Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Respiratory Physiology & Neurobiology 297 (2022) 103813

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol

Potential benefits of precise corticosteroid therapy for critical COVID-19

Qingquan Chen [a,1], Qiongxiu Yang [b,1], Yingying Fang [c], Gongping Chen [d,*], Xiaoting Lv [d,*]

[a] Department of Laboratory Medicine, Fujian Medical University, Fuzhou, Fujian, 350004, China
[b] Department of Gynecology and Obstetrics, 3rd People's Hospital of Yichang, Yichang, Hubei, 443000, China
[c] Department of Tuberculosis, 3rd People's Hospital of Yichang, Yichang, Hubei, 443000, China
[d] Department of Respiratory and Critical Care Medicine, First Affiliated Hospital of Fujian Medical University; Institute of Respiratory Disease, Fujian Medical University, Fuzhou, Fujian, 350005, China

ARTICLE INFO

Edited by Yu Ru Kou

Keywords:
COVID-19
Corticosteroid
Pulmonary fibrosis
Overall survival
Lymphocytes

ABSTRACT

This study was aimed to explore the precise dose of corticosteroid therapy in critical COVID-19. A total of forty-five critical COVID-19 patients were enrolled. The process of critical COVID-19 was divided into alveolitis and fibrosis stages. Most nonsurvivors died in fibrosis phase. Nonsurvivors had more dyspnea symptoms, fewer days of hospitalization, shorter duration of alveolitis and fibrosis. High-dose daily corticosteroid therapy (≥150 mg/d) was associated with shorter survival time and lower lymphocyte count in fibrosis phase. Moreover, a high cumulative dose (≥604 mg) was tied to longer duration of virus shedding, lower oxygenation index (OI), higher incidence of tracheal intubation, fewer lymphocytes and higher levels of C-reactive protein (CRP) and lactate dehydrogenase (LDH). In alveolitis phase, the low-to-moderate-dose daily corticosteroid therapy and a small cumulative dose reduced lymphocytes. In conclusion, low-to-moderate dose corticosteroids may be beneficial in the fibrosis phase. High-dose corticosteroid therapy in the fibrosis phase aggravates the severity of critical COVID-19.

1. Introduction

In December 2019, a series of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) broke out in Wuhan, Hubei, China. Since then, it has rapidly swept around the world with a basic reproductive number of 2.68 (95 % CI, 2.47–2.86) (Heymann and Shindo, 2020; Wu et al., 2020a, 2020b), leading the WHO to announce the event constitutes a Public Health Emergency of International Concern (PHEIC) (World Health Organization, 2020). The disease may quickly progress to life-threatening acute respiratory distress syndrome (ARDS) (Wu et al., 2020a, 2020b) and risk factors included older age, lymphocytes, organ and coagulation dysfunction (eg, higher lactate dehydrogenase (LDH), C-reactive protein (CRP), D-Dimer(DD)) (National Health Commission of the People's Republic of China, 2020).

The viral genes of 2019-nCoV and SARS-CoV are highly homologous. Lung tissue often presents with acute diffuse alveolar injury in the early stage of SARS-CoV infection and organic pneumonia and/or extensive fibrosis in the pathologically advanced stage (Bradley and Bryan, 2019; Ding et al., 2003; Ye et al., 2020). CT images and pathological findings of critical COVID-19 patients often have consistent manifestations. Chest CT images have been used to diagnose and monitor disease progression and evaluate therapeutic efficacy (National Health Commission of the People's Republic of China, 2020), even when COVID-19 patients had false-negative RT-PCR results (Fang and Zhang, 2020; Huang and Liu, 2020; Xie and Zhong, 2020). Bilateral distribution of ground-glass opacities (GGO) and early infiltration in the posterior and peripheral lungs are the major hallmarks of COVID-19 in Chest CT images (Pan and Ye, 2020; Ye et al., 2020; Zhou et al., 2020a, 2020b), consistent with pathological findings of COVID-19 patients died in 14 days with ARDS, including pneumocytes desquamation, hyaline membrane formation, interstitial monocytes and lymphocytes inflammatory infiltrates (Xu et al., 2020), indicating an acute alveolitis stage. Moreover, in the late stage, the incidence of air bronchogram, bronchiectasis, reticular pattern, and other fibrosis changes in severe cases was significantly higher than that in the mild case group, meaning that the disease had progressed to the pulmonary fibrosis stage (National Health Commission of the People's Republic of China, 2020;Ye et al., 2020; Zhou et al.,

* Corresponding author at: Department of Respiratory and Critical Care Medicine, First Affiliated Hospital of Fujian Medical University; Institute of Respiratory Disease, Fujian Medical University, Fuzhou, Fujian, 350005, China.
E-mail addresses: cgp3542@163.com (G. Chen), helenahelena@126.com (X. Lv).
[1] Co-First Author.

https://doi.org/10.1016/j.resp.2021.103813
Received 8 October 2021; Received in revised form 20 October 2021; Accepted 4 November 2021
Available online 18 November 2021

2020a, 2020b). This finding was further supported by autopsy results of critical COVID-19 patients who died in 17–19 days and which exhibited significant proliferation of type II alveolar epithelia, organization of exudates in some alveolar cavities, and pulmonary interstitial fibrosis (Yao et al., 2020).

