15.7–23.8)	< 0.001
ECMO, *n* (%) (95%CI)	35 (4.8) (3.3–6.6)	13 (3.8) (2.1–6.5)	22 (5.6) (3.5–8.3)	0.268
Viral negative conversion rate, *n/N* (%)	226/341 (66.3)	193/215 (89.8)	33/126 (26.2)	< 0.001
Duration of HFNO and NIV before IMV, days, median (IQR)	4 (1–7)	2(0–8)	4 (1–7)	0.039
ICU length of stay, days, median (IQR)	12 (6–25)	27 (13–28)	7 (4–12)	< 0.001

IQR interquartile range, *CI* confidence interval, *CRRT* continuous renal replacement therapy, *ECMO* extracorporeal membrane oxygenation, *FiO_2* fraction of inspired oxygen, *HFNO* high flow nasal oxygen, *ICU*, intensive care unit, *IMV* invasive mechanical ventilation, *PEEP* positive end expiratory pressure

D-dimer and hsc-TnI levels were relatively stable, but significantly higher in non-survivors than survivors. In the joint longitudinal model, there was significant difference between survivors and nonsurvivors with regards to dynamic changes of PaO_2/FiO_2 ratio, hs-CRP, LDH, D-dimer and hsc-TnI levels, but not lymphocyte count, over time during ICU stay (Fig. 2). Proportion of survivors and non-survivors receiving life-sustaining treatment are shown in Figure S3.

Discussion

In this large sample of 733 critically ill patients with COVID-19, we reported a high 28-day mortality of 53.8%, which might be explained by the high prevalence of organ dysfunction such as respiratory failure, shock and acute renal failure. In addition, independent risk factors of mortality were also identified.

The variation of mortality in critically ill patients with viral pneumonia might be explained, at least in part, by different etiologies. Current data suggested that pneumonia caused coronavirus was associated with a higher mortality than influenza virus. Yang et al. observed a 28-day mortality of 61.5% among 52 critically ill patients with COVID-19 [4], while two case series from the United States reported mortality of 50% and 67%, respectively [3, 5]. Likewise, pneumonia caused by the other two coronaviruses, i.e. SARS-CoV and MERS-CoV, was also associated with high mortality [">11–15]. In comparison, a much lower mortality (i.e. 17–40%) was reported in critically ill patients with influenza A (H1N1) pneumonia [16–18].

Acute respiratory failure represented the most common organ failure in patients with COVID-19. Therefore, mechanical ventilation was the mainstay in the treatment of severe hypoxemia. However, timing of IMV still remained controversial. Among 307 patients (41.9%) who received IMV during ICU stay in our study, duration of HFNO and NIV before IMV was 2 days longer in non-survivors, suggesting that delayed intubation might be associated with poor clinical outcome in patients with COVID-19. This was consistent with the interim guidance of WHO and China [7, 19], which strongly recommended that patients treated with HFNO or NIV should be closely monitored for clinical deterioration due to the high risk of treatment failure, and endotracheal intubation should be considered if the patient acutely deteriorated or did not improve after a short trial.

Apart from acute respiratory failure, critically ill patients also developed other organ dysfunction and/or failure, such as cardiac injury/shock, and acute renal failure. Almost 60% of patients in our study had evidence of cardiac injury (i.e. elevated hsc-TnI level), a common

