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Study on early markers of death in patients with COVID-19

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Abstract. – OBJECTIVE: Coronavirus disease 2019 (COVID-19) was first discovered in December 2019, and since then rapidly spread worldwide. Our study aimed to investigate the early indicators of death in patients suffering from severe and critical COVID-19.

PATIENTS AND METHODS: A retrospective cohort study was conducted on patients with severe and critical COVID-19, admitted to the Seventh Hospital of Wuhan. Clinical information was collected from electronic medical records according to standardized data collection tables. Patients were divided into non-survival and survival groups based on the disease outcome. Using univariate and multivariate logistic regression analysis, and calculating odds ratios (OR) and 95% confidence intervals (CI), independent risk factors for death in severe and critically ill COVID-19 patients were identified.

RESULTS: The median age of 162 patients (57.4% males) was 67.5 years old. Patients in the non-survival group had significantly higher white blood cell count, decreased lymphocyte count, anemia and thrombocytopenia compared to patients in the survival group ($p < 0.05$). A 28-day mortality rate of the study cohort was 31.5%. Multivariate logistic regression analysis showed that underlying heart disease, lymphocyte count < 1.0×10^9/L, glomerular filtration rate < 66, lactate > 2.2 mmol/L, higher Sequential Organ Failure Assessment (SOFA) score, lower oxygenation index (OR 1.748; 95% CI 1.024-2.984; p=0.041) and higher "multi-lobar infiltration, hypo lymphocytosis, bacterial co-infection, smoking history, hypertension and age" (MuLBSTA) score (OR 1.601; 95% CI 1.062-2.415; p=0.025) were risk factors associated with death in patients with severe and critical COVID-19.

CONCLUSIONS: Underlying heart disease, lymphocyte count, glomerular filtration rate, lactate, oxygenation index, SOFA score, and MuLBSTA score were associated with the risk of death in severe and critical COVID-19 patients.

Key Words:
COVID-19, Pneumonia, Severe disease, Death, Risk factors.

Introduction

December 2019 marked the onset of a global pandemic spread of novel coronavirus pneumonia (COVID-19) caused by SARS-CoV-2. As of March 5, 2021, the World Health Organization (WHO) reported a total of 116.09 million confirmed COVID-19 cases in 222 countries worldwide, with 2.57 million deaths. The pandemic has represented a serious challenge to the global healthcare system.

SARS-CoV-2 is a member of the same family of coronaviruses as the previous Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) coronaviruses pandemics[1]. However, COVID-19 is superior in terms of infectivity and pathogenicity. Studies[2,3] show that COVID-19 may affect the lungs, heart, kidneys, and even the digestive system of the patients, which indicates that the pathogenesis of this virus is more complex. Some studies showed that the mortality rate of novel coronavirus pneumonia worldwide ranges from 1.1%[4] to 33%[5]. As shown by Li et al[6] the mortality rate was 1.1% in non-critically ill patients and 32.5% in critically ill patients. Lai et al[7] reported that the mortality rate of COVID-19 is closely related to the national health resource guarantee capacity. However, in many countries, invasive ventilators and intensive care units fail to effectively treat all critically ill patients. Thus, it is crucial to determine death risk factors in COVID-19 patients, identify critically ill patients as early as possible, reasonably

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allocate medical resources, and timely modify the treatment plan, thus increasing the cure rate, and reducing the risk of death. This study analyzed the clinical characteristics of 162 patients with severe and critical COVID-19 to identify early death indicators in this cohort.

Patients and Methods

Study Methods and Subjects

Study subjects

A retrospective analysis was conducted on severe and critically ill (severe for short) COVID-19 patients admitted to the Seventh Hospital of Wuhan on January 11, 2020, with the diagnosis abiding by the Novel Coronavirus Infection Pneumonia Diagnosis and Treatment Protocol (3rd to 7th Edition)[8,9]. All patients were assessed by the Hebei Medical Team, and the treatment plan was developed based on the guidelines mentioned above. Inclusion criteria were as follows: (1) Aged ≥ 18 years. (2) Meets the diagnostic criteria of Novel Coronavirus Infection Pneumonia Diagnosis and Treatment Protocol (3rd to 7th Edition)[8,9]. (3) For severe cases, adult patients meeting any of the following: 1. respiratory rate (RR) ≥ 30 beats/min; 2. oxygen saturation ≤ 93%; 3. oxygen index ≤ 300 mmHg; 4. lesion progressed significantly more than 50% within 24-48 h, as indicated by the pulmonary imaging. (4) For critical cases, adult patients satisfying one of the following conditions: 1. respiratory failure, requiring mechanical ventilation, 2. shock, 3. combined with other organ failure, and require ICU monitoring and treatment. Patients with unknown final clinical outcomes were excluded.

The study was approved by the Second Hospital of Hebei Medical University (2020-R016). Because of the urgency of COVID-19-related research, the application for exemption from the informed consent signature was submitted and approved by the Ethics Committee. De-identification measures were taken to protect patient privacy.

Data Collection

Medical records of the enrolled patients were summarized and analyzed by the Hebei Medical Team. In addition, clinical information was collected from electronic medical records according to standardized data collection tables. Laboratory results were collected by performing the first test within 24 hours after the admission. To evaluate the risk of in-hospital mortality, patients were followed from admission to discharge (1 to 9 days). The primary outcome was in-hospital death, defined by the 28-day case fatality. All data were collected by two well-trained researchers adhering to the double-blind method. A third researcher conducted a final ruling in case of discrepancies in the interpretation between the two main reviewers. The onset date was defined as the date of symptoms onset, dyspnea was defined as the patient subjectively reporting labored and uncomfortable breathing, and acute respiratory distress syndrome (ARDS) was diagnosed based on the Berlin criteria[10]. Acute kidney injury was defined following Kidney Disease Improving Global Outcomes (KDIGO) criteria[11]; acute myocardial injury was defined by serum levels of cardiac markers (troponin T) above the 99th percentile upper limit, or novel abnormalities on electrocardiogram and echocardiography; disseminated intravascular coagulation (DIC) was defined in accordance with The International Society on Thrombosis and Hemostasis (ISTH)[12]. Secondary infection was diagnosed when the patient developed new clinical symptoms or signs of non-viral infection, or when positive cultures for novel pathogens were obtained from the lower respiratory tract or blood specimens after admission. The discharge criteria followed the Novel Coronavirus Infection Pneumonia Diagnosis and Treatment Protocol (3rd-7th edition) developed by the National Health Commission.