The underlying pathogenesis of severe influenza infection is characterized by overproduction of proinflammatory cytokines/chemokines and activated lymphocytes, leading to severe lung damage and delayed recovery (Louie et al., 2009; Mauad et al., 2010; Shieh et al., 2010; Yang et al., 2014; Yu et al., 2011; Zhao et al., 2012). Although corticosteroids were widely used in SARS, Middle East respiratory syndrome (MERS), and COVID-19 (Arabi et al., 2018;Huang et al., 2020; Stockman et al., 2006), the indication and curative effects of corticosteroid therapy are still disputed. Corticosteroid treatment may potentially decrease mortality and ameliorate acute lung injury induced by influenza A (H1N1) pdm09 virus (Li et al., 2012; Ottolini et al., 2003) and it may be beneficial for COVID-19 patients who developed ARDS on disease progression (Wu et al., 2020a, 2020b). Yet insufficient evidence exists to recommend corticosteroid treatment for 2019-nCoV lung injury (Russell et al., 2020). Current interim guidance from the WHO on the clinical management of SARS-CoV-2 infection advises against the use of corticosteroids unless otherwise indicated (World Health Organization, 2020), while the National Health Commission of the People's Republic of China has suggested that corticosteroid therapy could be used for progressive critical COVID-19 patients (National Health Commission of the People's Republic of China, 2020).

This study aimed to describe the clinical characteristics of critical COVID-19 patients and to explore the effects of different doses of adjuvant corticosteroid therapy in alveolitis and fibrosis stages according to the CT findings and its predictive value for clinical prognosis.

2. Materials and methods

2.1. Study design and participants

All patients aged fourteen or over were enrolled in the ICU ward of the Third People's Hospital of Yichang City (one of the mostly epidemic areas in China) from January 27 to March 20, 2020. According to the WHO interim guidance (World Health Organization, 2020), a total of 45 patients were subsequently confirmed as critical COVID-19 cases and jointly diagnosed by a Multidisciplinary diagnosis and treatment (MDT) team composed of infectious disease experts, respiratory medicine staff, critical care medical staff, and emergency medicine staff. Critical cases were met with any one of the following: respiratory failure and required mechanical ventilation, the occurrence of shock, and combined failure of other organs that required ICU monitoring and treatment (National Health Commission of the People's Republic of China, 2020). Patients who had previously received chronic corticosteroid therapy had been excluded. All discharged survivors were detected with twice negative nucleic acid tests of throat swab samples (National Health Commission of the People's Republic of China, 2020).

Systemic corticosteroid therapy in the disease course was defined as any intended therapeutic use of corticosteroids, including methylprednisolone, and/or prednisolone via oral or intravenous routes, but excluding inhalational therapy. Low-to-moderate-dose daily corticosteroids were defined as 25−150 $mg.d^{-1}$ methylprednisolone or equivalent, while high-dose daily corticosteroids were defined as ≥150 $mg.d^{-1}$ methylprednisolone or equivalent (Lamontagne et al., 2010; Tagami et al., 2015; Tang et al., 2009). No patients had received corticosteroid therapy at a certain dose range of 0−25 mg/d. Patients without corticosteroid treatment were classified as the corticosteroid-free group.

2.2. Cases collection

The cases were collected according to the methods of Xiao-Ting Lv et al. 2020[31].General information included age, gender, days from illness onset to hospital admission, history of living/traveling in the epidemic area, comorbidities such as chronic obstructive pulmonary disease (COPD), hypertension, coronary heart disease, cerebrovascular disease, diabetes, renal dysfunction, malignant tumors, administration of immunosuppressive agents and so on, clinical symptoms on admission (fever, cough, dyspnea, fatigue and others), duration of viral shedding, days of hospitalization, disease duration, duration of alveolitis and fibrosis phases, rate of shock, incidence of tracheal intubation, and time of tracheal intubation. Chest CT images were used to make a distinction between the alveolitis and fibrosis phases.

2.3. Laboratory inspection

The hemolytic agents for blood cell analysis were detected by the detection Kit (CF-294−754) ordered from Sysmex Co., Ltd. (Japan). Recommended reference range for the normal population of lymphocytes is (1.26–3.35) $\times 10^9$/L. The serum concentrations of CRP were detected by the detection Kit (no. P02219200) ordered from Getein Biotech Co., Ltd. (China). The recommended reference range for the normal population is (0–10) mg/L. The serum concentrations of D-dimer (DD) were detected by the detection Kit (no.C1.02.3602) ordered from Jiangsu Changxing Medical Technology Co., Ltd. (China). The recommended reference range for the normal population is (0–1.35) mg/L. The serum concentrations of LDH were detected by the detection Kit (no. A0701) ordered from Sichuan Chengdu New Health City Biological Co., Ltd. (China). The recommended reference range for the normal population is (109–245) U/L. The arterial partial pressure of oxygen (PaO2) were detected by a blood gas analyzer (i-STAT1 300) ordered from Abbott Laboratories (USA). Throat swab samples of the patients were collected and fluorescent PCR was used to detect the coronavirus RNA of SARS-CoV-2 by using the new coronavirus 2019-nCov nucleic acid detection kit (no. DA0930-DA0932) provided by Sun Yat-sen University Daan Gene Co., Ltd. (China). Those who were positive for RNA detection were identified as confirmed cases.

2.4. Statistical analysis

Statistical analysis was performed using the SPSS 18.0 software package (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as median (interquartile range, IQR) and compared by Mann-Whitney *U* test Comparisons were made by χ^2 test for categorical variables. Survival data were analyzed by using Kaplan-Meier survival curves and log-rank (Mantel-Cox) test. For all tests, a two-sided P value$<$0.05 was considered statistically significant.