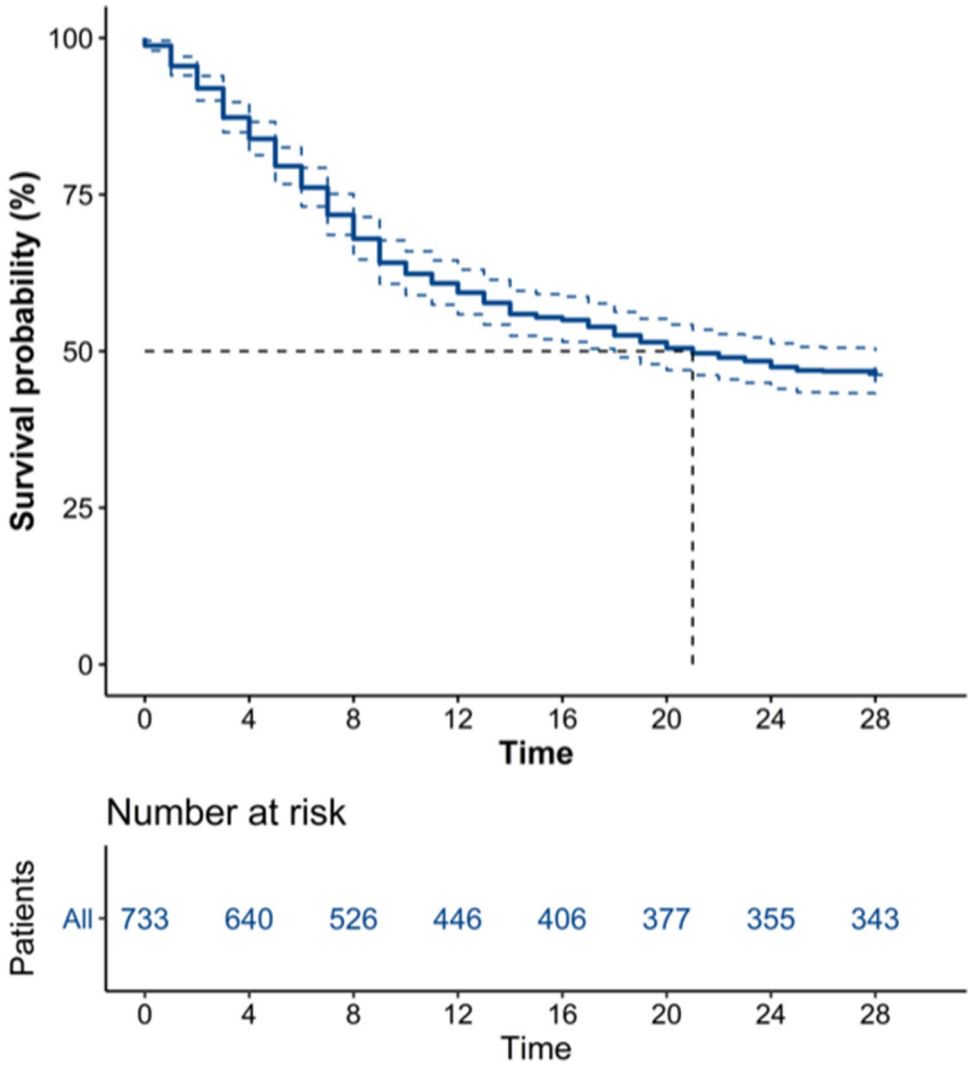

Fig. 1 Survival of critically ill patients with COVID-19 admitted to ICU. Dashed lines represent 95% CI

finding in previous studies of critically ill patients with COVID-19 [20–22]. Potential mechanisms of cardiac injury in patients with COVID-19 remained to be elucidated, but might be related to fulminant myocarditis due to direct viral infection, as well as type 2 myocardial infarction due to imbalance between myocardial oxygen supply and demand [23]. In addition, prevalence of cardiac injury was 63% in patients infected with influenza A (H7N9) virus, which was associated with lower probability of virus clearance and higher mortality [24]. In contrast, cardiac injury had not been reported in patients with SARS or MERS. Although it was possible that SARS-CoV-2 might cause injury to target organs different from that of SARS-CoV and MERS-CoV, a more plausible explanation would be the limited, if any, use of biomarkers of cardiac injury (e.g. hsc-TnI) in previous studies.

We compared changes of laboratory tests, organ dysfunction, and life-sustaining treatment over time in survivors and non-survivors. The changes of lymphocyte count and D-dimer level were similar to that in previous studies [25–27]. Our results further suggested persistent lymphocytopenia, hypoxemia, inflammation and cell injury might help discriminate those patients with poor treatment response and grave outcome. In addition, the pattern of organ dysfunction/failure as well as life-sustaining treatment over time improved our understanding of the demand of critical care resource among critically ill patients with COVID-19. We believed that these data might help those experiencing a surge of critically ill cases with COVID-19 to make a better preparation with regards to medical devices, medications, and human power.

