Clinical Course and Outcomes of 344 Intensive Care Patients with COVID-19

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Author Contributions

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Introduction

With the dramatic increase of confirmed cases with coronavirus disease 2019 (COVID-19) and increasing death toll in China, timely and effective management of severe and critically ill patients appears to be particularly important. Previous studies on COVID-19 mainly described the general features of patients (1). However, little attention has been paid to clinical characteristics and outcomes of intensive care patients, data of which are scarce but are of paramount importance to reduce mortality. Some of the results of these studies have been previously reported in the form of an abstract (2).

Methods

This study enrolled 344 severe and critically ill patients (intensive care patients) who were diagnosed with COVID-19 according to WHO interim guidance by positive result of a RT-PCR assay of nasal and (or) throat-swab specimens and were hospitalized in eight intensive care wards (totaling approximately 330 beds) in Tongji hospital from January 25 through February 25, 2020. The intensive care wards staff intensivists and specialist nurses in intensive care, and were equipped with continuous vital signs monitoring, respiratory support including non-invasive and invasive ventilators, high-flow nasal cannula (HFNC) oxygen therapy, and extracorporeal membrane oxygenation (ECMO). We collected demographic, clinical, laboratory and radiologic findings, treatment and outcome data from electronic medical records. The illness severity of COVID-19 was defined according to the Chinese management guideline for COVID-19 (version 6.0) (3). Cytokines were measured by a chemiluminescent immunometric assay (Immulite 1000; Diagnostic Products, Gwynedd,

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UK). Acute respiratory distress syndrome (ARDS) was diagnosed according to the Berlin Definition and septic shock was defined according to the 2016 Third International Consensus Definition (4, 5). Disseminated intravascular coagulation (DIC) was defined by the International Society of Thrombosis and Haemostasis (ISTH) and acute kidney injury (AKI) was diagnosed according to the KDIGO clinical practice guidelines (6). Myocardial damage was diagnosed according to the serum levels of cardiac biomarkers or new abnormalities in electrocardiography and echocardiography. Liver injury was diagnosed according to elevation of bilirubin and aminotransferase. Rhabdomyolysis was diagnosed on the basis of the serum level of Creatine kinase and myoglobin. Survival endpoint was 28-day mortality after admission to the intensive care ward. The Ethics Commission of Tongji hospital approved this study, with a waiver of informed consent. Continuous variables were described as median (IQR) while categorical variables were expressed as frequencies (%). Statistical analyses were conducted with R3.6.2 using a Fisher's exact test for categorical data and Mann-Whitney test for continuous data; Kaplan-Meier estimator and Cox regression were used for survival analysis. Correlations were measured by Spearman method (ρ). For unadjusted comparisons, a two-sided $P<0.05$ was considered statistically significant.

Results

Characteristics and treatment

Of the 344 intensive care patients (**Table**), non-survivors are generally older than survivors, with a higher proportion aged over 60 years, and every ten-year increase in age was

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associated with a 58% additional risk (HR: 1.58, 95% CI: 1.38-1.81, *P*<0.001). Dyspnea was more common in non-survivors, accompanied with a significantly higher respiratory rate and lower SpO_2/FiO_2 (S/F) ratio; S/F was negatively correlated (ρ=-0.68) with the incidence of ARDS, and every ten-unit increase in S/F correlated with a 10% decrease in fatality (HR: 0.90, 95% CI: 0.88-0.92, *P*<0.001). 128 out of 145 (88.3%) patients who developed ARDS died at 28-day. Non-survivors were more likely to bear original comorbidities (all, *P*≤0.05). Lymphcytopenia occurred in 237 (69.5%) and was predominant in non-survivors (91.6% *vs* 55.7%, *P*<0.001); higher lymphocyte count was significantly associated with decreasing mortality (HR: 0.1, 95% CI: 0.06-0.18, *P*<0.001). 283 (82.3%) patients received antiviral agents, and 266 (77.3%) received antibacterial agents. Other supportive treatments including gamma globulin (156, 45.3%), muscle relaxant (38, 11.0%), and glucocorticoids (225, 65.4%) were given to the patients. Two (0.6%) patients were treated with ECMO and nine (2.6%) with continuous renal replacement therapy.