3. Results

3.1. Clinical presentation of patients with critical COVID-19

Patients were included and divided into nonsurvivors (n = 17) and survivors (n = 28) groups. Nonsurvivors had fewer days of hospitalization, a shorter duration of disease in both alveolitis and fibrosis stages, and more dyspnea symptoms than survivors (P = 0.0003, 0.001, and 0.015, respectively). There was no significant difference between the two groups in age (P = 0.806), gender (P = 0.463), days from illness onset to hospital admission (P = 0.564), duration of viral shedding (P = 0.071), or history of living/traveling in Wuhan city (P = 0.051) as well as complications. Compared with survivors, nonsurvivors had lower OI ($P < 0.0001$), higher rates of shock ($P < 0.0001$), increased incidence of tracheal intubation, and longer tracheal intubation time (P = 0.0001 and 0.001, respectively) during hospitalization. Significantly elevated levels of LDH, CRP and DD, fewer lymphocytes as well as a greatly increased degree of LDH and CRP in the fibrosis stage was demonstrated in nonsurvivors compared survivors (Table 1).

Table 1
Univariate predictors of adverse event and laboratory findings in patients with critical COVID-19.

Variables	Groups		
	Non-survivors(n = 17)	Survivors (n = 28)	P value
Age, year	69.0(63.5–78.0)	68.5 (56.0–77.0)	–
Gender (%)			–
Male	11(64.7)	15(53.6)	
Female	6(35.3)	13(46.4)	
Days from illness onset to hospital admission	5.0(2.0–10.0)	5.5(4.0–8.0)	–
Living/traveling in Wuhan city	14(82.4)	15(53.6)	–
Comorbidity on admission			
COPD (%)	3(17.6)	3(10.7)	–
Coronary heart disease (%)	7(41.2)	6(21.4)	–
Diabetes (%)	5(29.4)	7(25.0)	–
Hypertension (%)	10(58.8)	11(39.3)	–
Cerebrovascular disease (%)	3(17.6)	7(25.0)	–
Renal dysfunction (%)	2(11.8)	5(17.9)	–
Malignant tumors (%)	2(11.8)	3(10.7)	–
Administration of immunosuppressive agents (%)	1(5.9)	0(0.0)	–
Others[†]	7(41.2)	6(21.4)	–
Clinical symptoms on admission			
Fever	13(76.5)	24(85.7)	–
Cough	7(41.2)	18(64.3)	–
Dyspnea	9(52.9)	4(14.3)	.015
Fatigue	5(29.4)	4(14.3)	–
Others[‡]	5(29.4)	4(14.3)	–
Duration of viral shedding (day)	8.0(6.0–18.0)	12.5(9.0–21.5)	–
Days of hospitalization	14.0(8.0–24.5)	33.5 (18.3–38.8)	.0003
Disease duration(day) [§]	23.0(15.5–29.5)	39.0 (26.3–45.8)	.001
Duration of alveolitis phase (day)	12.0(8.0–17.5)	17.5 (14.3–21.0)	.005
Duration of fibrosis phase (day)	10.0(5.5–15.5)	20.0 (12.0–26.0)	.006
Lowest OI (PaO2/FiO2, mmHg)	48.0(37.0–67.5)	206.0 (90.5–240.0)	< .0001
Rate of shock (%)	13(76.5)	1(3.6)	< .0001
Incidence of tracheal intubation (%)	10(58.8)	1(3.6)	.0001
Time of tracheal intubation (day)	4.0(0.0–7.0)	0.0(0.0–0.0)	.0001
Highest LDH in alveolitis stage (U/L)	499.0 (327.0–682.8)	365.0 (283.0–495.5)	–
Highest LDH in fibrosis stage (U/L)	1303.0 (847.3–2922.8)	277.5 (224.3–341.3)	< .0001
Increase degree of LDH (U/L) [¶]	−495.0 (-2333.8–313.8)	94.0 (-15.0–140.0)	< .0001
Highest CRP in alveolitis stage (mg/L)	66.2(26.1–160.5)	77.0 (52.9–124.5)	–
Highest CRP in fibrosis stage (mg/L)	162.4 (115.7–202.0)	21.6 (10.3–65.0)	< .0001
Increase degree of CRP (mg/L) [¶]	−131.8(−160.0 to −8.0)	45.5(0.4–86.0)	.0001
Lowest lymphocytes in alveolitis stage ($\times 10^9$)	0.47(0.35–0.64)	0.57 (0.49–0.72)	–
Lowest lymphocytes in fibrosis stage ($\times 10^9$)	0.34(0.13–0.38)	0.73 (0.52–0.93)	< .0001
Increase degree of lymphocytes ($\times 10^9$) [¶]	0.20(0.00–0.38)	−0.17 (-0.44–0.08)	.019
Highest DD in alveolitis stage (mg/L)	4.6(0.9–10.3)	2.1(0.8–13.0)	–
Highest DD in fibrosis stage (mg/L)	17.4(11.3–39.3)	3.4(1.5–17.4)	.001
Increase degree of DD (mg/L) [¶]	−11.6(-32.8–0.5)	0.1(-2.2–4.1)	.026

[†] Thyroid dysfunction, prostatic hyperplasia, schizophrenia.
[‡] Arthralgia, sputum, dizziness, nausea, chest pain, diarrhea.
[§] Time from illness onset to death or discharge, days.
[¶] Difference between alveolitis and fibrosis stages.

