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Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China

Chaomin Wu, MD; Xiaoyan Chen, MD; Yanping Cai, MD; Jia'an Xia, MD; Xing Zhou, MD; Sha Xu, MD; Hanping Huang, MD; Li Zhang, MD; Xia Zhou, MD; Chunling Du, MD; Yuye Zhang, BD; Juan Song, BD; Sijiao Wang, BD; Yencheng Chao, MD; Zeyong Yang, MD; Jie Xu, MD; Xin Zhou, MD; Dechang Chen, MD; Weining Xiong, MD; Lei Xu, MD; Feng Zhou, MD; Jinjun Jiang, MD; Chunxue Bai, MD; Junhua Zheng, MD; Yuanlin Song, MD

IMPORTANCE Coronavirus disease 2019 (COVID-19) is an emerging infectious disease that was first reported in Wuhan, China, and has subsequently spread worldwide. Risk factors for the clinical outcomes of COVID-19 pneumonia have not yet been well delineated.

OBJECTIVE To describe the clinical characteristics and outcomes in patients with COVID-19 pneumonia who developed acute respiratory distress syndrome (ARDS) or died.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study of 201 patients with confirmed COVID-19 pneumonia admitted to Wuhan Jinyintan Hospital in China between December 25, 2019, and January 26, 2020. The final date of follow-up was February 13, 2020.

EXPOSURES Confirmed COVID-19 pneumonia.

MAIN OUTCOMES AND MEASURES The development of ARDS and death. Epidemiological, demographic, clinical, laboratory, management, treatment, and outcome data were also collected and analyzed.

RESULTS Of 201 patients, the median age was 51 years (interquartile range, 43-60 years), and 128 (63.7%) patients were men. Eighty-four patients (41.8%) developed ARDS, and of those 84 patients, 44 (52.4%) died. In those who developed ARDS, compared with those who did not, more patients presented with dyspnea (50 of 84 [59.5%] patients and 30 of 117 [25.6%] patients, respectively [difference, 33.9%; 95% CI, 19.7%-48.1%]) and had comorbidities such as hypertension (23 of 84 [27.4%] patients and 16 of 117 [13.7%] patients, respectively [difference, 13.7%; 95% CI, 1.3%-26.1%]) and diabetes (16 of 84 [19.0%] patients and 6 of 117 [5.1%] patients, respectively [difference, 13.9%; 95% CI, 3.6%-24.2%]). In bivariate Cox regression analysis, risk factors associated with the development of ARDS and progression from ARDS to death included older age (hazard ratio [HR], 3.26; 95% CI 2.08-5.11; and HR, 6.17; 95% CI, 3.26-11.67, respectively), neutrophilia (HR, 1.14; 95% CI, 1.09-1.19; and HR, 1.08; 95% CI, 1.01-1.17, respectively), and organ and coagulation dysfunction (eg, higher lactate dehydrogenase [HR, 1.61; 95% CI, 1.44-1.79; and HR, 1.30; 95% CI, 1.11-1.52, respectively] and D-dimer [HR, 1.03; 95% CI, 1.01-1.04; and HR, 1.02; 95% CI, 1.01-1.04, respectively]). High fever (≥39 °C) was associated with higher likelihood of ARDS development (HR, 1.77; 95% CI, 1.11-2.84) and lower likelihood of death (HR, 0.41; 95% CI, 0.21-0.82). Among patients with ARDS, treatment with methylprednisolone decreased the risk of death (HR, 0.38; 95% CI, 0.20-0.72).

CONCLUSIONS AND RELEVANCE Older age was associated with greater risk of development of ARDS and death likely owing to less rigorous immune response. Although high fever was associated with the development of ARDS, it was also associated with better outcomes among patients with ARDS. Moreover, treatment with methylprednisolone may be beneficial for patients who develop ARDS.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Authors: Yuanlin Song, MD, Department of Pulmonary and Critical Care Medicine, Zhongshan Hospital, Fudan University, 180 Fenglin Rd, Shanghai 200032, China (ylsong70_02@163.com); Junhua Zheng, MD, Department of Urology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, 85 Wujin Rd, Shanghai 200080, China (zhengjh0471@sina.com).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, Hubei Province, China and has subsequently spread to other regions of China and 37 countries, including the United States, Japan, Australia, and France.[1] SARS-CoV-2, which belongs to a unique clade of the sarbecovirus subgenus of the Orthocoronavirinae subfamily, was identified as the pathogen of coronavirus disease 2019 (COVID-19) in January 2020.[2]

As reported by Huang et al,[3] patients with COVID-19 present primarily with fever, myalgia or fatigue, and dry cough. Although most patients are thought to have a favorable prognosis, older patients and those with chronic underlying conditions may have worse outcomes. Patients with severe illness may develop dyspnea and hypoxemia within 1 week after onset of the disease, which may quickly progress to acute respiratory distress syndrome (ARDS) or end-organ failure.[4] Certain epidemiological features and clinical characteristics of COVID-19 have been previously reported.[3-5] However, these studies were based on relatively small sample sizes, and risk factors leading to poor clinical outcomes have not been well delineated. In this study, we report the clinical characteristics and factors associated with developing ARDS after hospital admission and progression from ARDS to death in patients with COVID-19 pneumonia from a single hospital in Wuhan, China.

Key Points

Question What clinical characteristics are associated with the development of acute respiratory distress syndrome (ARDS) and progression from ARDS to death among patients with coronavirus disease 2019 (COVID-19) pneumonia?

Findings In this cohort study involving 201 patients with confirmed COVID-19 pneumonia, risk factors associated with the development of ARDS and progression from ARDS to death included older age, neutrophilia, and organ and coagulation dysfunction. Treatment with methylprednisolone may be beneficial for patients who develop ARDS.

Meaning Risk for developing ARDS included factors consistent with immune activation; older age was associated with both ARDS development and death, likely owing to less robust immune responses.

Methods

Study Population

This is a retrospective cohort study of 201 patients aged 21 to 83 years with confirmed COVID-19 pneumonia hospitalized at Jinyintan Hospital in Wuhan, China. All patients were diagnosed with COVID-19 pneumonia according to World Health Organization interim guidance.[6] According to hospital data, patients were admitted from December 25, 2019, to January 26, 2020. Of 201 patients, 10 have been described previously by Chen et al[4] and Huang et al.[3] The ethics committee of Jinyintan Hospital approved this study and granted a waiver of informed consent from study participants.

Procedures

A trained team of physicians and medical students reviewed and collected epidemiological, clinical, and outcomes data from electronic medical records. Patients were followed up to February 13, 2020. The individual components of all definitions of clinical outcomes were recorded separately and checked by 2 authors (C.W. and X.C.). Patient confidentiality was protected by assigning a deidentified patient identification, and the electronic data was stored in a locked, password-protected computer.