Statistical Analysis

All statistical analyses were conducted with SPSS (ver. 22.0; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean (MEAN), median (MEDIAN) and interquartile range (IQR). When sample distribution conformed to normal distribution, a two-sample *t*-test was performed to compare mean values; otherwise, the Mann-Whitney U test was adopted to compare the difference in median. For categorical variables, frequency and percentage were used. χ^2 test was performed to compare the difference. Correction or Fisher's exact test was used as required. Statistical significance was considered at $p < 0.05$. The univariate logistic regression analysis was conducted to screen variables, as jointly analyzed by experienced clinicians and statisticians. After adjusting for confounding factors, independent risk factors were determined through binary logistic regression analysis by calculating odds ratio (OR) with 95% confidence interval (95% CI); survival curves were plotted with the Kaplan-Meier method of the log-rank test.

Results

Characteristics of the Study Cohort

A total of 550 patients satisfied the diagnostic criteria for COVID-19. Of them, 378 cases of mild and common disease and 10 severe cases with unknown final clinical outcomes were excluded. The remaining 162 severe and critical cases were included in the analysis and divided into the non-survival group (n=51), and the survival group (n=111) based on the outcome. The median age of patients was 67.5 years [interquartile range (IRQ), 59.5 to 74]. The cohort had 93 (57.4%) male and 63 (43.6%) female patients (Table I). The median hospital stay was 23 days (IRQ, 13 to 30). The negative conversion time of nucleic acid reached 13 days (IQR, 8-19).

Laboratory Examination

As summarized in Table II, patients in the non-survival group had significantly elevated white blood cell count, decreased lymphocyte count, anemia, and thrombocytopenia compared to the survival group ($p < 0.05$). Procalcitonin levels in the non-survival group were significantly higher (p=0.008). In terms of cardiac function indexes, myocardial enzymes troponin and N-terminal pro-brain natriuretic peptide (NT-proBNP) were statistically significantly increased in the non-survival group of patients compared to the survival one ($p < 0.001$). Aspartate aminotransferase was markedly increased in the non-survival group, and 100.0% of patients had hypoproteinemia (p=0.009). There was an increase in D-dimer in 27 non-survival patients (p=0.006). The non-survival group had elevated creatinine levels, and significantly downregulated glomerular filtration rate compared to the survival group (p=0.008). For blood gas analysis, most of the patients (74.3%) in the non-survival group had an oxygenation index (OI) of less than 300 on admission. Of them, 15 patients had less than 100, a significantly higher proportion compared to the survival group ($p < 0.001$). Hyperlactatemia was similarly more likely to appear in patients in the non-survival group (p=0.001). (Table II, Figure 1).

Table I. Demographics and clinical characteristics of patients with severe COVID-19

Variables	Total (n = 162)	Non-survivors (n = 51)	Survivors (n = 111)	p-value
Age, years, n (%)				
≤ 44	12 (7.4%)	2 (3.9%)	10 (9.0%)	0.219
45-59	29 (17.9%)	4 (7.8%)	25 (22.5%)	0.219
≥ 60	121 (74.7%)	45 (88.2%)	76 (68.5%)	0.219
Sex, n (%)				
Male	93 (57.4%)	32 (62.7%)	61 (55.0%)	0.352
Female	69 (42.6%)	19 (37.3%)	50 (45.0%)	0.352
Comorbidity, n (%)				
Hypertension	74 (45.7%)	25 (49.0%)	49 (44.1%)	0.563
Diabetes	34 (21.0%)	14 (27.5%)	20 (18.0%)	0.171
Cardiovascular disease	22 (13.6%)	13 (25.5%)	9 (8.1%)	0.003
Malignancy	7 (4.3%)	6 (11.8%)	1 (0.9%)	0.006
Cerebrovascular disease	8 (4.9%)	2 (3.9%)	6 (5.4%)	0.988
Chronic pulmonary disease	7 (4.3%)	2 (3.9%)	5 (4.5%)	1.000
Chronic liver disease	4 (2.5%)	1 (2.0%)	3 (2.7%)	1.000
Hyperlipidemia	4 (2.5%)	1 (2.0%)	3 (2.7%)	1.000
Symptoms onset to median (range- days)				
Admission	9.5 (7 - 12)	8 (7 - 11.5)	10 (7 - 12.5)	0.289
Dyspnea	3 (0 - 8)	1.5 (0 - 7)	3.5 (0 - 9.75)	0.340
Mechanical ventilation	10 (7 - 15)	10 (7 - 15)	10 (6 - 16)	0.838
ARDS	10 (7 - 15)	10 (7 - 15)	10 (6 - 16)	0.838
SOFA	4 (3 - 5)	4 (4 - 6)	4 (3 - 4)	< 0.001
qSOFA	0 (0 - 0)	0 (0 - 1)	0 (0 - 0)	0.418
MuLBSTA				
≥ 12	114 (70.4%)	44 (86.3%)	70 (63.1%)	0.003
< 12	48 (29.6%)	7 (13.7%)	41 (36.9%)	0.003

The data were expressed as median (IQR), n (%) data. ARDS: acute respiratory distress syndrome; SOFA: Sequential Organ Failure Assessment; MuLBSTA: multi-lobar infiltration, hypo lymphocytosis, bacterial co-infection, smoking history, hypertension and age.

Table II. Laboratory results of patients with severe COVID-19 on hospital admission.