3.2. Imaging features of critical COVID-19

Chest CT imaging findings in our study confirmed that all critical patients had both alveolitis and fibrosis stages, consistent with the existing literature reports (National Health Commission of the People's Republic of China, 2020; Zhou et al., 2020a, 2020b). Diffuse pulmonary infiltration was evident shown in the alveolitis stage, at which point period tracheal intubation and invasive mechanical ventilation were often performed as patients' condition deteriorated (Fig. 1A). After a few days of treatment with different doses of corticosteroids, some patients were extubated as lesions of GGO exhibited reduced and slight range (Fig. 1B). Only a small number of nonsurvivors failed to pass through the crisis of the alveolitis stage and died in the alveolitis stage (3/17). The illness frequently progressed into the fibrosis stage, characterized by consolidation and obvious changes of diffuse interstitial fibrosis including signs of air bronchogram sign, bronchiectasis, and reticular pattern were shown on Chest CT (Fig. 1C). Notably, most nonsurvivors died in the fibrosis phase (14/17). Due to a few days of treatment with corticosteroids in the fibrosis stage, interstitial fibrosis was absorbed gradually, and Chest CT in survivors exhibited a scanty amount of shadows of irregular linear or fibrotic reticular appearance accompanied by bronchiectasis (Fig. 1D–F).

3.3. Relationship between lymphocyte counts and corticosteroid therapy in patients with critical COVID-19

The cutoff point of the cumulative dose of corticosteroids administrated in the alveolitis phase for differentiating nonsurvivors from survivors was 180 mg, according to the receiver operating characteristic curve (ROC) analysis. Therefore, cases were divided into three groups based on cumulative dose of corticosteroids in the alveolitis phase: a corticosteroid-free group, a low-to-moderate dose group (less than 180 mg), and a high dose group (more than 180 mg). Our results showed that a high cumulative dose (Fig. 2A) and a low-to-moderate daily dose of corticosteroid therapy (Fig. 2B) positively reduced the counts of peripheral lymphocytes.

The cutoff point for the cumulative dose of corticosteroids administrated in the fibrosis phase for differentiating nonsurvivors from survivors was 604 mg, according to the ROC analysis. Additionally, the cumulative doses of corticosteroids administrated in the fibrosis phase were divided into three groups: a corticosteroid-free group, a low-to-moderate group (less than 604 mg) and a high dose group (more than 604 mg). Compared with corticosteroid-free treatment and low-to-moderate dose corticosteroid therapy, high cumulative dose (Fig. 2C) and the high daily dose of corticosteroid therapy (Fig. 2D) tended to have lower levels of lymphocytes in the fibrosis phase. Moreover, the median survival interval in the high daily dose of corticosteroid therapy group (≥150 mg/d) was markedly shorter than the low-to-moderate (25–150 mg/d) or free corticosteroid group (26.0 vs 39.0, P = 0.0004; 26.0 vs 29.0, P = 0.001, respectively) during the fibrosis phase (Fig. 2F), although there was no difference among these groups in the alveolitis