To identify SARS-CoV-2 infection, throat swab samples were obtained from all patients at admission and tested using real-time reverse transcriptase–polymerase chain reaction assays according to the same protocol described previously.[3] The pathogenic detection was determined in 4 institutions (Chinese Center for Disease Control and Prevention, Chinese Academy of Medical Sciences, Academy of Military Medical Sciences, and Wuhan Institute of Virology of the Chinese Academy of Sciences) as described previously.[4] Other respiratory pathogens, including respiratory syncytial virus, adenovirus, parainfluenza virus, influenza A virus, and influenza B virus, were also detected by real-time reverse transcriptase–polymerase chain reaction assays in 173 patients. Possible bacterial or fungal pathogens were detected by sputum culture. Additionally, patients underwent blood routine blood test, coagulation, and biochemical tests and chest x-rays or computed tomography. The most intense level of oxygen support during hospitalization (nasal cannula, noninvasive mechanical ventilation [NMV], invasive mechanical ventilation [IMV], or IMV with extracorporeal membrane oxygenation [ECMO]) was recorded. The majority of the clinical data used in this study was collected from the first day of hospital admission unless indicated otherwise. To minimize interference of treatment during hospitalization, the highest patient temperature was defined using the self-reported highest temperature prior to hospital admission. Older age was classified as 65 years or older. Fever and high fever were classified as 37.3 °C or higher and 39 °C or higher, respectively.

Outcomes

Two outcomes were evaluated: development of ARDS and death among those with ARDS. World Health Organization interim guidance was used to define ARDS.[6]

Statistical Analysis

Descriptive analyses of the variables were expressed as median (interquartile range [IQR]), or number (%). Differences in distributions of patient characteristics by outcome subgroups are reported using differences with 95% CIs. Categorical data were compared using the $\chi 2$ test or the Fisher exact test. Nonnormal distributed continuous data were compared using Mann-Whitney-Wilcoxon test.

Bivariate Cox proportional hazard ratio (HR) models were used to determine HRs and 95% CIs between individual factors on the development of ARDS or progression from ARDS to death. Sample size varied because of missing data (summarized in **Tables 1** and **2**). Survival curves were developed using

Table 1. Demographic Characteristics of Patients With Coronavirus Disease 2019 Pneumonia

Study population	No. (%)
No. of patients	201
Age, median (IQR), y	51 (43-60)
≥65	40 (19.9)
<65	161 (80.1)
Highest patient temperature, median (IQR), °C	38.8 (38.3-39.0)
≥39 (high fever)	77 (38.3)
<39	93 (46.3)
Gender	
Male	128 (63.7)
Female	73 (36.3)
Wuhan seafood market exposure	99 (49.3)
Date of illness onset	
Before December 5, 2019	1 (0.5)
December 6-31, 2019	114 (56.7)
January 1-14, 2020	76 (37.8)
After January 15, 2020	10 (5.0)
Initial common symptoms	
Fever	188 (93.5)
Cough	163 (81.1)
Productive cough	83 (41.3)
Dyspnea	80 (39.8)
Fatigue or myalgia	65 (32.3)
Chest imaging, infiltrate[a]	
Unilateral	10 (5.0)
Bilateral	191 (95.0)
Comorbidities	
Hypertension	39 (19.4)
Diabetes	22 (10.9)
Cardiovascular disease	8 (4.0)
Liver disease	7 (3.5)
Nervous system disease	7 (3.5)
Chronic lung disease	5 (2.5)
Chronic kidney disease	2 (1.0)
Endocrine system disease[b]	2 (1.0)
Tumor	1 (0.5)
Other respiratory pathogen infection	
Other viruses (n = 173)	1 (0.6)
Bacteria[c] (n = 148)	0
Treatment in hospital	
Oxygen therapy	165 (82.1)
Nasal cannula	98 (48.8)
NMV	61 (30.3)
IMV	5 (2.5)
IMV with ECMO	1 (0.5)
Methylprednisolone	62 (30.8)
Therapy	
Antibiotic	196 (97.5)
Antiviral	170 (84.6)
Immunomodulator[d]	70 (34.8)
Antioxidant[e]	106 (52.7)
Clinical outcomes	
ARDS	84 (41.8)
ICU admission	53 (26.4)
Death	44 (21.9)

Abbreviations: ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range; NMV, noninvasive mechanical ventilation (including high flow supply and face mask).

[a] Including chest x-ray and computed tomography scan.

[b] Not including diabetes.

[c] Including 2 patients with positive results for tuberculosis antibodies.

[d] Including immunoglobulin, thymosin, and recombinant human granulocyte colony stimulating factor.

[e] Including glutathione and N-acetyl-L-cysteine.

the Kaplan-Meier method with log-rank test. Time to events (ARDS or death) were defined as the time from hospital admission to events.

The analyses regarding different factors were based on nonmissing data, and missing data were not imputed. All tests were 2-sided, and a *P* value less than .05 was considered statistically significant. All analyses were performed with SPSS, version 23.0 (IBM SPSS), or R software, version 3.6.0 (R Foundation for Statistical Computing).

Results

Demographics and Characteristics

A total of 201 patients were included in this study (Table 1). The median age was 51 years (IQR, 43-60 years), and 128 (63.7%) were male. The most commonly self-reported symptoms at onset of illness were fever (n = 188 [93.5%]), cough (n = 163 [81.1%]), productive cough (n = 83 [41.3%]), dyspnea (n = 80 [39.8%]), and fatigue or myalgia (n = 65 [32.3%]). The majority (n = 154 [76.6%]) of patients had fever with cough; 74 (36.8%) had fever with dyspnea; 66 (32.8%) had fever with fatigue, myalgia, or headache; and only 13 (6.5%) presented with fever alone (eTable 1 in the Supplement). A total of 191 (95.0%) patients had findings of bilateral infiltrates on radiographic imaging, while 10 (5.0%) patients had unilateral infiltrates. Sixty-six (32.8%) patients had comorbidities, including hypertension (n = 39 [19.4%]), diabetes (n = 22 [10.9%]), liver disease (n = 7 [3.5%]), nervous system disease (n = 7 [3.5%]), chronic lung disease (n = 5 [2.5%]), chronic kidney disease (n = 2 [1.0%]), endocrine system diseases not including diabetes (n = 2 [1.0%]), and tumors (n = 1 [0.5%]). Most (n = 173 [86.1%]) patients were tested for 9 additional respiratory pathogens. Bacteria and fungi cultures were collected from 148 (73.6%) patients. Only 1 patient was coinfected with influenza A virus.