Table 3 Univariate and multivariate Cox regression proportional-hazards model of risk factors associated with 28-day mortality in COVID-19 patients

Variables	Univariate				Multivariate			
	HR	95% CI		*P* value	HR	95% CI		*P* value
Age	1.038	1.029	1.047	< 0.001	1.024	1.015	1.034	< 0.001
Male	1.278	1.030	1.586	0.026				
Hypertension	1.375	1.126	1.679	0.002				
Malignancies	1.909	1.174	3.106	0.009	1.950	1.186	3.204	0.008
Smoking	1.553	1.081	2.230	0.017				
SOFA	1.218	1.184	1.252	< 0.001				
APACHE II	1.104	1.090	1.119	< 0.001	1.037	1.011	1.063	0.005
PaO_2/FiO_2 ratio	0.993	0.992	0.995	< 0.001	0.996	0.995	0.998	< 0.001
Lymphocyte	0.874	0.722	1.057	0.164				
LDH	1.000	1.000	1.000	< 0.001				
Albumin	0.8958	0.879	0.913	< 0.001	0.938	0.918	0.959	< 0.001
CRP	1.005	1.004	1.007	< 0.001				
INR < 0.97, s, reference								
0.97–1.09, s	1.522	1.085	2.137	0.015				
1.10–1.22, s	1.941	1.391	2.707	< 0.001				
> 1.22, s	3.931	2.872	5.380	< 0.001				
D-dimer	1.021	1.016	1.025	< 0.001	1.006	1.000	1.011	0.035
Creatinine < 56.9, umol/L, reference								
56.9–70.6, umol/L	1.038	0.761	1.416	0.815				
70.7–93, umol/L	1.453	1.084	1.948	0.012	1.411	1.014	1.962	0.041
> 93, umol/L	2.207	1.659	2.936	< 0.001	1.636	1.167	2.293	0.004
hscTnI < 10.2 reference								
10.2–27.7	1.170	0.848	1.613	0.339				
27.8–103.5	1.628	1.202	2.204	0.002				
> 103.5	3.182	2.388	4.240	< 0.001	1.453	1.048	2.014	0.025
NIV at ICU admission	1.403	1.121	1.756	0.003				
HFNO at ICU admission	1.102	0.901	1.347	0.345				

APACHE acute physiological and chronic health evaluation, *AST* aspartate aminotransferase, *CRP* C-reactive protein, *FiO_2* fraction inspired oxygen concentration, *INR* international normalized ratio, *LDH* lactate dehydrogenase, *PaO_2* pulse oxygen saturation, *SOFA* sequential organ failure assessment

Previous studies showed that the relationship between sex and mortality remained controversial in patients with infection/sepsis. A retrospective study reported that male sepsis had a higher 90-day mortality rate than female. However, a study of 563,155 sepsis patients also reported that female was independently associated with increased mortality [28]. In line with patients with SARS, MERS or influenza A (H1N1) pneumonia [11, 17, 18], we found that male was not associated with increased mortality in critically ill patients with COVID-19. As in other studies [26], D-dimer were independent risk factors of mortality in patients with COVID-19.

Our study was subject to limitations. First, this was a retrospective study during a pandemic with 10–20% rate of missing data, which might introduce bias in study results. Second, we only enrolled patients who were admitted into ICU in January and February 2020, when medical resources were overwhelmed by the surge of COVID-19 cases. Critically ill patients with COVID-19 who were treated in the ICU in March and April might have a different disease pattern and, possibly, clinical outcome. Third, we did not collect data with regards to complications such as secondary infection, bleeding, and thromboembolism. As a matter of fact, coagulopathy and thromboembolism had been reported with prevalence up to 30% in ICU patients with COVID-19 [29, 30]. Forth, we did not report cause of death in critically ill patients with COVID-19. However, severe hypoxemia was the leading cause of death among critically ill patients with COVID-19 in our previous study, followed by circulatory shock [31]. Fifth, 13.6% of our patients still remained in the hospital at the end of follow-up, i.e. 28 days after ICU admission. Long-term clinical outcome might be only available with longer follow-up.