Variables	Total (n = 162)		Non-survivors (n = 51)		Survivors (n = 111)		p-value
			Blood tests, n/total n (%)				
WBC (10^9/L)							
< 4	21/146	(14.4%)	6/49	(12.2%)	15/97	(15.5%)	< 0.001
4 - 10	95/146	(65.1%)	26/49	(53.1%)	69//97	(71.1%)	< 0.001
> 10	30/146	(20.5%)	17/49	(34.7%)	13/97	(13.4%)	< 0.001
NE (%)							
40 - 75	39/146	(26.7%)	9/49	(18.4%)	30/97	(30.9%)	0.105
> 75	107/146	(73.3%)	40/49	(81.6%)	67/97	(69.1%)	0.105
LN (%)							
< 20	123/146	(84.2%)	42/49	(85.7%)	81/97	(83.5%)	0.729
20 - 50	23/146	(15.8%)	7/49	(14.3%)	16/97	(16.5%)	0.729
LN (19/L)							
< 1.0	107/146	(73.3%)	43/49	(87.8%)	64/97	(66.0%)	0.005
≥ 1.0	39/146	(26.7%)	6/49	(12.2%)	33/97	(34.0%)	0.005
Hb (g/L)							
Normal	104/146	(71.2%)	29/49	(59.2%)	75/97	(77.3%)	0.022
Decreased	42/146	(28.8%)	20/49	(40.8%)	22/97	(22.7%)	0.022
Plt (10^9/L)							
< 100	10/146	(6.8%)	8/49	(16.3%)	2/97	(2.1%)	0.004
≥ 100	136/146	(93.2%)	41/49	(83.7%)	95/97	(97.9%)	0.004
			Inflammatory parameters-no./total No. (%)				
PCT (ng/ml)							
≤ 0.1	54/125	(43.2%)	10/39	(25.6%)	44/86	(51.2%)	0.008
> 0.1	71/125	(56.8%)	29/39	(74.4%)	42/86	(48.8%)	0.008
hsCRP (mg/L)							
≤ 3	3/104	(2.9%)	0/36	(0.0%)	3/68	(4.4%)	0.550
> 3	101/104	(97.1%)	36/36	(1.0%)	65/68	(95.6%)	0.550
ESR (mm/h)							
≤ 15	2/44	(4.5%)	2/18	(11.1%)	0/26	(0.0%)	0.162
> 15	42/44	(95.5%)	16/18	(88.9%)	26/26	(100.0%)	0.162
			Myocardial enzyme-No./total No. (%)				
CKMB (ng/ML)							
≤ 6.22	111/124	(89.5%)	27/38	(71.1%)	84/86	(97.7%)	< 0.001
> 6.22	13/124	(10.5%)	11/38	(28.9%)	2/86	(2.3%)	< 0.001
cTnT (ng/ml)							
≤ 0.014	73/138	(52.9%)	13/43	(30.2%)	60/95	(63.2%)	< 0.001
> 0.014	65/138	(47.1%)	30/43	(69.8%)	35/95	(36.8%)	< 0.001
			Heart Failure Indicator-No./total No. (%)				
NT-proBNP (pg/ml)							
≤ 222	24/83	(28.9%)	2/32	(6.3%)	22/51	(43.1%)	0.001
> 222	59/83	(71.1%)	30/32	(93.8%)	29/51	(56.9%)	0.001
			Liver function-No./total No. (%)				
Alanine transaminase (IU/L)							
≤ 40	122/153	(79.7%)	37/51	(72.5%)	85/102	(83.3%)	0.118
> 40	31/153	(20.3%)	14/51	(27.5%)	17/102	(16.7%)	0.118
Aspartate aminotransferase (IU/L)							
≤ 35	86/153	(56.2%)	15/51	(29.4%)	71/102	(69.6%)	< 0.001
> 35	67/153	(43.8%)	36/51	(70.6%)	31/102	(30.4%)	< 0.001
Albumin (g/L)							
< 40	141/153	(92.2%)	51/51	(100.0%)	90/102	(88.2%)	0.009
40 - 55	12/153	(7.8%)	0/51	(0.0%)	12/102	(11.8%)	0.009

(continued)

Table II *(continued)*. Laboratory results of patients with severe COVID-19 on hospital admission.

Variables	Total (n = 162)		Non-survivors (n = 51)		Survivors (n = 111)		*p*-value
Coagulation Function, n/total n (%)							
APTT(S)							
24.6 - 35.4	107/123	(87.0%)	34/36	(94.4%)	73/87	(83.9%)	0.244
> 35.4	15/123	(12.2%)	2/36	(5.6%)	13/87	(14.9%)	0.244
D - dimer (μg/ml)							
≤ 0.243	23/95	(24.2%)	1/28	(3.6%)	22/67	(32.8%)	0.006
> 0.243	72/95	(75.8%)	27/28	(96.4%)	45/67	(67.2%)	0.006
Electrolyte, n/total n (%)							
K + (mmol/L)							
> 5.3	17/149	(11.4%)	16/51	(31.4%)	1/98	(1.0%)	0.003
3.5 - 5.3	91/149	(61.1%)	31/51	(60.8%)	60/98	(61.2%)	0.003
< 3.5	41/149	(27.5%)	4/51	(7.8%)	37/98	(37.8%)	0.003
Na + (mmol/L)							
< 137	37/149	(24.8%)	12/51	(23.5%)	25/98	(25.5%)	0.002
137 - 147	101/149	(67.8%)	30/51	(58.8%)	71/98	(72.4%)	0.002
> 147	11/149	(7.4%)	9/51	(17.6%)	2/98	(2.0%)	0.002
Renal Function, n/total n (%)							
Creatinine (μmol/L)							
≤ 111	141/152	(92.8%)	43/51	(84.3%)	98/101	(97.0%)	0.012
> 111	11/152	(7.2%)	8/51	(15.7%)	3/101	(3.0%)	0.012
GFR							
< 66	18/152	(11.8%)	11/51	(21.6%)	7/101	(6.9%)	0.008
≥ 66	134/152	(88.2%)	40/51	(78.4%)	94/101	(93.1%)	0.008
Arterial blood gas analysis, n/total n (%)							
PH							
< 7.35	13/135	(9.6%)	8/41	(19.5%)	5/94	(5.3%)	0.053
7.35 - 7.45	72/135	(53.3%)	20/41	(48.8%)	52/94	(55.3%)	0.053
> 7.45	50/135	(37.0%)	13/41	(31.7%)	37/94	(39.4%)	0.053
OI							
< 100	19/135	(14.1%)	15/41	(36.6%)	4/94	(4.3%)	< 0.001
100 - 300	80/135	(59.3%)	19/41	(46.3%)	61/94	(64.9%)	< 0.001
> 300	36/135	(26.7%)	7/41	(17.1%)	29/94	(30.9%)	< 0.001
pCO_2 (mmHg)							
< 35	43/135	(31.9%)	22/41	(53.7%)	21/94	(22.3%)	0.001
35 - 45	72/135	(53.3%)	13/41	(31.7%)	59/94	(62.8%)	0.001
> 45	20/135	(14.8%)	6/41	(14.6%)	14/94	(14.9%)	0.001
Lac (mmol/L)							
≤ 2.2	94/135	(69.6%)	20/41	(48.8%)	74/94	(78.7%)	0.001
> 2.2	41/135	(30.4%)	21/41	(51.2%)	20/94	(21.3%)	0.001

The data were expressed in n/N (%), N represented the total number of patients with available data. WBC: leukocyte count; NE: neutrophil count; LN: lymphocytes; Hb: hemoglobin count; Plt: platelet count; PCT: procalcitonin; hsCRP: hypersensitive C- reactive protein; ESR: erythrocyte sedimentation rate; CKMB: creatine kinase myocardial band; cTnT: cardiac troponin T; NT-proBNP: N-terminal pro-brain natriuretic peptide; APTT: activated partial thromboplastin time; K+: potassium ions; Na+: sodium ions; GFR: glomerular filtration rate; PH: Pondus Hydrogenii; OI: oxygenation index; pCO_2: partial pressure of CO_2; Lac: lactic acid.