Treatments in Hospital

Of the 201 patients, 165 (82.1%) required oxygen support in the hospital (Table 1). The most intense level was recorded, in-

Table 2. Initial Laboratory Indices of Patients With Coronavirus Disease 2019 Pneumonia

Tests in study population	Reference values	No. of patients tested	Value, median (IQR)	No. of patients with value deviation from reference (%)
Hematologic				
White blood cells, $\times10^9$/mL	3.5-9.5	197	5.94 (3.80-9.08)	46 (23.4)[a]
Neutrophils, $\times10^9$/mL	1.8-6.3	197	4.47 (2.32-7.70)	68 (34.5)[a]
Lymphocytes, $\times10^9$/mL	1.1-3.2	197	0.91 (0.60-1.29)	126 (64.0)[b]
Monocytes, $\times10^9$/mL	0.1-0.6	197	0.33 (0.22-0.44)	18 (9.1)[a]
Platelets, $\times10^9$/mL	125-350	197	180.00 (137.00-241.50)	37 (18.8)[b]
CD3, /μL	NA	97	607.00 (430.50-830.50)	NA
CD4, /μL	NA	97	353.00 (226.50-499.00)	NA
CD8, /μL	NA	97	236.00 (142.50-314.50)	NA
Biochemical				
Total bilirubin, mg/dL	0-26	198	11.45 (9.00-14.75)	10 (5.1)[a]
AST, U/L	15-40	198	33.00 (26.00-45.00)	59 (29.8)[a]
ALT, U/L	9-50	198	31.00 (19.75-47.00)	43 (21.7)[a]
Total protein, g/L	65-85	198	63.90(59.78-67.00)	113 (57.1)[b]
Albumin, g/L	40-55	198	32.75 (29.10-35.40)	195 (98.5)[b]
Globulin, g/L	20-40	198	30.65 (28.58-33.72)	8 (4.0)[a]
Prealbumin, mg/L	200-430	187	121.00 (87.00-157.00)	164 (87.7)[b]
Urea, mM	3.6-9.5	198	4.80 (3.68-6.10)	9 (4.5)[a]
Creatinine, μM	57-111	198	72.20 (57.68-83.00)	9 (4.5)[a]
Glucose, mM	3.9-6.1	197	6.00 (5.00-7.95)	89 (45.2)[a]
CK-MB, U/L	0-24	198	15.00 (12.00-20.00)	9 (4.5)[a]
Cholinesterase, U/L	5000-12000	185	7776.00 (6427.00-9216.50)	11 (6.0)[b]
Cystatin C, mg/L	0.6-1.55	182	0.88 (0.74-1.05)	10 (5.5)[a]
LDH, U/L	120-150	198	307.50 (232.25-389.25)	194 (98.0)[a]
α-HBDH, U/L	72-182	194	252.50 (195.25-337.50)	148 (76.3)[a]
LDL, mM	2.1-3.37	195	2.06 (1.60-2.58)	94 (48.2)[b]
Infection-related indices				
hs-CRP, mg/L	0-5	194	42.40 (14.15-92.68)	166 (85.6)[a]
IL-6, pg/L	0-7	123	6.98 (5.46-9.02)	60 (48.8)[a]
ESR, mm/h	0-15	194	49.30 (40.00-66.88)	182 (93.8)[a]
Serum ferritin, ng/mL	21.8-274.66	163	594.00 (315.69-1266.16)	128 (78.5)[a]
Coagulation function				
PT, s	10.5-13.5	195	11.10 (10.20-11.90)	4 (2.1)[a]
APTT, s	21-37	195	28.70 (23.30-33.70)	19 (9.7)[a]
D-dimer, μg/mL	0-1.5	189	0.61 (0.35-1.28)	44 (23.3)[a]

Abbreviations: α-HBDH, α-hydroxybutyric dehydrogenase; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CK-MB, creatine kinase muscle-brain isoform; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; IQR, interquartile range; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; PT, prothrombin time.

[a] Above reference.

[b] Below reference.

cluding nasal cannula (n = 98 [48.8%]), NMV (n = 61 [30.3%]), IMV (n = 5 [2.5%]), or IMV with ECMO (n = 1 [0.5%]). Among 201 patients, most (n = 196 [97.5%]) received empirical antibiotic treatment and antiviral therapy (n = 170 [84.6%]), including oseltamivir (n = 134 [66.7%]), ganciclovir (n = 81 [40.3%]), lopinavir/ritonavir (n = 30 [14.9%]), and interferon alfa (n = 22 [10.9%]). More than half (n = 106 [52.7%]) of patients received antioxidant therapy, including glutathione and N-acetyl-L-cysteine. Methylprednisolone was given to 62 (30.8%) patients, and immunomodulators, including immunoglobulin, thymosin, and recombinant human granulocyte colony stimulating factor, were given to 70 (34.8%) patients.

Laboratory Indices

Laboratory findings on hospital admission are summarized in Table 2. Of 194 patients, 166 (85.6%) demonstrated increased high-sensitivity C-reactive protein. More than half (126 of 197 [64.0%]) of this cohort had lymphocytopenia. About one-third (68 of 197 [34.5%]) of patients had neutrophilia. Approximately one-quarter (46 of 197 [23.4%]) of patients had leukocytosis. Some patients demonstrated liver injury with elevated aspartate aminotransferase (AST; 59 of 198 [29.8%]) and alanine aminotransferase (ALT; 43 of 198 [21.7%]). Most patients presented with an elevated myocardial indices: 194 of 198 (98.0%) had elevated lactate dehydrogenase (LDH), and 9 of 198 (4.5%) had an elevated creatine kinase muscle-brain isoform. Few patients had kidney injury indicated by elevated plasma urea (9 of 198 [4.5%]) and serum creatinine (9 of 198 [4.5%]). Of 195 patients, 4 (2.1%) presented with prolonged prothrombin times (PTs).

Clinical Outcomes

As of February 13, 2020, 144 of the total 201 patients (71.6%) were discharged from the hospital. The median hospital stay was 13 days (IQR, 10-16 days), and 13 (6.5%) patients were still hospitalized. Of the entire cohort, 84 (41.8%) patients developed ARDS, 53 (26.4%) were admitted to the intensive care unit,

67 (33.3%) received mechanical ventilation, and 44 (21.9%) died. Among the 67 patients who received mechanical ventilation, 44 (65.7%) died, 14 (20.9%) were discharged from the hospital, and 9 (13.4%) remained hospitalized. The median time from admission to developing ARDS was 2 days (IQR, 1-4 days). All of the patients who died had developed ARDS and received mechanical ventilation.