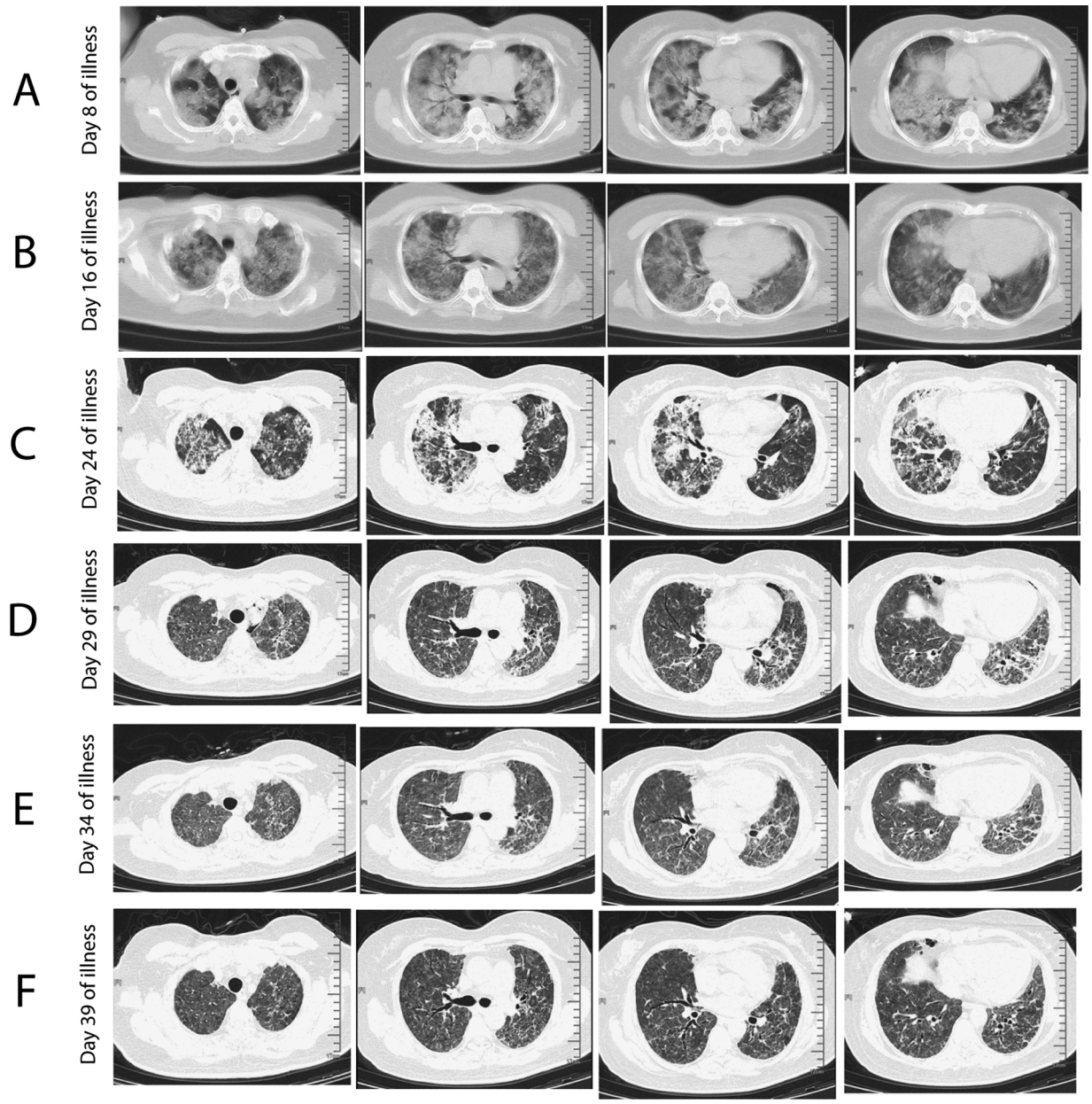

Fig. 1. Chest CT of a 54-year-old woman (survivor, case 1) with critical COVID-19 in different phases.
(A) Chest CT showed multifocal and bilateral GGO in alveolitis stage (Day 8 of illness). Tracheal intubation and invasive mechanical ventilation was performed as patient's condition deteriorated. (B) After few days of treatment with low-to-moderate-dose corticosteroid (80 mg/d) and invasive mechanical ventilation, we performed extubation and the second Chest CT exhibited reduced and slight range of GGO in alveolitis stage (Day 16 of illness). (C) As the illness progressed again, diffuses changes of interstitial fibrosis such as such as air bronchogram sign, bronchiectasis and reticular pattern were showed on Chest CT (Day 24 of illness). (D–E) After few days of treatment with low-to-moderate-dose corticosteroid (120 mg/d) and invasive mechanical ventilation in fibrosis stage, interstitial fibrosis lesions were absorbed gradually (Day 29 of illness and Day 34 of illness). (F) The last CT before discharge showed scanty amount of shadows of irregular linear or fibrotic reticular appearances accompanied by bronchiectasis (Day 39 of illness).

phase (Fig. 2E).

3.4. Association between laboratory findings and corticosteroid therapy in patients with critical COVID-19

There was no difference in the duration of viral shedding between patients treated with different doses of corticosteroids in the alveolitis phase (Fig. 3A). However, in the fibrosis phase, a high cumulative dose of corticosteroid therapy (≥604 mg) was significantly associated with longer duration of virus shedding, lower OI, a higher incidence of tracheal intubation, and higher levels of CRP and LDH, when compared to corticosteroid-free and low-to-moderate dose of corticosteroid therapy (less than 604 mg) (Fig. 3B, C, E, and G). Additionally, the rates of shock complications in patients treated with the high cumulative dose of corticosteroid were higher than the corticosteroid-free group, although there was no difference between high and low-to-moderate doses of corticosteroid therapy groups (Fig. 3D). Serum DD levels did not differ between groups (Fig. 3H).

4. Discussion

Our results showed that comprising of 45 hospitalized critical COVID-19 patients, among whom 73.3 % were older than 60 years. Most nonsurvivors of critical COVID-19 patients in the study died in the