Treatment and Mortality

All patients received intermittent or continuous oxygen inhalation therapy to mitigate clinical symptoms (Table III). Patients in the non-survival group had a significantly higher rate of invasive mechanical ventilation than the survival group ($p < 0.001$).

Patients in the non-survival group had a significantly higher rate of glucocorticoid treatment than the survival group (p=0.008). Vasoactive drugs were administered in 34 patients in the non-survival group, noticeably higher than in the survival group ($p < 0.001$).

The 28-day mortality rate of the patients in the study was 31.5%. As shown in Table III, mortality in the non-survival group resulted from multiple organ failure (70.6%), respiratory failure (23.5%), circulatory failure (3.9%), and septic shock (2%).

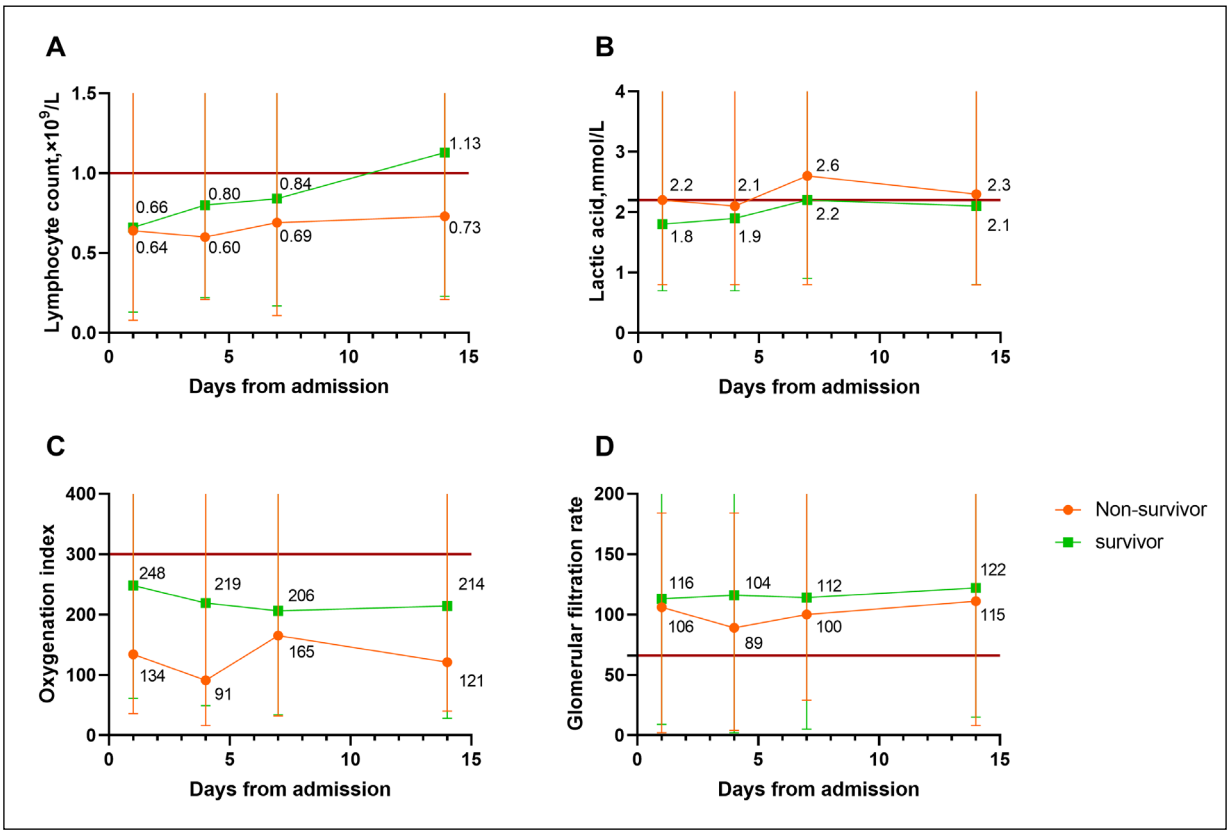

Figure 1. Changes in laboratory parameters in patients with severe COVID-19 infection. The changes in lymphocyte counts (**A**), lactic acid (**B**), oxygenation index (**C**), glomerular filtration rate (**D**) were recorded. There were statistically significant differences in lactic acid level, oxygenation index, glomerular filtration rate on the first day after admission and glomerular filtration rate on the fourth day after admission between the non-survival and survival groups ($p < 0.05$). The normal values of the parameters are shown as solid red lines.

Analysis of Early Warning Factors for Death of Critical Patients

Multivariate logistic regression analysis and survival curves showed that underlying heart disease, lymphocyte count < 1.0×10^9/L (OR=14.636), glomerular filtration rate < 66 (OR=12.130), lactic acid > 2.2 mmol/L (OR=10.627), lower oxygen index, higher Sequential Organ Failure Assessment (SOFA) (OR=1.748) and "multi-lobar infiltration, hypo lymphocytosis, bacterial co-infection, smoking history, hypertension and age" (MuLBSTA) scores (OR=1.601) were early warning factors of death in critical patients (Table IV; Figure 2).

Discussion

In this study, clinical data of 162 patients with severe COVID-19 were analyzed and compared in terms of demographics, clinical characteristics, existing chronic comorbidities, laboratory test results, complications, treatment, and short-term prognosis. Our results show that patients with severe COVID-19 were older, had higher rates of comorbidities, lower lymphocyte counts and glomerular filtration rates, higher lactate levels, lower oxygen index, and higher SOFA and MuLBSTA scores. We showed that the underlying heart disease, lymphocyte count < 1.0×10^9/L, glomerular filtration rate < 66, lactate > 2.2 mmol/L, lower oxygen index, and higher SOFA and MuLBSTA scores could be considered early warning indicators of death in critical patients. These parameters can be used to screen critically patients, not only to improve their prognosis but also to lower the consumption of medical resources and an overall economic burden on the healthcare system.