Table 3 demonstrates that when compared with patients without ARDS, patients with ARDS were older (difference, 12.0 years; 95% CI, 8.0-16.0 years; $P < .001$) and had higher temperature prior to admission (difference, 0.30 °C; 95% CI, 0.00-0.50 °C; $P = .004$). More patients with ARDS presented with initial symptoms of dyspnea compared with those without ARDS (difference, 33.9%; 95% CI, 19.7%-48.1%; $P < .001$). Compared with patients without ARDS, patients with ARDS had a higher proportion of comorbidities, including hypertension (difference, 13.7%; 95% CI, 1.3%-26.1%; $P = .02$) and diabetes (difference, 13.9%; 95% CI, 3.6%-24.2%; $P = .002$). In addition, when compared with patients who did not have ARDS, patients who developed ARDS were less likely to be treated with antiviral therapy (difference, −14.4%; 95% CI, −26.0% to −2.9%; $P = .005$) and more likely to be treated with methylprednisolone (difference, 49.3%; 95% CI, 36.4%-62.1%; $P < .001$). Of 84 patients with ARDS, 61 (72.6%) received NMV, 17 (20.2%) received nasal cannula, 5 (6.0%) received IMV, and 1 (1.2%) received IMV with ECMO.

Compared with patients without ARDS, for patients with ARDS, the value of liver damage indices (total bilirubin [difference, 1.90 mg/dL; 95% CI, 0.60-3.30 mg/dL; $P = .004$]), renal dysfunction indices (urea [difference, 1.69 mM; 95% CI, 1.10-2.29 mM; $P < .001$]), inflammation-related indices (interleukin-6 [IL-6] [difference, 0.93 pg/L; 95% CI, 0.07-1.98 pg/L; $P = .03$]), and coagulation function indices (D-dimer [difference, 0.52 μg/mL; 95% CI, 0.21-0.94 μg/mL; $P < .001$]) were significantly elevated. However, lymphocyte counts (difference, -0.34×10^9/mL; 95% CI, -0.47 to -0.22×10^9/mL; $P < .001$) and CD8 T cells (difference, −66.00 cells/μL; 95% CI, −129.00 to −7.00 cells/μL; $P = .03$) were significantly decreased.

As summarized in **Table 4**, older age (≥65 years old), high fever (≥39 °C), comorbidities (eg, hypertension, diabetes), neutrophilia, lymphocytopenia (as well as lower CD3 and CD4 T-cell counts), elevated end-organ related indices (eg, AST, urea, LDH), elevated inflammation-related indices (high-sensitivity C-reactive protein and serum ferritin), and elevated coagulation function-related indicators (PT and D-dimer) were significantly associated with higher risks of the development of ARDS. Patients who received treatment with methylprednisolone appear to have been sicker than patients who did not receive it. Specifically, a higher proportion of patients who received methylprednisolone were classified into a higher grade on the Pneumonia Severity Index[7] compared with patients who did not receive methylprednisolone ($P = .01$; eTable 2 in the Supplement).

In the subgroup of patients who developed ARDS, patients who ultimately died were older (difference, 18.0 years; 95% CI, 13.0-23.0 years; $P < .001$) and had lower proportion of high fever (difference, −31.8%; 95% CI, −56.5% to −7.1%; $P = .007$) than those who survived. They also had higher proportions of hypertension (difference, 18.9%; 95% CI, −2.0% to 39.7%; $P = .05$). The patients who died were less likely to be treated with antiviral therapy (difference, −40.7%; 95% CI, −58.5% to −22.9%; $P < .001$). Regarding the most intense level of oxygen support among the 44 ARDS patients who died, 38 (86.4%) received NMV, 5 (11.4%) received IMV, and 1 (2.3%) received IMV with ECMO.

For patients with ARDS who died, the value of liver damage indices (total bilirubin [difference, 2.60 mg/dL; 95% CI, 0.30-5.20 mg/dL; $P = .03$]), renal dysfunction indices (urea [difference, 1.50 mM; 95% CI, 0.50-2.70 mM; $P = .004$]), inflammation-related indices (IL-6 [difference, 3.88 pg/L; 95% CI, 2.20-6.13 pg/L; $P < .001$]), and coagulation function indices (D-dimer [difference, 2.10 μg/mL; 95% CI, 0.89-5.27 μg/mL; $P = .001$]) were significantly elevated compared with patients with ARDS who survived. However, lymphocyte counts (difference, -0.23×10^9/mL; 95% CI, -0.41 to -0.07×10^9/mL; $P = .004$) and CD8 T cells (difference, −134 cells/μL; 95% CI, −221 to −10 cells/μL; $P = .05$) were significantly decreased (Table 3).

Bivariate Cox models showed that several factors related to the development of ARDS were not associated with death, which included comorbidities, lymphocyte counts, CD3 and CD4 T-cell counts, AST, prealbumin, creatinine, glucose, low-density lipoprotein, serum ferritin, and PT. However, IL-6 was statistically significantly associated with death (Table 4). Although high fever was associated with higher likelihood of developing ARDS (HR, 1.77; 95% CI, 1.11-2.84), it was negatively associated with death (HR, 0.41; 95% CI, 0.21-0.82).

Finally, among the patients with ARDS, of those who received methylprednisolone treatment, 23 of 50 (46.0%) patients died, while of those who did not receive methylprednisolone treatment, 21 of 34 (61.8%) died. The administration of methylprednisolone appears to have reduced the risk of death in patients with ARDS (HR, 0.38; 95% CI, 0.20-0.72; $P = .003$) (**Figure**).

Discussion

In this cohort study, we reported the clinical characteristics and risk factors associated with clinical outcomes in patients with COVID-19 pneumonia who developed ARDS after admission, as well as those who progressed from ARDS to death. Patients who received methylprednisolone treatment were much more likely to develop ARDS likely owing to confounding by indication; specifically, sicker patients were more likely to be given methylprednisolone. However, administration of methylprednisolone appeared to reduce the risk of death in patients with ARDS. These findings suggest that for patients with COVID-19 pneumonia, methylprednisolone treatment may be beneficial for those who have developed ARDS on disease progression. However, these results should be interpreted with caution owing to potential bias and residual confounding in this observational study with a small sample size. Double-blinded randomized clinical trials should be conducted to validate these results.