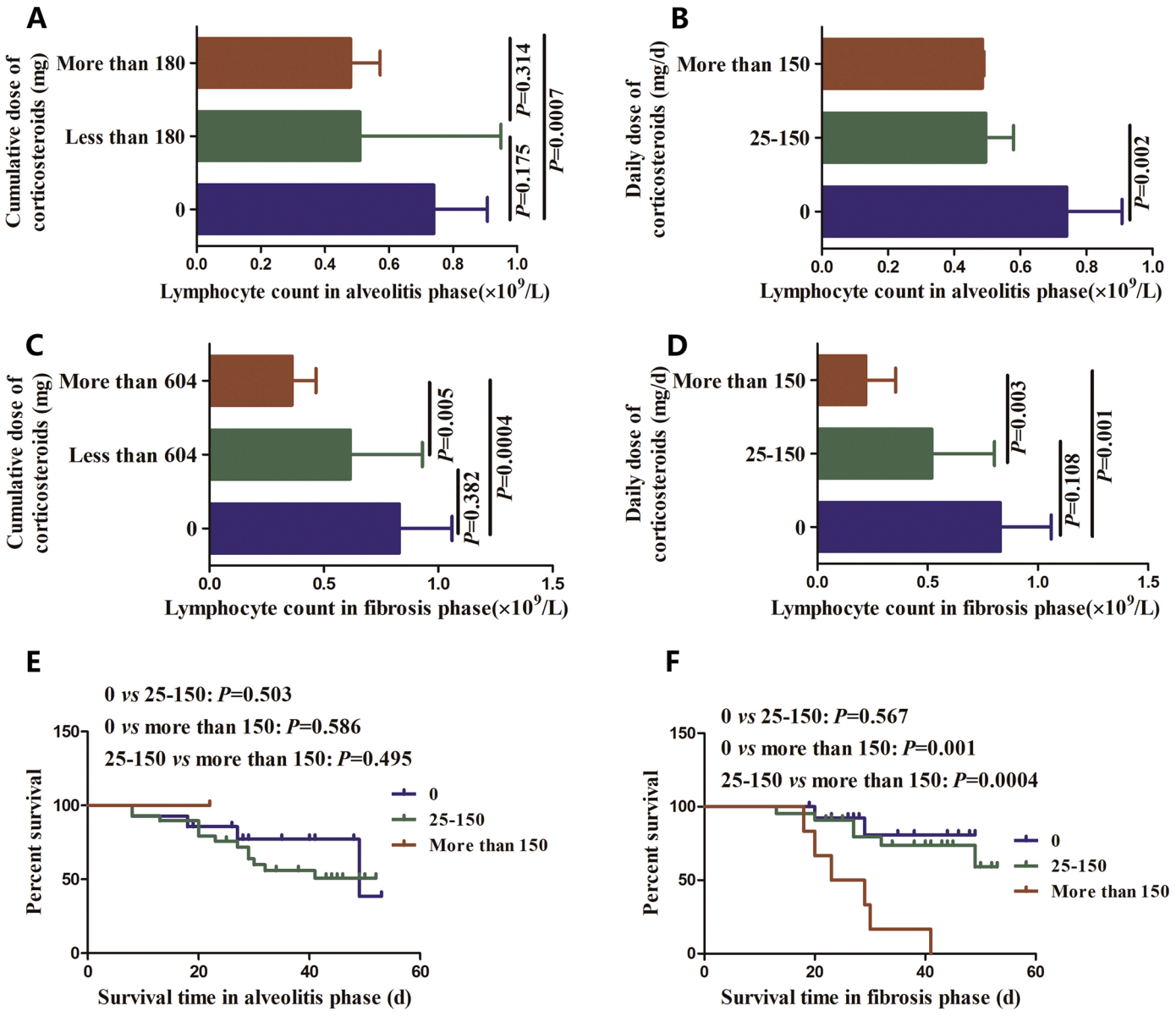

Fig. 2. The relationship between lymphocyte count and corticosteroid therapy in patients with critical COVID-19.
(A–B) In alveolitis phase, a relatively small cumulative dose of corticosteroid (≥180 mg, according to the ROC analysis) and a low-to-moderate-dose daily corticosteroid therapy (25−150 mg/d) can reduce the counts of peripheral lymphocytes. (C–D) In fibrosis phase, the high-dose daily corticosteroid therapy (≥150 mg/d) and high cumulative dose (≥604 mg, according to the ROC analysis) corticosteroid therapy was associated with significantly lower levels of lymphocyte, compared with corticosteroid-free treatment and low-to-moderate daily dose corticosteroid therapy (25−150 mg/d). The relationship between the survival time and the dose of corticosteroid therapy in the alveolitis phase (E) or fibrosis phase (F) was analyzed by Kaplan-Meier analysis and log-rank test. Although there was no difference in survival time between patients with different doses corticosteroids in alveolitis phase, patients with high daily dose corticosteroid (≥150 mg/d) had a significantly shorter survival days compared to corticosteroid-free treatment and low-to-moderate daily dose corticosteroid therapy in fibrosis phase.

fibrosis phase (14/17) and had a shorter duration of alveolitis and fibrosis, more severe symptoms of dyspnea at its onset, lower OI, higher rate of shock, increased incidence of tracheal intubation and longer time of tracheal intubation. Our study also demonstrated elevated levels of LDH, CRP, and DD, fewer lymphocytes in the fibrosis stage in non-survivors than survivors, as well as an increased degree of LDH and CRP in the alveolitis and fibrosis stages of nonsurvivors. In addition, high-dose daily corticosteroid therapy (≥150 mg/d) was significantly associated with a shorter survival time and lower levels of peripheral lymphocytes in the fibrosis phase. High cumulative dose (≥604 mg) in the fibrosis phase was also associated with a longer duration of virus shedding, lower OI, higher incidence of tracheal intubation, higher incidences of shock, fewer lymphocytes and higher levels of CRP and LDH than corticosteroid-free and low cumulative dose group (<604 mg). In the alveolitis phase, even a low-to-moderate-dose daily corticosteroid therapy (25−150 mg/d) and a relatively small cumulative dose (≥180 mg) can reduce the counts of lymphocytes, although different doses of corticosteroids yielded no difference in patient survival time.

Stratified analysis of critical COVID-19 patients with different stages was performed according to the Chest CT imaging findings of alveolitis and fibrosis stages. In the alveolitis phase, our results showed that even small-dose corticosteroid therapy could reduce the counts of lymphocytes, but there was no difference in survival time and duration of viral shedding between patients treated with different corticosteroids dose. Only a small number of nonsurvivors failed to pass through the crisis of alveolitis stage and died in the alveolitis stage (3/17). Previous studies on ARDS revealed that low-to-moderate dose corticosteroids reduced mortality significantly, but high-dose (>2.0 mg kg−1·d−1