As indicated by numerous existing studies, age acts as a vital risk factor for respiratory diseases[4,8,13]. According to Ferguson et al[14], the average fatality rate of respiratory diseases for adults under 60 years is less than 0.2%, and increases to 9.3% in adults over 80 years old. Even in cases of associated comorbidities, the death risk of young

Table III. Complications, treatment, and cause of death in patients with severe COVID-19.

Variables	Total (n = 162)		Non-survivors (n = 51)		Survivors (n = 111)		p-value
Complications n., %							
Acute myocardial injury	69	(42.6%)	33	(64.7%)	36	(32.4%)	< 0.001
Secondary infection	76	(46.9%)	46	(90.2%)	20	(18.0%)	< 0.001
ARDS	58	(35.8%)	45	(88.2%)	13	(11.7%)	< 0.001
Acute kidney injury	31	(19.1%)	20	(39.2%)	11	(9.9%)	< 0.001
Shock	38	(23.5%)	38	(74.5%)	0	(0.0%)	< 0.001
DIC	11	(6.8%)	11	(21.6%)	0	(0.0%)	< 0.001
Treatment n., %							
Antiviral therapy	149	(92.0%)	48	(94.1%)	101	(91.0%)	0.712
Antibacterial therapy							
one kind	35	(21.6%)	9	(17.6%)	26	(23.4%)	0.376
≥ two kinds	125	(77.2%)	42	(82.4%)	83	(74.8%)	0.376
Antifungal therapy	5	(3.1%)	3	(5.9%)	2	(1.8%)	0.365
Glucocorticoids therapy	110	(67.9%)	42	(82.4%)	68	(61.3%)	0.008
Immunotherapy							
Human immunoglobulin	13	(8.0%)	6	(11.8%)	7	(6.3%)	0.235
Thymosin	2	(1.2%)	2	(3.9%)	0	(0.0%)	0.098
Vasoactive drug	34	(21.0%)	34	(66.7%)	0	(0.0%)	< 0.001
CRRT	2	(1.2%)	2	(3.9%)	0	(0.0%)	0.098
Respiratory support-n., %							
Nasal catheter/Mask oxygen	100	(61.7%)	5	(9.8%)	95	(85.6%)	< 0.001
High-flow nasal cannula	3	(1.9%)	2	(3.9%)	1	(0.9%)	< 0.001
Noninvasive ventilation	28	(17.3%)	19	(37.3%)	9	(8.1%)	< 0.001
Invasive ventilation	31	(19.1%)	25	(49.0%)	6	(5.4%)	< 0.001
ECMO	0	(0.0%)	0	(0.0%)	0	(0.0%)	< 0.001
Cause of death-n, %							
MODS			36/51	(70.6%)			
Simple respiratory failure			12/51	(23.5%)			
Simple circulatory failure			4/51	(3.9%)			
Simple septic shock			1/51	(2.0%)			
Negative conversion time of RNA							
Detection, Median (IQR)-days	13 (8 - 19)		7 (4.75 - 12.75)		13 (9 - 19)		0.067
Length of hospital stay,							
Median (IQR)-days	23 (13 - 30)		18 (12.5 - 28)		24 (15 - 31)		0.123

The data were expressed in n (%). ECMO: extracorporeal membrane pulmonary oxygenation; ARDS: acute respiratory distress syndrome; DIC: Disseminated intravascular coagulation; IQR: interquartile range.

people remained lower than that of most elderly patients. As suggested from recent data released by the Center for Disease Control and Prevention (CDC)[15], 80% of hospital and outpatient deaths occurred in adults over 65 years, with the age > 85 years associated with the worse prognosis[13-15]. Our study found that the average age of severe COVID-19 patients was 65.56 years, consistent with previous studies[14,16]. We may speculate that the circulation and the cellular immune function that decline with aging lead to decreased levels of immunoglobulin M and interferon, downregulation of T cells, diminished cell division and proliferation, and lower chemotaxis and phagocytic ability of neutrophils, thus increasing susceptibility of the elderly population to viral infections and higher mortality rates[17]. We also found that elderly patients in our study accounted for 74.7% of all critical patients and 88.2% of all deaths. Although the difference between the two groups of patients in our study was not statistically significant, our results further emphasize the susceptibility of elderly patients to viral infection and suggest that this group of patients requires special attention by healthcare providers.

In terms of comorbidities, our study showed that hypertension, diabetes, and heart disease were most common in critical patients. As indicated from a previous meta-analysis of 46,248 COVID-19 patients, critically ill patients mostly suffered from chronic diseases such as hypertension (OR 2.36), respiratory disease (OR 2.46), and cardiovascular disease (OR 3.42)[18]. Studies[2,19] indicated that angiotensin-converting enzyme 2 (ACE2) is the channel through which SARS-CoV-2 enters the human body. Other studies[10,13]

Table IV. Early warning indicators for the mortality of severe cases with COVID-19.