Ventilatory support

35 (10.2%) patients were treated with HFNC, of whom 23 (65.7%) also received invasive ventilation. Of the 12 patients who received HFNC only, 7 (58.3%) died at 28-day. 134 (40.6%) patients were treated with mechanical ventilation (either non-invasive or invasive), of whom 34 received treatment of non-invasive ventilation only, 27 (79.4%) died at 28-day, while invasive ventilation was given to 100 patients with 97 (97%) deaths at 28-day; median duration from admission to invasive ventilation was 5 (IQR: 1-8) days, and median duration of invasive ventilation was 4 (IQR: 3-8) days. Of the 145 patients who developed ARDS, 100 (69.0%) were treated with invasive ventilation.

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Clinical course and outcomes

133 (38.7%) patients died at 28 days with a median survival of 25 days (**Figure**); median duration from admission to death was 10 (IQR: 6-15) days for non-survivors. Of the 211 survivors, 185 (87.7%) were discharged. Median duration from onset of symptoms to laboratory confirmation of infection by RT-PCR was 8 (IQR: 5–11) days. In survivors, median duration from positive RT-PCR result to negative was 12 (IQR: 9–15) days while in non-survivors median duration from infection confirmation to death was 15 (IQR: 10–19) days (**Figure**).

Discussion

This report, to our knowledge, is the largest case series of intensive care COVID-19 patients with informative laboratory characteristics, detailed clinical course and outcome.

In our cohort, non-survivors are older than survivors, which is consistent with an earlier study (7). We did not observe survival differences regarding gender, but result of previous study was an inconsistent trend (8). Compared to survivors, non-survivors presented with more common dyspnea and a higher respiratory rate, indicating more attention should be paid to vital signs changes with respect to respiratory rate for intensive care patients. A previous study revealed that original comorbidities were potential risk factors (8), and we observed that hypertension is significantly differentially distributed between non-survivors (69 [52.3%]) and survivors (72 [34.1%]), and 62 out of 141 (44.0%) patients with hypertension had medication history of taking ACE inhibitors. Given that ACE2 plays a dual role of vasopeptidase and SARS virus receptor, we speculated that hypertensive patients

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with COVID-19 might be more likely to become critically ill (9). Additionally, S/F may be a useful and non-invasive predictive marker, which was defined by the Kigali modification of the Berlin definition and had good correlation with the diagnosis of ARDS (10). Given a large patient flow during epidemic conditions, this indicator could be flexibly used for screening and monitoring.

Lymphcytopenia occurred in almost 70% and was predominant in non-survivors, which contradicts a previous study with relatively small size (8). Lymphocytopenia is a prominent feature of critically ill patients with SARS (11) and MERS, which is the result of apoptosis of lymphocytes (12), thus lymphocyte depletion could be harmful and lymphocyte count might serve as another prognostic factor for SARS-CoV2. Additionally, we observed a higher level of hs-CRP, along with other inflammatory markers, which is consistent with relevant reports of SARS and MERS (13). Unexpectedly, non-survivors however showed a higher level of IL-2R. Highly expressed IL-2R initiates autoreactive cytotoxic CD8+ T cell-mediated autoimmunity. Meanwhile, IL-2 stimulates the proliferation of natural killer cells that highly express IL-2R, promoting the release of cytokines, further inducing the lethal “cytokine storm” (14). We also observed that factors like red blood cell distribution width, lactate dehydrogenase and coagulation index were up-regulated in non-survivors which is probably due to the active participation in inflammatory response. It has been reported that chest CT imaging can be more sensitive compared to RT-PCT in diagnosis (15), and we reasoned that CT might even show guiding significance in the critical stage of COVID-19. The high mortality rate of patients who received mechanical ventilation, which may be partly due to the centralized admission of a large number of intensive care patients in February and the fact

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that patients were sometimes transferred late to the hospital, made us question the effectiveness of non-invasive ventilation treatment or HFNC in the first line, and whether the early use of invasive ventilation would improve prognosis may be worth further study in a larger cohort.

In summary, in this single-center case series study, older patients with comorbidities are at dramatically increased risk of mortality. Real-time monitoring of S/F and regular measurements of lymphocyte count and inflammatory markers may be essential to disease management.

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Conflict of Interest Disclosures

The authors declare no competing interests.