Table 3. Clinical Characteristics and Initial Laboratory Indices Among Patients With and Without ARDS

Clinical characteristics	All patients				Patients with ARDS			
	Without ARDS, No. (%) (n = 117)	With ARDS, No. (%) (n = 84)	Difference (95% CI)[a]	*P* value[b]	Alive, No. (%) (n = 40)	Died, No. (%) (n = 44)	Difference (95% CI)[a]	*P* value[b]
Age, median (IQR), y	48.0 (40.0 to 54.0)	58.5 (50.0 to 69.0)	12.0 (8.0 to 16.0)	<.001	50.0 (40.3 to 56.8)	68.5 (59.3 to 75.0)	18.0 (13.0 to 23.0)	<.001
Highest patient temperature, median (IQR), °C	38.60 (38.2 to 39.0)	39.0 (38.5 to 39.6)	0.3 (0.0 to 0.5)	.004	39.0 (38.5 to 39.7)	38.9 (38.0 to 39.2)	−0.3 (−0.6 to 0.0)	.05
≥39 (high fever)	36 (36.4)	41 (57.7)	21.3 (5.3 to 37.5)	.006	27 (73.0)	14 (41.2)	−31.8 (−56.5 to −7.1)	.007
<39	63 (63.6)	30 (42.3)			10 (27.0)	20 (58.8)		
Gender								
Male	68 (58.1)	60 (71.4)	13.3 (−0.9 to 27.5)	.05	31 (77.5)	29 (65.9)	−11.6 (−33.0 to 9.9)	.24
Female	49 (41.9)	24 (28.6)			9 (22.5)	15 (34.1)		
Initial symptoms								
Fever	110 (94.0)	78 (92.9)	−1.2 (−9.2 to 6.8)	.74	39 (97.5)	39 (88.6)	−8.9 (−21.8 to 4.1)	.25
Cough	95 (81.2)	68 (81.0)	−0.2 (−11.5 to 11.0)	.97	35 (87.5)	33 (75.0)	−12.5 (−31.3 to 6.3)	.15
Productive cough	42 (35.9)	41 (48.8)	12.9 (−1.9 to 27.7)	.07	22 (55.0)	19 (43.2)	−11.8 (−35.5 to 11.8)	.28
Dyspnea	30 (25.6)	50 (59.5)	33.9 (19.7 to 48.1)	<.001	21 (52.5)	29 (65.9)	13.4 (−9.8 to 36.7)	.21
Fatigue or myalgia	38 (32.5)	27 (32.1)	−0.3 (−13.8 to 13.1)	.96	12 (30.0)	15 (34.1)	4.1 (−18.2 to 26.4)	.69
Comorbidities								
Hypertension	16 (13.7)	23 (27.4)	13.7 (1.3 to 26.1)	.02	7 (17.5)	16 (36.4)	18.9 (−2.0 to 39.7)	.05
Diabetes	6 (5.1)	16 (19.0)	13.9 (3.6 to 24.2)	.002	5 (12.5)	11 (25.0)	12.5 (−6.3 to 31.3)	.15
Cardiac disease	3 (2.6)	5 (6.0)	3.4 (−3.4 to 10.2)	.40	4 (10.0)	4 (9.1)	−0.9 (−14.4 to 12.6)	.13
Treatment in hospital								
Oxygen therapy[c]								
Nasal cannula	81 (69.2)	17 (20.2)	−49.0 (−62.0 to −36.0)	<.001	17 (42.5)	0	−42.5 (−60.2 to −24.8)	<.001
NMV	0	61 (72.6)	72.6 (62.1 to 83.2)		23 (57.5)	38 (86.4)	28.9 (8.1 to 49.6)	
IMV	0	5 (6.0)	6.0 (−0.1 to 12.0)		0	5 (11.4)	11.4 (−0.4 to 23.1)	
IMV with ECMO	0	1 (1.2)	1.2 (−2.2 to 4.5)		0	1 (2.3)	2.3 (−4.4 to 8.9)	
Methylprednisolone	12 (10.3)	50 (59.5)	49.3 (36.4 to 62.1)	<.001	27 (67.5)	23 (52.3)	−15.2 (−38.3 to 7.9)	.16
Antibiotic therapy	113 (96.6)	83 (98.8)	2.2 (−2.8 to 7.3)	.59	40 (100.0)	43 (97.7)	−2.3 (−8.9 to 4.4)	>.99
Antiviral therapy	106 (90.6)	64 (76.2)	−14.4 (−26.0 to −2.9)	.005	39 (97.5)	25 (56.8)	−40.7 (−58.5 to −22.9)	<.001
Laboratory findings, value, median (IQR)								
Hematologic								
White blood cells, $\times 10^9$/mL	5.02 (3.37 to 7.18)	8.32 (5.07 to 11.20)	2.56 (1.56 to 3.63)	<.001	6.62 (4.79 to 11.23)	8.61 (5.90 to 11.44)	1.11 (−0.76 to 3.08)	.19
Neutrophils, $\times 10^9$/mL	3.06 (2.03 to 5.56)	7.04 (3.98 to 10.12)	2.99 (1.97 to 4.06)	<.001	5.91 (3.39 to 9.70)	7.43 (5.15 to 10.60)	1.30 (−0.44 to 3.17)	.14
Lymphocytes, $\times 10^9$/mL	1.08 (0.72 to 1.45)	0.67 (0.49 to 0.99)	−0.34 (−0.47 to −0.22)	<.001	0.80 (0.56 to 1.17)	0.59 (0.48 to 0.74)	−0.23 (−0.41 to −0.07)	.004
Monocytes, $\times 10^9$/mL	0.34 (0.24 to 0.43)	0.29 (0.20 to 0.44)	−0.03 (−0.08 to 0.01)	.15	0.35 (0.20 to 0.44)	0.25 (0.20 to 0.45)	−0.03 (−0.12 to 0.05)	.41
Platelets, $\times 10^9$/mL	178.00 (140.00 to 239.50)	187.00 (124.50 to 252.50)	−4.00 (−27.00 to 20.00)	.73	204.00 (137.25 to 262.75)	162.00 (110.50 to 231.00)	−31.00 (−65.00 to 5.00)	.10
CD3, /μL	633.00 (467.00 to 846.00)	446.50 (231.00 to 633.75)	−215.00 (−358.00 to −73.00)	.003	563.00 (281.00 to 769.50)	264.00 (222.00 to 448.00)	−237.00 (−471.00 to 40.00)	.07
CD4, /μL	371.00 (283.00 to 572.00)	234.00 (136.75 to 398.00)	−138.00 (−224.00 to −51.00)	.004	286.00 (132.00 to 449.50)	166.00 (128.50 to 312.50)	−81.00 (−264.00 to 55.00)	.25
CD8, /μL	241.00 (159.00 to 323.00)	157.50 (76.00 to 289.50)	−66.00 (−129.00 to −7.00)	.03	273.00 (88.00 to 316.00)	96.00 (67.00 to 143.50)	−134.00 (−221.00 to −10.00)	.05

(continued)

Table 3. Clinical Characteristics and Initial Laboratory Indices Among Patients With and Without ARDS (continued)