Variables	Univariable		Multivariable	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Demographics and clinical characteristics				
Age, years				
< 60	1 (ref)			
≥ 60	3.454 (1.348-8.853)	0.010	3.284 (0.726-14.857)	0.123
Sex				
Male	1.381 (0.700-2.724)	0.352		
Female	1 (ref)			
Comorbidity				
Hypertension	1.316 (0.677-2.558)	0.418		
Diabetes	1.722 (0.787-3.766)	0.174		
Heart disease	3.877 (1.533-9.807)	0.004	2.521 (0.344-18.490)	0.045
Malignancy	14.667 (1.717-125.311)	0.014	4.506 (2.268-7.149)	0.998
Temperature, °C				
< 38.0	1 (ref)			
≥ 38.0	1.403 (0.666-2.954)	0.373		
Symptom				
More than one sign or symptom	0.526 (0.153-1.810)	0.308		
Fever, cough and dyspnea	0.732 (0.373-1.437)	0.365		
Radiographic and laboratory findings				
Radiographic findings[a]				
Bilateral pneumonia	2.381 (0.259-21.902)	0.444		
Unilateral pneumonia	1 (ref)			
Leucocytes ($\times 10^9$/L)				
< 4	1.062 (0.372-3.030)	0.911		
4 < WBC < 10	1 (ref)			
WBC > 10	3.470 (1.481-8.131)	0.004		
Lymphocyte count ($\times 10^9$/L)				
LN < 1.0	7.994 (3.635-17.580)	<0.001	14.636 (2.256-94.965)	0.005
LN ≥ 1.0	1 (ref)			
Procalcitonin (ng/ml)				
PCT > 0.1	3.038 (1.320 - 6.995)	0.009	0.682 (0.154-3.015)	0.614
PCT ≤ 0.1	1 (ref)			
Troponin T (ng/ml)				
CTnT > 0.014	3.956 (1.826-8.569)	< 0.001	0.688 (0.162-2.912)	0.611
CTnT ≤ 0.014	1 (ref)			
D-dimer (μg/ml)				
Didmer > 0.243	13.200 (1.682-103.570)	0.014	0.891 (0.274-50.624)	0.713
Didmer ≤ 0.243	1 (ref)			
Glomerular filtration rate				
< 66	3.693 (1.335-10.213)	0.012	12.130 (1.378-106.799)	0.025
≥ 66	1 (ref)			
Oxygenation index	0.996 (0.993-1.000)	0.025	0.992 (0.984-0.999)	0.035
Lactic acid (mmol/L)				
Lac > 2.2	3.700 (1.695-8.079)	0.001	10.627 (2.010-56.173)	0.005
Lac ≤ 2.2	1 (ref)			
SOFA	1.427 (1.102-1.848)	0.007	1.748 (1.024-2.984)	0.041
qSOFA	1.372 (0.639-2.942)	0.417		
MuLBSTA	1.301 (1.134-1.492)	< 0.001	1.601 (1.062-2.415)	0.025

Univariable and multivariable logistic regression analyses were performed, and 12 variables were selected for further multivariable after removing confounding factors. OR: odds ratio. [a]: Radiographic findings include the findings of both chest X-ray and lung CT scan. WBC: leukocyte count; LN: lymphocytes; PCT: procalcitonin; cTnT: cardiac troponin T; Lac: lactic acid; SOFA: sequential organ failure assessment; qSOFA: quick sequential organ failure assessment; MuLBSTA: multi-lobar infiltration, hypo lymphocytosis, bacterial co-infection, smoking history, hypertension and age.

confirmed the correlation between ACE2 expression and hypertension. In our study, this may partially explain the high prevalence of severe COVID-19 in hypertensive patients.

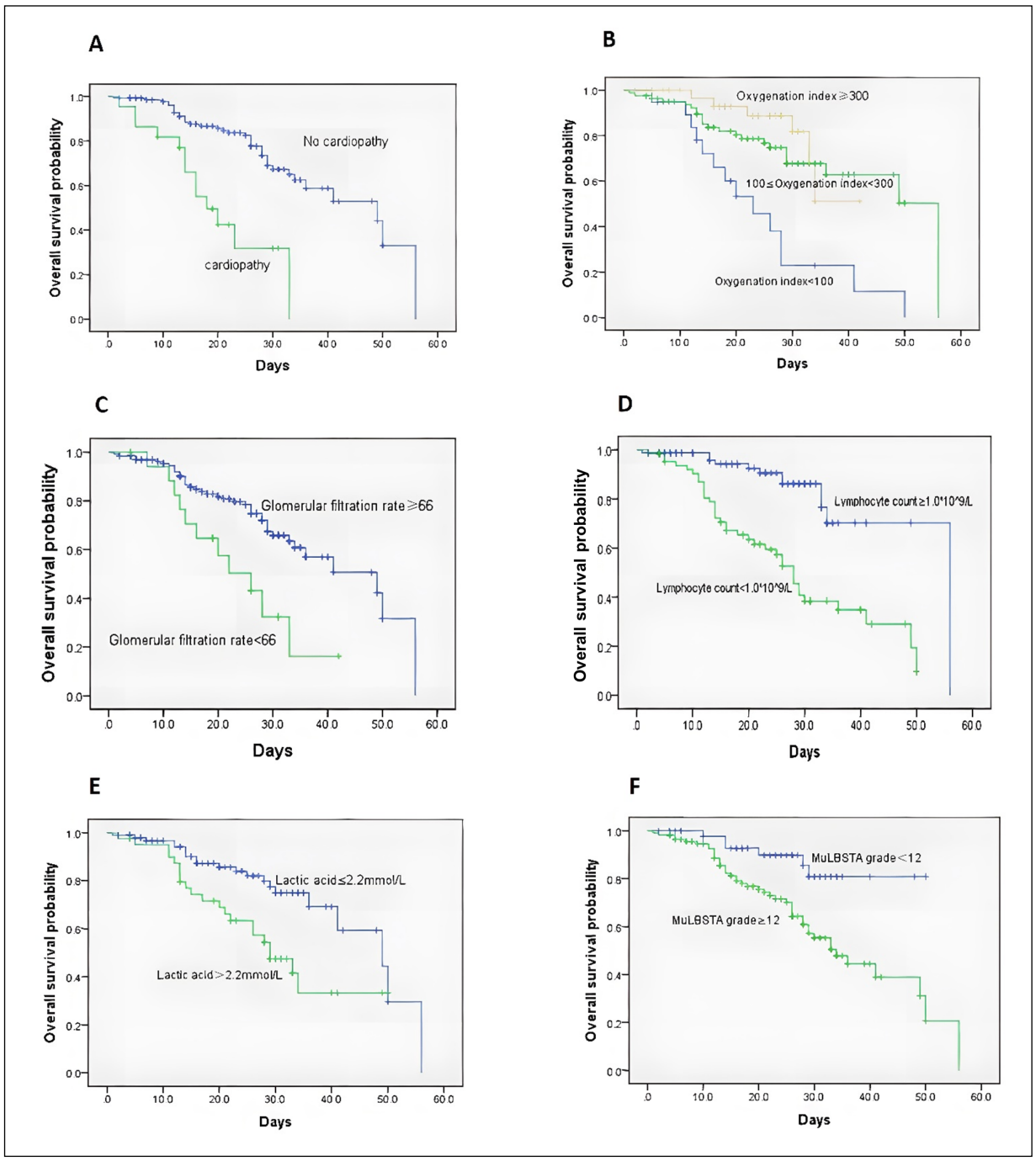

Figure 2. Survival curves of severe COVID-19 patients. The relationship between cardiovascular disease (**A**), oxygenation index (**B**), glomerular filtration rate (**C**), lymphocyte count (**D**), lactic acid (**E**), and MulBSTA score (**F**) and mortality in patients with severe COVID-19 was recorded. The differences were statistically significant (log-rank $p < 0.05$).