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Figure. Kaplan-Meier curve showing a 28-day median survival of 312 intensive care patients in this cohort (32 out of 344 patients lack records of survival time); timeline showing the time span from symptoms onset (median) to three important events

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Table. Presenting characteristics of intensive care patients with COVID-19

	All patients* (n = 344)	Survivors (n = 211)	Non-survivors (n = 133)	*P*
Age, years	64 (52-72)	57 (47-69)	70 (62-77)	<0.001
Age range, years				<0.001
≤60	150 (43.6)	118 (55.9)	32 (24.1)	
>60	194 (56.4)	93 (44.1)	101 (75.9)	
Gender, male	179 (52.0)	105 (49.8)	74 (55.6)	0.341
Signs and symptoms				
Fever	301 (87.5)	186 (88.2)	115 (86.5)	0.770
Dry cough	233 (67.7)	137 (64.9)	96 (72.2)	0.200
Dyspnea	208 (60.5)	108 (51.2)	100 (75.2)	<0.001
Fatigue	167 (48.5)	102 (48.3)	65 (48.9)	1.000
Expectoration	135 (39.2)	82 (38.9)	53 (39.8)	0.945
Diarrhea	92 (26.7)	63 (29.9)	29 (21.8)	0.129
Anorexia	91 (26.5)	57 (27.0)	34 (25.6)	0.864
Original comorbidities or medication history				
Hypertension	141 (41.0)	72 (34.1)	69 (52.3)	0.001
ACE inhibitors	62 (18.0)	32 (15.2)	30 (22.6)	0.083
Diabetes	64 (18.6)	34 (16.1)	30 (22.9)	0.155
Cardiovascular disease	40 (11.6)	18 (8.5)	22 (16.5)	0.030
COPD	16 (4.7)	3 (1.4)	13 (9.8)	0.001
Vital signs				
Respiratory rate, rpm	21 (20-25)	20 (20-22)	24 (20-31)	<0.001
Heart rate, bpm	90 (80-104)	90 (80-104)	93 (82-108)	0.116
SpO_2/FiO_2	279 (157-328)	297 (272-448)	114 (89-224)	<0.001
Laboratory findings at admission				
Routine blood test				
White blood cells, $\times10^9$/L	6.2 (4.5-8.9)	5.3 (4.0-6.9)	9.1 (6.1-13.3)	<0.001
lymphocytes, $\times10^9$/L	0.9 (0.6-1.2)	1.0 (0.8-1.4)	0.6 (0.4-0.7)	<0.001
Neutrophils, $\times10^9$/L	4.7 (2.9-7.6)	3.7 (2.5-5.3)	8.0 (5.5-12.2)	<0.001
Platelets, $\times10^9$/L	189 (142-257)	211 (161-290)	159 (112-218)	<0.001
Red cell distribution width	12.4 (11.9-13.2)	12.3 (11.8-13.0)	12.7 (12.2-13.7)	<0.001
Inflammatory marker				
hs-CRP, mg/L	55 (14-106)	28 (6-67)	101 (61-153)	<0.001
PCT, ng/ml	0.09 (0.04-0.23)	0.04 (0.03-0.09)	0.21 (0.13-0.70)	<0.001
IL-2R, U/ml	811 (546-1154)	716 (458-954)	1098 (721-1512)	<0.001
IL-6, pg/ml	27.2 (5.9-60.1)	10.8 (2.7-37.4)	61.1 (29.9-132.2)	<0.001
IL-8, pg/ml	17.2 (9.1-34.0)	12.5 (6.9-20.8)	28.3 (14.7-59.1)	<0.001
IL-10, pg/ml	6.1 (2.5-10.6)	2.5 (2.5-7.0)	10.5 (5.9-18.5)	<0.001
TNF-α, pg/ml	8.8 (6.6-11.7)	8.2 (6.1-10.2)	10.7 (7.5-15.9)	<0.001
Coagulation index				