Clinical characteristics	All patients				Patients with ARDS			
	Without ARDS, No. (%) (n = 117)	With ARDS, No. (%) (n = 84)	Difference (95% CI)[a]	*P* value[b]	Alive, No. (%) (n = 40)	Died, No. (%) (n = 44)	Difference (95% CI)[a]	*P* value[b]
Biochemical								
Total bilirubin, mg/dL	10.50 (8.60 to 13.65)	12.90 (9.50 to 17.05)	1.90 (0.60 to 3.30)	.004	11.65 (9.33 to 15.15)	14.50 (10.35 to 19.80)	2.60 (0.30 to 5.20)	.03
AST, U/L	30.00 (24.00 to 38.50)	38.00 (30.50 to 53.00)	9.00 (5.00 to 12.00)	<.001	38.50 (32.25 to 57.25)	37.00 (30.00 to 52.00)	−4.00 (−10.00 to 2.00)	.21
ALT, U/L	27.00 (18.00 to 41.50)	35.00 (21.50 to 52.50)	7.00 (2.00 to 13.00)	.01	35.00 (23.25 to 55.25)	39.00 (20.50 to 52.50)	−2.00 (−11.00 to 8.00)	.71
Total protein, g/L	64.30 (60.95 to 67.25)	63.50 (57.40 to 66.85)	−1.40 (−3.10 to 0.30)	.11	63.90 (57.83 to 67.60)	62.70 (56.90 to 65.95)	−1.60 (−4.40 to 1.00)	.21
Albumin, g/L	33.70 (30.95 to 36.30)	30.40 (27.15 to 33.35)	−3.50 (−4.60 to −2.30)	<.001	31.35 (27.70 to 34.20)	29.10 (26.20 to 31.55)	−2.30 (−4.10 to −0.70)	.007
Globulin, g/L	30.00 (28.25 to 32.55)	31.60 (29.35 to 35.05)	1.60 (0.60 to 2.80)	.004	30.70 (29.40 to 33.52)	32.90 (29.10 to 36.30)	1.50 (−0.50 to 3.50)	.18
Prealbumin, mg/L	136.00 (99.50 to 170.00)	100.50 (76.75 to 128.00)	−37.00 (−52.00 to −23.00)	<.001	101.00 (83.50 to 146.00)	100.00 (67.00 to 123.00)	−11.00 (−31.00 to 10.00)	.30
Urea, mM	4.30 (3.40 to 5.40)	5.80 (4.45 to 7.90)	1.69 (1.10 to 2.29)	<.001	4.94 (4.00 to 6.90)	7.40 (5.10 to 8.75)	1.50 (0.50 to 2.70)	.004
Creatinine, μM	68.70 (57.45 to 81.05)	74.60 (57.90 to 92.35)	5.60 (−0.20 to 11.50)	.06	78.65 (59.73 to 93.30)	73.00 (57.45 to 86.70)	−4.77 (−15.30 to 4.80)	.30
Glucose, mM	5.40 (4.90 to 6.50)	7.40 (5.70 to 10.08)	1.60 (1.00 to 2.40)	<.001	7.80 (5.40 to 10.40)	7.10 (5.95 to 9.95)	0.10 (−1.40 to 1.20)	.92
CK-MB, U/L	15.00 (12.00 to 19.00)	17.00 (13.00 to 20.50)	2.00 (0.00 to 3.00)	.01	16.00 (13.00 to 20.75)	17.00 (13.00 to 20.00)	0.00 (−3.00 to 3.00)	.93
Cholinesterase, U/L	8070.00 (7210.00 to 9741.00)	6955.00 (5707.50 to 8498.00)	−1237.67 (−1782.00 to −654.00)	<.001	7948.00 (6498.50 to 9152.00)	6384.00 (5472.50 to 7757.00)	−1274.00 (−2111.00 to −399.00)	.005
Cystatin C, mg/L	0.84 (0.72 to 0.93)	0.97 (0.82 to 1.22)	0.16 (0.09 to 0.24)	<.001	0.94 (0.73 to 1.08)	1.08 (0.84 to 1.42)	0.19 (0.04 to 0.35)	.01
LDH, U/L	257.00 (211.00 to 320.50)	396.00 (320.00 to 521.00)	136.00 (106.00 to 168.00)	<.001	349.50 (293.50 to 416.00)	484.00 (351.00 to 568.50)	112.00 (50.00 to 173.00)	.001
α-HBDH, U/L	217.00 (179.00 to 277.00)	333.00 (252.50 to 477.00)	118.00 (86.00 to 151.00)	<.001	301.50 (228.75 to 366.25)	417.00 (290.50 to 495.00)	112.00 (45.00 to 174.00)	.001
LDL, mM	2.16 (1.74 to 2.72)	1.88 (1.50 to 2.47)	−0.29 (−0.50 to −0.08)	.007	2.00 (1.60 to 2.48)	1.67 (1.30 to 2.42)	−0.16 (−0.50 to 0.17)	.30
Infection-related indices								
hs-CRP, mg/L	23.40 (6.65 to 57.80)	83.00 (39.45 to 152.40)	46.70 (32.50 to 64.00)	<.001	69.20 (26.60 to 120.80)	90.85 (44.55 to >160)	17.92 (−8.60 to 45.00)	.17
IL-6, pg/L	6.29 (5.36 to 7.83)	7.39 (5.63 to 10.89)	0.93 (0.07 to 1.98)	.03	6.05 (5.12 to 6.99)	10.07 (7.36 to 14.80)	3.88 (2.20 to 6.13)	<.001
ESR, mm/h	47.70 (40.00 to 64.30)	52.40 (40.00 to 71.00)	4.00 (−2.00 to 11.60)	.20	51.60 (40.00 to 70.00)	59.50 (39.50 to 72.50)	1.80 (−9.00 to 14.51)	.74
Serum ferritin, ng/mL	457.66 (223.73 to 702.65)	1029.28 (546.26 to >2000)	545.50 (332.15 to 754.44)	<.001	853.00 (330.33 to 1968.57)	1096.21 (559.41 to >2000)	102.55 (−185.63 to 412.71)	.34
Coagulation function								
PT, s	10.60 (10.10 to 11.50)	11.70 (11.10 to 12.45)	1.00 (0.70 to 1.30)	<.001	11.75 (10.95 to 12.45)	11.60 (11.10 to 12.45)	0.00 (−0.50 to 0.60)	.87
APTT, s	29.75 (25.55 to 32.85)	26.00 (22.55 to 35.00)	−1.70 (−3.90 to 0.60)	.13	29.60 (24.00 to 35.75)	24.10 (22.25 to 28.35)	−3.10 (−7.00 to −0.20)	.04
D-dimer, μg/mL	0.52 (0.33 to 0.93)	1.16 (0.46 to 5.37)	0.52 (0.21 to 0.94)	<.001	0.49 (0.31 to 1.18)	3.95 (1.15 to 10.96)	2.10 (0.89 to 5.27)	.001

Abbreviations: α-HBDH, α-hydroxybutyric dehydrogenase; ARDS, acute respiratory distress syndrome; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CK-MB, creatine kinase muscle-brain isoform; ECMO, extracorporeal membrane oxygenation; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; IMV, invasive mechanical ventilation; IQR, interquartile range; NMV, noninvasive mechanical ventilation (including high flow supply and face mask); LDH, lactate dehydrogenase; LDL, low-density lipoprotein; PT, prothrombin time.