Our statistical analysis identified heart disease as a risk factor for death in severe COVID-19 patients. It is possible that patients with underlying heart diseases are in a long-term stress state and tend to have low immunity and, therefore, are more likely to develop acute cardiovascular events and severe diseases when infected with SARS-CoV-2 due to diminished cardiac function[20,21].

In our study, decreased glomerular filtration rate was confirmed as another predictor of poor prognosis in COVID-19 patients. Previous studies[22,23] long confirmed that kidney injury is

associated with an increased risk of death. Zhou et al[24] reported that the probability of acute kidney injury (AKI) was nearly 50 times higher among COVID-19 non-survivors than among survivors. Though the etiology of COVID-19-related AKI is still unclear, some studies[25] suggested that it may result from several days of high fever and dehydration after diarrhea, high levels of positive end-expiratory pressure, multiple organ failure, or direct viral damage. In addition, some COVID-19 patients have a history of insidious chronic kidney disease (CKD), exhibiting a proinflammatory state and functional defects in innate and adaptive immune cell populations[26], predisposing them to the upper respiratory tract and lung inflammation. However, a previous national cross-sectional survey[27] of hospitalized adult patients in China showed that while the detection rate of AKI was 0.99% according to KDIGO criteria after the frequency of detection of serum creatinine was regulated, the incidence of AKI increased to 11.6%[28]. Therefore, current guidelines recommend that serum creatinine measurements should be performed more frequently in COVID-19 patients to achieve early detection of renal injury and improve prognosis. In addition, blood lactate levels > 2 mmol/L have an early warning effect, which is related to increased anaerobic metabolism and renal impairment attributed to hypoxia after infection in critical patients.

We found that the rate of secondary infection, ARDS, shock, acute myocardial injury, acute kidney injury, and disseminated intravascular coagulation (DIC) were significantly higher in the non-survival group of patients. A total of 36 (70.5%) patients in this group were diagnosed with multiple organ failure. The damage of SARS-CoV-2 to the lungs may be related to the role of inflammatory cells and their released mediators and cytokines that cause pulmonary capillary injury, affect gas exchange function, and lead to respiratory failure. Additionally, SARS-CoV-2 may further induce multiple organ dysfunction syndrome and even multiple organ failures, causing death. For this reason, different oxygen therapy modalities should be actively adopted in the treatment to improve respiratory failure and tissue hypoxia. Our results show that the mean survival time of patients in the group using invasive mechanical ventilation was significantly prolonged as opposed to patients receiving nasal cannula/mask oxygen inhalation ($p < 0.05$). These results demonstrate that effective and timely mechanical ventilation can extend the treatment time and improve the prognosis.

High SOFA and MuLBSTA scores in our study were early warning factors for poor prognosis in COVID-19 patients. The SOFA score is generally known as a good diagnostic indicator of sepsis and septic shock, reflecting the degree of multiple organ dysfunction. Though bacterial infection is generally considered the main cause of sepsis, viral infection can also contribute. Zhou et al[29] reported that nearly 40% of sepsis attributed to community-acquired pneumonia in adults resulted from viral infection. In addition, Chen et al[30] confirmed the significance of the MuLBSTA scoring system as an early warning model for COVID-19.

This study has some limitations. First, even though this is a retrospective study, some medical history records may not be sufficiently accurate or detailed due to the urgency of the pandemic. Second, it is a single-center study with a relatively small number of patients included. Multi-center large-scale clinical studies should be conducted to further determine the early warning factors in COVID-19 progression. Third, we evaluated the relationship between early markers and death by the multivariable regression model, which makes it difficult to address the interaction and non-linearity of the relationship between covariates and outcome.

Conclusions

In conclusion, underlying heart disease, lymphocyte count < 1.0×10^9/L, glomerular filtration rate < 66, lactic acid > 2.2 mmol/L, lower oxygen and index, high SOFA score and MuLBSTA score could be considered as early warning indicators for the death of patients with severe COVID-19. Early identification of changes in these indicators in potentially severe patients may slow down the disease progression and improve overall outcomes.

Ethics Approval

The study was approved by the Institutional Ethics Board of the No. 7 Hospital of Wuhan and the Second Hospital of Hebei Medical University (#2020-R016).

Informed Consent

Individual written consent was waived due to the non-interventional and retrospective nature of this study.

Availability of Data and Materials

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

Conflict of Interest
The authors declare that they have no competing interests.

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Authors' Contributions
BYG and XFG contributed equally to this article. YDY and XFG were responsible for the organization and coordination of the trial. BYY and XWG were the chief investigators and were responsible for the data analysis. YDY, YBY, and YDG developed the trial design. All authors contributed to the writing of the final manuscript. All members contributed to the management or administration of the trial.