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Prothrombin time, s	14.3 (13.5-15.4)	13.9 (13.3-14.5)	15.4 (14.3-17.4)	<0.001
D-Dimer, μg/ml	1.3 (0.5-5.0)	0.7 (0.4-1.5)	5.1 (1.7-31.5)	<0.001
INR	1.1 (1.0-1.2)	1.1 (1.0-1.1)	1.2 (1.1-1.4)	<0.001
Cardiac biomarkers				
High-sensitivity cardiac troponin I, pg/ml	9.7 (2.9-44.4)	3.4 (1.4-8.7)	46.7 (11.2-801.3)	<0.001
Myo, ng/ml	75 (32-199)	31 (20-55)	179 (103-367)	<0.001
CK-MB, ng/ml	1.5 (0.5-3.2)	0.4 (0.3-1.2)	2.5 (1.2-6.1)	<0.001
Biochemistry†				
ALT, U/L, (≤41)	24 (15-38)	21 (14-36)	29 (19-42)	0.001
AST, U/L, (≤41)	31 (22-47)	27 (20-37)	43 (28-66)	<0.001
Albumin, g/L, (35-52)	34 (30-37)	36 (33-39)	31 (28-34)	<0.001
TBIL, μmol/L, (≤26.0)	10.2 (7.3-14.2)	8.5 (6.3-11.3)	12.9 (9.8-19.2)	<0.001
Cr, μmol/L, (59-104)	74 (58-93)	66 (56.3-86)	86 (67-111)	<0.001
BUN, mmol/L, (3.6-9.5)	5.3 (3.8-8.3)	4.3 (3.2-5.8)	8.3 (5.9-12.1)	<0.001
CK, U/L, (≤170)	109 (60-242)	81 (39-139)	168 (96-387)	<0.001
LDH, U/L, (135-225)	338 (237-491)	271 (205-347)	525 (419-676)	<0.001
e-GFR, ml/min/1.73m^2,(>90)	87 (70-101)	93 (78-107)	74 (55-91)	<0.001
Glu, mmol/L, (3.9-6.1)	6.8 (5.7-9.0)	6.1 (5.2-7.8)	8.2 (6.6-11.4)	<0.001
Radiologic manifestation				<0.001
GGO	164 (47.7)	101 (50.8)	63 (54.8)	
Local patchy opacities	38 (11.0)	35 (17.6)	3 (2.6)	
Bilateral patchy opacities	110 (32.0)	61 (30.7)	49 (42.6)	
Organ function injury				
ARDS	145 (42.2)	17 (8.1)	128 (97.0)	<0.001
Septic shock	114 (33.1)	2 (0.9)	112 (84.2)	<0.001
DIC	71 (20.6)	1 (0.5)	70 (52.6)	<0.001
AKI	86 (25.0)	6 (2.8)	80 (60.2)	<0.001
Myocardial damage	111 (32.3)	4 (1.9)	107 (80.5)	<0.001
Liver injury	54 (15.7)	9 (4.3)	45 (33.8)	<0.001
Rhabdomyolysis	9 (2.6)	0 (0)	9 (6.9)	<0.001
Ventilatory support throughout the course				
HFNC oxygen therapy	35 (10.2)	7 (3.3)	28 (21.1)	<0.001
NIV	34 (9.9)	7 (3.3)	27 (20.3)	<0.001
IV	100 (29.1)	3 (1.4)	97 (72.9)	<0.001

Abbreviations: COPD: chronic obstructive pulmonary disease; GGO: ground-glass opacity; ARDS: acute respiratory distress syndrome; DIC: disseminated intravascular coagulation; AKI: acute kidney injury; HFNC: high-flow nasal cannula; NIV: non-invasive ventilation; IV: invasive ventilation

*The percentage represented the frequency divided by the total cohort size (n=344), while percentages in subgroups were calculated according to contingency table with missing data removed first.

†Normal ranges of listed biochemical parameters were indicated in parentheses.

All records were measured at admission to intensive care wards unless otherwise indicated.

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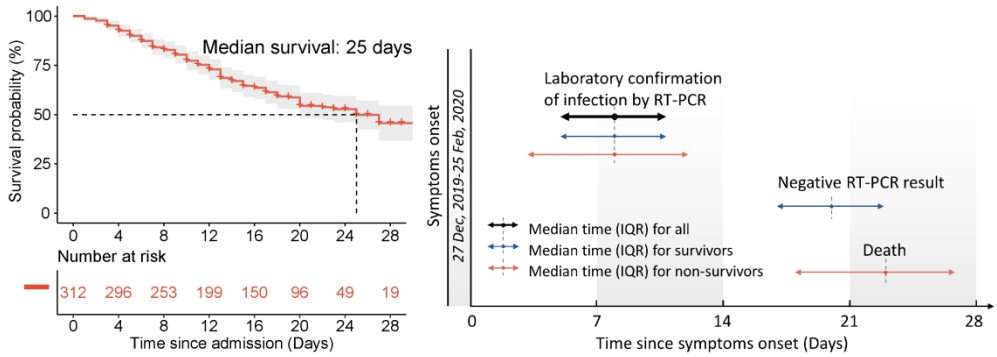

Figure. Kaplan-Meier curve showing a 28-day median survival of 312 intensive care patients in this cohort (32 out of 344 patients lack records of survival time); timeline showing the time span from symptoms onset (median) to three important events

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