[a] Difference in location for continuous variables (by Hodges-Lehmann method) and in percentage for categorical variables (With ARDS vs Without ARDS or Died vs Alive).

[b] Mann-Whitney-Wilcoxon was used for continuous variables, and χ^2 test was used for categorical variables, if not specified.

[c] Fisher exact test.

Table 4. Bivariate Cox Regression of Factors Associated With ARDS Development or Progression From ARDS to Death

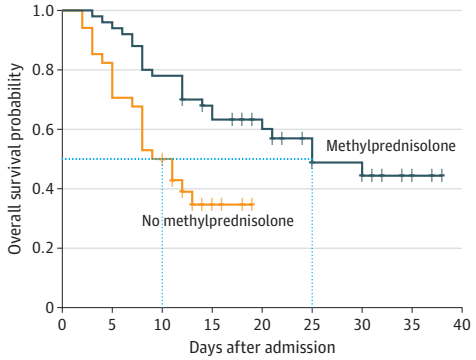
	ARDS		Death	
Patient characteristics and findings	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Clinical characteristics				
Age (≥65 vs <65), y	3.26 (2.08-5.11)	<.001	6.17 (3.26-11.67)	<.001
Gender (male vs female)	1.47 (0.92-2.36)	.11	0.56 (0.30-1.05)	.07
Highest patient temperature (≥39 °C vs <39 °C)	1.77 (1.11-2.84)	.02	0.41 (0.21-0.82)	.01
Comorbidities				
Hypertension (yes vs no)	1.82 (1.13-2.95)	.01	1.70 (0.92-3.14)	.09
Diabetes (yes vs no)	2.34 (1.35-4.05)	.002	1.58 (0.80-3.13)	.19
Laboratory findings				
Hematologic				
Neutrophils, 10^9/mL	1.14 (1.09-1.19)	<.001	1.08 (1.01-1.17)	.03
Lymphocytes,10^9/mL	0.37 (0.21-0.63)	<.001	0.51 (0.22-1.17)	.11
CD3, 100/mL	0.83 (0.72-0.96)	.01	0.81 (0.59-1.11)	.19
CD4, 100/mL	0.74 (0.59-0.93)	.01	0.83 (0.51-1.35)	.45
CD8, 100/mL	0.74 (0.53-1.04)	.08	0.51 (0.24-1.09)	.08
Biochemical				
Total bilirubin, mg/dL	1.05 (1.02-1.08)	.001	1.07 (1.02-1.12)	.003
AST, U/L	1.02 (1.01-1.03)	<.001	0.99 (0.98-1.01)	.45
ALT, U/L	1.00 (1.00-1.01)	.09	1.00 (0.98-1.01)	.43
Albumin, 10 g/L	0.49 (0.37-0.66)	<.001	0.19 (0.07-0.49)	.001
Globulin, 10 g/L	2.32 (1.45-3.71)	<.001	1.91 (1.01-3.61)	.05
Prealbumin, mg/L	0.99 (0.98-0.99)	<.001	1.00 (0.99-1.00)	.31
Urea, mM	1.13 (1.09-1.18)	<.001	1.13 (1.06-1.20)	<.001
Creatinine, 10 μM	1.05 (1.01-1.10)	.02	1.04 (0.97-1.11)	.31
Glucose, mM	1.13 (1.08-1.19)	<.001	1.00 (0.92-1.08)	.92
CK-MB, U/L	1.01 (1.00-1.02)	.12	0.99 (0.97-1.01)	.46
Cholinesterase, $\times 10^3$U/L	0.81 (0.73-0.90)	<.001	0.84 (0.73-0.97)	.02
Cystatin C, mg/L	1.69 (1.31-2.19)	<.001	1.80 (1.28-2.53)	.001
LDH, 100 U/L	1.61 (1.44-1.79)	<.001	1.30 (1.11-1.52)	.001
α-HBDH, 100 U/L	1.74 (1.52-1.99)	<.001	1.34 (1.13-1.60)	.001
LDL, mM	0.63 (0.44-0.88)	.008	0.84 (0.54-1.31)	.45
Infection-related indices				
hs-CRP, mg/L (>5 vs ≤5)	4.81 (1.52-15.27)	.008	NA	NA
IL-6, pg/L	1.02 (1.00-1.05)	.09	1.03 (1.01-1.05)	.01
ESR, mm/h	1.01 (1.00-1.02)	.19	1.01 (0.99-1.02)	.32
Serum ferritin, ng/mL (>300 vs ≤300)	3.53 (1.52-8.16)	.003	5.28 (0.72-38.48)	.10
Coagulation function				
PT, s	1.56 (1.32-1.83)	<.001	1.08 (0.84-1.38)	.54
APTT, s	0.97 (0.94-1.01)	.13	0.96 (0.91-1.00)	.06
D-dimer, μg/mL	1.03 (1.01-1.04)	<.001	1.02 (1.01-1.04)	.002

Abbreviations: α-HBDH, α-hydroxybutyric dehydrogenase; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CK-MB, creatine kinase muscle-brain isoform; ESR, erythrocyte sedimentation rate; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; NA, not available; PT, prothrombin time.

The risk factors related to the development of ARDS and progression from ARDS to death included older age, neutrophilia, and organ and coagulation dysfunction (eg, higher LDH and D-dimer). In addition, we observed that several factors associated with the development of ARDS were not associated with death (eg, comorbidities, lymphocyte counts, CD3 and CD4 T-cell counts, AST, prealbumin, creatinine, glucose, low-density lipoprotein, serum ferritin, PT). Moreover, the difference in median D-dimer between the death and survival groups was larger than that between the ARDS and non-ARDS groups, which suggests that disseminated intravascular coagulation was on the pathway to death in some patients. Interestingly, although high fever was positively associated with development of ARDS, it was negatively related to death, which is consistent with results noted in a study by Schell-Chaple et al.[8] However, the differences in patient temperature between the groups were very small and self-reported before hospital admission, thus the data regarding high fever should be cautiously interpreted.