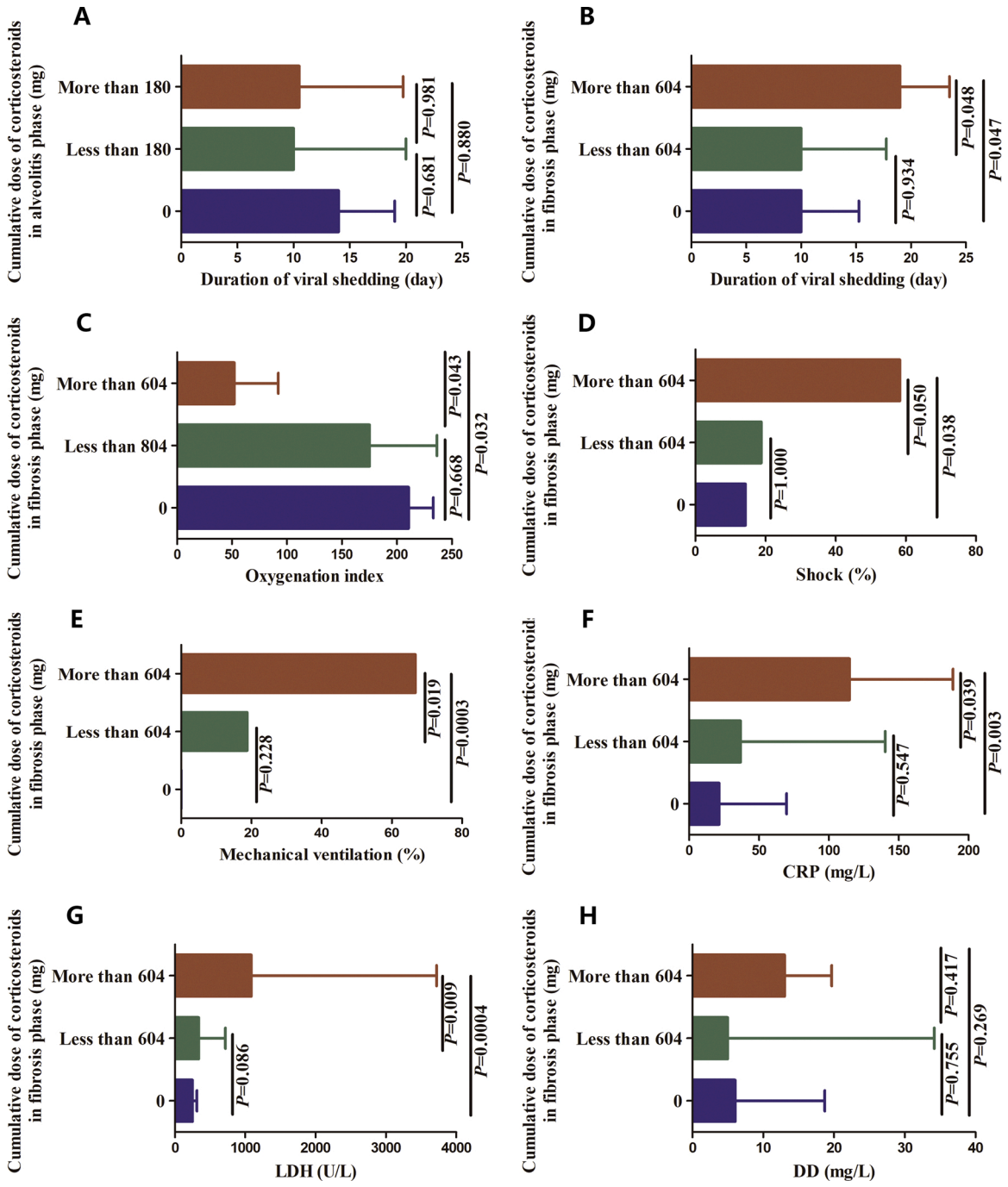

Fig. 3. Association between laboratory findings and the corticosteroid therapy in patients with critical COVID-19.
(A) In alveolitis phase, there were no differences in duration of viral shedding between patients treated with different doses of corticosteroid. (B–C, E–G) In fibrosis phase, high cumulative dose of corticosteroid therapy(≥604 mg) was associated with longer duration of virus shedding, lower OI, higher incidence of tracheal intubation and higher levels of CRP and LDH than corticosteroid-free and low-to-moderate dose of corticosteroids therapy (<604 mg). (D) High cumulative dose of corticosteroid also positively related to higher rates of shock complications when compared to corticosteroid-free therapy. (H) There was no difference in DD levels between patients treated with different doses of corticosteroids.

methylprednisolone) daily corticosteroid therapy had no such benefit (Lamontagne et al., 2010; Tang et al., 2009). Although early corticosteroid treatment was associated with a higher subsequent plasma viral load in SARS (Lee et al., 2004a), corticosteroids could be used for COVID-19 patients with progressive deterioration of OI, rapid progress of imaging and short hyperactivation time of inflammatory reaction. Early treatment of corticosteroids may be an independent prognostic factor in patients with IPF-AE (Atsumi et al., 2018). A proper dose of corticosteroid therapy in the first 3–5 days could enhance oxygen saturation (SaO2) and arterial oxygen tension (PaO2)/inspiratory oxygen fraction (FiO2), and might not increase ICU mortality in critical COVID-19 patients, thus precise corticosteroid therapy may have potential benefits for critical COVID-19 in the alveolitis phase (National Health Commission of the People's Republic of China, 2020; Zhou et al., 2020a, 2020b). Severe COVID-19 cases showed elevated levels of proinflammatory cytokines (TNF-α, IL-1, and IL-6) and chemokines (IL-8) compared to mild cases, and pathological findings in COVID-19 patients showed pneumocytes desquamation, hyaline membrane

formation, interstitial monocytes and lymphocytes inflammatory infiltrates, indicating acute respiratory distress syndrome (Xu et al., 2020), which were similar to the results in SARS and MERS (Min et al., 2016; Wong et al., 2004). Cytokine storms made damaged tissues worse, leading to diffuse lung infiltration as showed on our Chest CT in the alveolitis stage. Low-to-moderate dose corticosteroids might have multiple effects on damaged tissues through inhibiting immune-related cytokines in the acute alveolitis phase, therefore low-to-moderate dose corticosteroids might help critical patients through the inflammation storm without delaying the clearance of SARS-CoV2 virus RNA in the alveolitis phase.