References

1) Tirelli U, Cirrito C, Pavanello M, Chirumbolo S, Franzini M, Berretta M. Lung cancer and COVID-19: problems and perspectives. Eur Rev Med Pharmacol Sci 2023; 27: 5918-5926.
2) Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H, Farzan M. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003; 426: 450-454.
3) Zaitoun NA, Zaitoun MM, ElMaghawry HA, Amer SA, Abdalkader AM. SARS-CoV-2 infection among preterm deliveries: frequency, determinants, effects. A retrospective cohort study in 2022. Eur Rev Med Pharmacol Sci 2023; 27: 4772-4781.
4) Guan WJ, Ni ZY, Hu Y, Liang WH, Qu CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS, China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020; 382: 1708-1720.
5) Buckner FS, McCulloch DJ, Atluri V, Blain M, McGuffin SA, Nalla AK, Huang ML, Greninger AL, Jerome KR, Cohen SA, Neme S, Green ML, Chu HY, Kim HN. Clinical Features and Outcomes of 105 Hospitalized Patients With COVID-19 in Seattle, Washington. Clin Infect Dis 2020; 71: 2167-2173.
6) Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, Shin J, Zhou M, Wu B, Yang Z, Zhang C, Yue J, Zhang Z, Renz H, Liu X, Xie J, Xie M, Zhao J. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol 2020; 146: 110-118.
7) Lai CC, Wang CY, Wang YH, Hsueh SC, Ko WC, Hsueh PR. Global epidemiology of coronavirus disease 2019 (COVID-19): disease incidence, daily cumulative index, mortality, and their association with country healthcare resources and economic status. Int J Antimicrob Agents 2020; 55: 105946.
8) General Office of National Health Committee, Office of State Administration of Traditional Chinese Medicine. Notice on the issuance of a program for the diagnosis and treatment of novel coronavirus (2019-nCoV) infected pneumonia (Trial Version 3). Available at: http://www.nhc.gov.cn/xcs/zhengcwj/202001/f492c9153ea9437bb587ce2ffcbee1fa.shtml (2020).
9) National Health Commission. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7). Chin Med J (Engl) 2020; 133: 1087-1095.
10) The ARDS Definition Task Force*. Acute Respiratory Distress Syndrome: The Berlin Definition. JAMA 2012; 307: 2526-2533.
11) Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, Herzog CA, Joannidis M, Kribben A, Levey AS, MacLeod AM, Mehta RL, Murray PT, Naicker S, Opal M, Schaefer F, Schetz M, Uchino S. Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney International Supplements 2012; 2: 1-138.
12) Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005; 3: 692-694.
13) Alic T, Zehir S. Have mortality rates in elderly patients with hip fractures changed during pandemic?. Eur Rev Med Pharmacol Sci 2023; 27: 524-531.
14) Ferguson NM, Laydon D, Nedjati-Gilani G, Imai N, Ainslie K, Baguelin M, Bhatia S, Boonyasiri A, Cucunubá Z, Cuomo-Danne G, Dighe A, Fu H, Gaythorpe K, Thompson H, Verity R, Volz R, Wang H, Wang Y, Walker PGT, Walters C, Winskill P, Whittaker C, Donnelly CA, Riley S, Ghani AC. Report 9: Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand. MRC Centre for Global Infectious Disease Analysis, 2020. Available at: https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-9-impact-of-npis-on-covid-19/
15) Bialek S, Boundy E, Bowen V, Chow N, Cohn A, Dowling N, Ellington S, Gierke R, Hall A, MacNeil J, Patel P, Peacock G, Pilishvili T, Razzaghi

H, Reed N, Ritchey M, Sauber-Schatz E,. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) - United States, February 12-March 16, 2020. Weekly 2020; 69: 343-346.

16) Du Y, Tu L, Zhu P, Mu M. Wang R, Yang P, Wang X, Hu C, Ping R, Hu P, Li T, Cao F, Chang C, Hu Q, Jin Y, Xu G. Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan. A Retrospective Observational Study. Am J Respir Crit Care Med 2020; 201: 1372-1379.

17) Sun H, Ning R, Tao Y, Yu C, Deng X, Zhao C, Meng S, Tang F, Xu D. Risk Factors for Mortality in 244 Older Adults With COVID-19 in Wuhan, China: A Retrospective Study. J Am Geriatr Soc 2020; 68: E19-E23.

18) Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, Ji R, Wang H, Wang Y, Zhou Y. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis 2020; 94: 91-95.

19) Crackower MA, Sarao R, Oudit GY, Yagil C, Kozieradzki I, Scanga SE, Oliveira-dos-Santos A, da Costa J, Zhang L, Pei Y, Scholey J, Ferrario CM, Manoukian AS, Chappell MC, Backx PH, Yagil Y, Penninger JM. Angiotensin-converting enzyme 2 is an essential regulator of heart function. Nature 2002; 417: 822-828.

20) Giovinazzo F, Vaccaro A, Pascale MM, Cardella F, Frongillo F, Galiandro F, Sganga G, Agnes S. SARS-CoV-2 infection in adult liver transplantation recipients: a systematic review of risk factors for mortality and immunosuppression role. Eur Rev Med Pharmacol Sci 2023; 27: 1695-1707.

21) Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, Li Q, Jiang C, Zhou Y, Liu S, Ye C, Zhang P, Xiong Y, Guo, Tang W. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect 2020; 81: e16-e25.

22) Chu KH, Tsang WK, Tang CS, Lam MF, Lai FM, To KF, Fung KS, Tang HL, Yan WW, Chan HWH, Lai TST, Tong KL, Lai KL. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. Kidney Int 2005; 67: 698-705.

23) Shi H, Peng Q, Zhou XL, Zhu SP, Sun SY. Use of angiotensin-converting enzyme inhibitors or receptor blockers is associated with reduced mortality in patients with post-acute kidney injury: meta-analysis. Eur Rev Med Pharmacol Sci 2021; 25: 4900-4908.

24) Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054-1062.

25) Cecconi M, Piovani D, Brunetta E, Aghemo A, Greco M, Ciccarelli M, Angelini C, Voza A, Omodei P, Vespa E, Pugliese N, Parigi T, Folci M, Danese S, Bonovas S. Early Predictors of Clinical Deterioration in a Cohort of 239 Patients Hospitalized for Covid-19 Infection in Lombardy, Italy. J Clin Med 2020; 9: 1548.

26) Betjes MGH. Immune cell dysfunction and inflammation in end-stage renal disease. Nat Rev Nephrol 2013; 9: 255-265.

27) Yang L, Xing G, Wang L. Acute kidney injury in China: a cross-sectional survey. Lancet 2015; 386: 1465-1471.

28) Xu X, Nie S, Liu Z, Chen C, Xu G, Zha Y, Qian J, Liu B, Han S, Xu A, Xu X, Hou FF. Epidemiology and Clinical Correlates of AKI in Chinese Hospitalized Adults. Clin J Am Soc Nephrol 2015; 10: 1510-1518.

29) Zhou F, Wang Y, Liu Y, Liu X, Gu L, Zhang X, Pu Z, Yang G, Liu B, Nie Q, Xue B, Feng J, Guo Q, Liu J, Fan H, Chen J, Zhang Y, Xu Z, Pang M, Chen Y, Nie X, Cai Z, Xu J, Peng K, Liu X, Xiang P, Zhang Z, Jiang S, Su X, Zhang J, Liu Y, Jin X, Jiang R, Dong J, Song Y, Zhou H, Wang C, Cao B, CAP-China Network. Disease severity and clinical outcomes of community-acquired pneumonia caused by non-influenza respiratory viruses in adults: a multicentre prospective registry study from the CAP-China Network. Eur Respir J 2019; 54: 1802406.

30) Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507-513.