The pathogenesis of highly pathogenic human coronavirus is still not completely understood. Cytokine storm and viral evasion of cellular immune responses are thought to play

Figure. Survival Curve in Patients With Acute Respiratory Distress Syndrome Who Did and Did Not Receive Methylprednisolone Treatment



No. at risk

No methylprednisolone	34	28	17	4	0	0	0	0	0
Methylprednisolone	50	48	39	29	20	14	11	4	0

Administration of methylprednisolone reduced the risk of death (hazard ratio, 0.38; 95% CI, 0.20-0.72; *P* = .003).

important roles in disease severity.[9] Neutrophilia was found in both the peripheral blood[10] and lung[11] of patients with SARS-CoV. The severity of lung damage correlated with extensive pulmonary infiltration of neutrophils and macrophages and higher numbers of these cells in the peripheral blood in patients with Middle East respiratory syndrome.[12-14] Neutrophils are the main source of chemokines and cytokines. The generation of cytokine storm can lead to ARDS, which is a leading cause of death in patients with severe acute respiratory syndrome[15] and Middle East respiratory syndrome.[14] In this study, patients with COVID-19 pneumonia who had developed ARDS had significantly higher neutrophil counts than did those without ARDS, perhaps leading to the activation of neutrophils to execute an immune response against the virus, but also contributing to cytokine storm. This may partly explain the positive association of high fever and ARDS found at the early stages of COVID-19. In addition, considering that older age is associated with declined immune competence,[16] the results of the present study showed that older age was associated with both ARDS and death. Therefore, older age related to death may be due to less robust immune responses.

The results of this study show that higher CD3 and CD4 T-cell counts might protect patients from developing ARDS, but similar results were not observed when examined for death, possibly because of limited sample size. CD8 counts were significantly higher in those who were alive. These results indicate the important roles of CD4 and CD8 T cells in COVID-19 pneumonia. Earlier studies have revealed that SARS-CoV, which was reported to share the same cell entry receptors with SARS-CoV-2,[17,18] could infect immune cells, including T lymphocytes, monocytes, and macrophages.[19] The CD3, CD4, and CD8 T-cell counts decreased at the onset of illness; this decrease persisted until the recovery period of SARS-CoV pneumonia.[19] In addition, CD4 and CD8 T-cell counts decreased in the peripheral blood specimen of patients with fatal SARS-CoV pneumonia[10,20,21], which was consistent with these results that patients with COVID-19 pneumonia and ARDS presented with lymphocytopenia (CD3, CD4, and CD8 T cells). Studies demonstrated that T-cell responses can inhibit the overactivation of innate immunity.[22] T cells were reported to help clear SARS-CoV, and a suboptimal T-cell response was found to cause pathological changes observed in mice with SARS-CoV.[23] We hypothesized that persistent and gradual increases in lymphocyte responses might be required for effective immunity against SARS-CoV-2 infection. Further studies are needed to characterize the role of the neutrophil and lymphocyte response or that of CD4 and CD8 T-cell immune response in SARS-CoV-2 infection.

Limitations

This study has several limitations. First, owing to limited medical resources, only patients with relatively severe COVID-19 pneumonia were hospitalized during this period. Second, this study was conducted at a single-center hospital with limited sample size. As such, this study may have included disproportionately more patients with poor outcomes. There may also be a selection bias when identifying factors that influence the clinical outcomes. A larger cohort study of patients with COVID-19 pneumonia from Wuhan, China, other cities in China, and other countries would help to further define the clinical characteristics and risk factors of the disease.

Conclusions

Older age was associated with greater risk of developing ARDS and death, likely because of less rigorous immune response. Although fever was associated with the development of ARDS, it was also associated with better outcomes. Several factors related to the development of ARDS were not associated with death, which indicates that different pathophysiological changes from hospital admission to development of ARDS and from development of ARDS to death may exist. Moreover, treatment with methylprednisolone may be beneficial for patients who develop ARDS. Double-blinded randomized clinical trials to determine the most effective treatments for COVID-19 are still needed.

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Author Affiliations: Department of Pulmonary Medicine, QingPu Branch of Zhongshan Hospital Affiliated to Fudan University, Shanghai, China (Wu, Du, F. Zhou, Y. Song); Infection Division, Wuhan Jinyintan Hospital, Wuhan, China (Wu, Cai, X. Zhou, S. Xu); Department of Pulmonary and Critical Care Medicine, Zhongshan Hospital, Fudan University, Shanghai, China (Wu, X. Chen, Y. Zhang, J. Song, Wang, Chao, Jiang, Bai, Y. Song); Tuberculosis and Respiratory Department, Wuhan Jinyintan Hospital, Wuhan, China (Xia, Huang, L. Zhang, X. Zhou); Department of Anesthesiology, International Peace Maternity and Child Health Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China (Yang); Department of Infectious Diseases, Fengxian Guhua Hospital, Shanghai, China (J. Xu); Department of Pulmonary Medicine, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China (X. Zhou); Department of Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China (D. Chen); Department of Respiratory Medicine, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China (Xiong); Department of Emergency Medicine, Shanghai Pudong New Area Gongli Hospital, Shanghai, China (L. Xu); Shanghai Respiratory Research Institute, Shanghai, China

(Bai, Y. Song); Department of Urology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China (Zheng); National Clinical Research Center for Aging and Medicine, Huashan Hospital, Fudan University, Shanghai, China (Y. Song).

Author Contributions: Drs Song and Zheng had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Wu, X. Chen, Cai, and Xia contributed equally and share first authorship. Drs Song and Zheng contributed equally to the study.
Study concept and design: Wu, X. Chen, Cai, Xia, Zheng, Y. Song.
Acquisition, analysis, or interpretation of data: X. Chen, Xing Zhou, S. Xu, Huang, L. Zhang, Xia Zhou, Du, Y. Zhang, J. Song, Wang, Chao, Yang, J. Xu, Xin Zhou, D. Chen, Xiong, L. Xu, F. Zhou, Jiang, Bai.
Drafting of the manuscript: X. Chen, Xia, Xing Zhou, S. Xu, Huang, L. Zhang, Xia Zhou, Du, Y. Zhang, J. Song, Wang, Chao, Yang, J. Xu, Xin Zhou, D. Chen, Xiong, L. Xu, F. Zhou, Jiang, Bai.
Critical revision of the manuscript for important intellectual content: Wu, X. Chen, Cai, Xia, Du, Zheng, Y. Song.
Statistical analysis: X. Chen, Y. Song.
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Study supervision: Zheng, Y. Song.

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