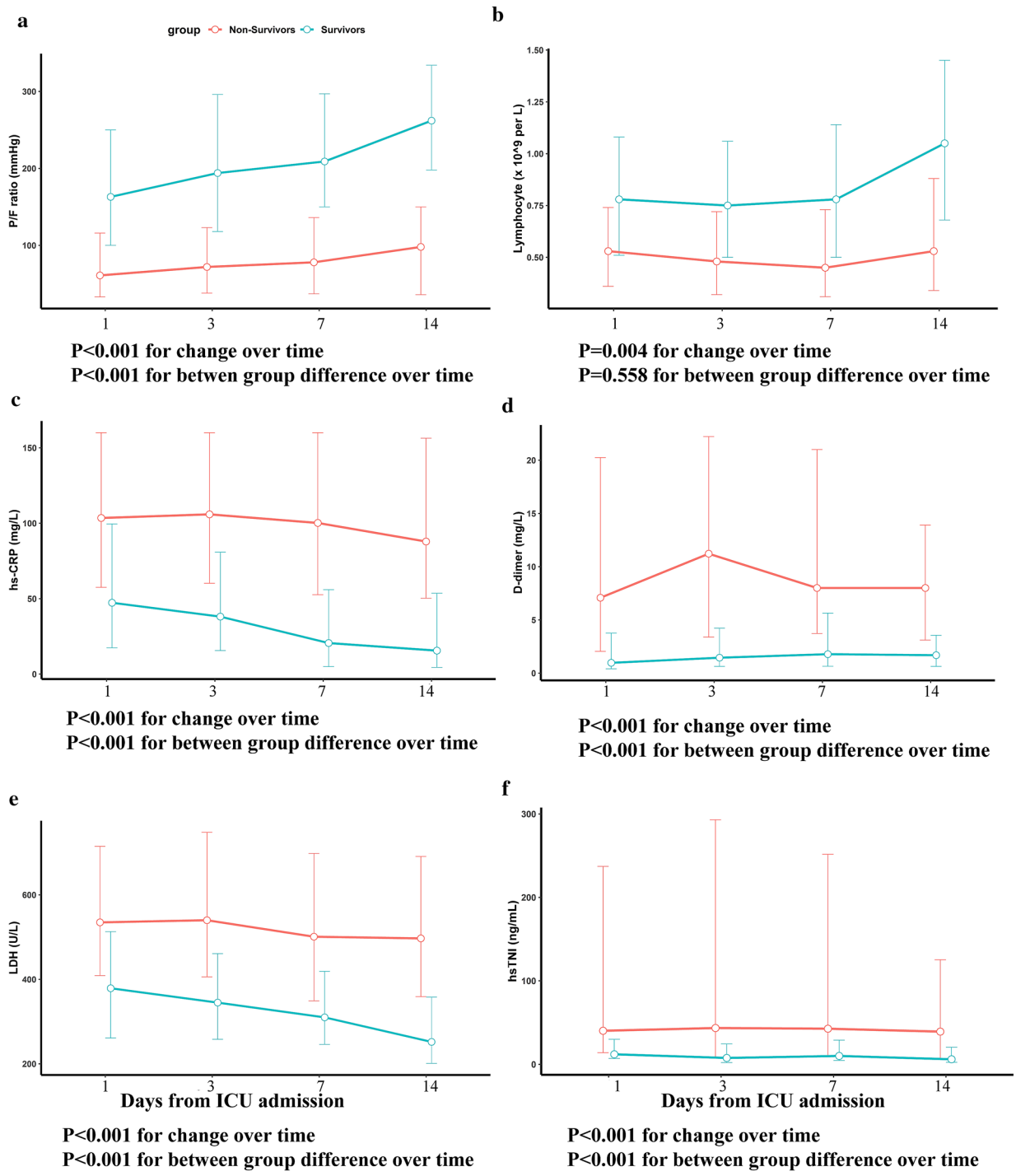

Fig. 2 Temporal changes in laboratory markers from ICU admission in critically ill patients with COVID-19. Figure shows temporal changes in P/F ratio (**a**), lymphocytes (**b**), hs-CRP (c), D-dimer (**d**), LDH (**e**), and hsc-TnI (**f**). Differences between survivors and non-survivors were significant for all time points shown. *hs-CRP* high-sensitive C-reactive protein, *LDH* lactate dehydrogenase, *hsc-TnI* high-sensitivity cardiac troponin I

In conclusion, in this case series of critically ill patients with COVID-19 who were admitted into the ICU, more than half patients died at day 28. The higher percentage of organ failure in these patients indicated a significant demand for critical care resources.

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Author contributions
JX, WW, SL, YH, MH, JL, ZT, HQ and BD had the idea for and designed the study; ZT, BD and HQ supervised the study; JX, YW and HK did the statistical analysis. All authors contributed to acquisition, analysis, or interpretation of data. JX and BD wrote the manuscript. All authors revised the report and approved the final version before submission.

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Compliance with ethical standards

Conflicts of interest
We declare no competing interests.

Ethical statement
Approval of the ethics committee of Jin Yin-tan Hospital (KY-2020-10.02), Wuhan, China.

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