Our study showed that most nonsurvivors died in the fibrosis phase, indicating that this rapidly progressing fibrosis stage may be more dangerous than the alveolitis stage. However, the critical COVID-19 patients did not benefit from the high-dose daily corticosteroid therapy (≥150 mg/d) or high integral dose (≥604 mg) in the fibrosis phase. A high cumulative dose (≥604 mg) in the fibrosis phase was also associated with a longer duration of virus shedding, lower OI, higher incidence of tracheal intubation, higher rates of shock complications, fewer lymphocytes and higher levels of CRP and LDH. High-dose corticosteroid therapy might exacerbate the development of critical COVID-19 in the fibrosis phase, resulting in increased mortality, although the harmful effects were not present in the low-to-moderate dose and corticosteroid-free groups.

In the fibrosis stage of critical COVID-19, there were many possible causes for the harmful effect of high-dose corticosteroids. On the one hand, our Chest CT in the fibrosis stage indicated that interstitial fibrosis caused by the disease might lead to respiratory failure. Studies have also that critical COVID-19 patients had lighter exudation of alveolar fluid and cellulose, less hyaline membrane, significantly altered proliferation of type II alveolar epithelial cells and bronchial mucosal epithelial cells, alveolar fleshy changes, and pathological interstitial fibrosis (Yao et al., 2020), indicating that the inflammation storm was ameliorated in the fibrosis stage, which would render high-dose corticosteroid therapy less effective than in the alveolitis phase. Thus, low-to-moderate-dose corticosteroid treatment may yield enough improvement of lung injury so as to reduce mortality in the fibrosis stage. On the other hand, our results showed that high-dose corticosteroid therapy delayed the clearance of SARS-CoV2 virus RNA in the fibrosis stage. Previous studies found that corticosteroid treatment delayed the clearance of viral RNA of MERS-CoV and SARS-CoV, increased complications including psychosis, diabetes, and avascular necrosis in SARS, and increased mortality of influenza (Arabi et al., 2018; Huang et al., 2020; Lee et al., 2004a, b; Li et al., 2004; Ni et al., 2019; World Health Organization, 2020; Xiao et al., 2004). In addition, lymphocytes, such as virus-specific CD4 and CD8 T cells, play a critical role in clearing the virus to provide partial protection and reduce symptoms, and the acute phase of SARS in humans is associated with a severe reduction in the number of T cells in the blood (Channappanavar et al., 2014). As most of the infiltrated lymphocytes in lung tissues were CD4-positive T cells, both helper T cells and suppressor T cells in peripheral blood were below normal levels, and a lower level of helper T cells was found in the severe group (Qin et al., 2020). Morbidity and mortality of SARS-CoV and MERS-CoV may be higher in the immunocompromised elderly than in younger adults (Peiris et al., 2003; Perlman and Dandekar, 2005; Perlman and Netland, 2009; Talbot, 2017). As humans age, there are progressive declines in the percentage of total lymphocytes, the absolute numbers of T and B cells, and the ratio of CD4 to CD8 T cells (Amadori et al., 1995; Valiathan et al., 2016). Notably, a high proportion of critical COVID-19 patients in our study (73.3 %) were older than 60 years, and high-dose corticosteroid therapy indeed induced lower levels of peripheral lymphocytes. The decreased lymphocytes in the fibrosis stage may be one reason for the delayed clearance of SARS-CoV2 virus RNA in high-dose corticosteroid therapy, followed by lower OI, higher incidence of tracheal intubation, a higher rate of shock complications and higher levels of CRP and LDH, which indicated the condition aggravation and significantly shorter survival time.

5. Conclusion

The progressive fibrosis stage of critical COVID-19 patients may be more dangerous than the alveolitis stage. According to the progression of the disease, low-to-moderate dose corticosteroids may be beneficial for critical COVID-19 patients in the fibrosis phase, while they should be used carefully in the alveolitis stage. High-dose corticosteroid therapy in the fibrosis phase aggravates the severity of critical COVID-19, resulting in increased mortality in the fibrosis phase.

Author contributions

Chen GP, Chen QQ and Lv XT designed the research study and contributed the concept and definition of intellectual content; Fang YY and Yang XQ contributed literature search, clinical studies, experimental studies, data acquisition, data analysis and statistical analysis; Lv XT and Chen QQ contributed manuscript preparation, manuscript editing and manuscript review. All authors have read and approved the final manuscript. Lv XT, Chen GP, Chen QQ and Yang XQ contributed equally to this work and take responsibility for the integrity of the work as a whole from inception to published article.

Ethics

The protocols for the study and informed consent were approved by the ethics committee of First Affiliated Hospital of Fujian Medical University (Approval No. MRCTA, ECFAH of FMU [2020]153).

Declaration of Competing Interest

We declare that we have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

Thanks to all medical teams that went to Hubei province to battle the COVID-19 epidemic. This work was supported by the National Natural Science Foundation of China (no. 81800070 to Xiaoting Lv), the Nature Science Research Project of Fujian Province (no. 2021J01222 to Xiaoting Lv), and the Leading Project Foundation of Science and Technology of Fujian Province (no. 2021Y0096 to Gongping Chen).

References

Amadori, A., Zamarchi, R., De Silvestro, G., Forza, G., Cavatton, G., Danieli, G.A., Clementi, M., Chieco-Bianchi, L., 1995. Genetic control of the CD4/CD8 T-cell ratio in humans. Nat. Med. 1, 1279–1283. https://doi.org/10.1038/nm1295-1279.

Arabi, Y.M., Mandourah, Y., Al-Hameed, F., Sindi, A.A., Almekhlafi, G.A., Hussein, M.A., Jose, J., Pinto, R., Al-Omari, A., Kharaba, A., Almotairi, A., Al Khatib, K., Alraddadi, B., Shalhoub, S., Abdulmomen, A., Qushmaq, I., Mady, A., Solaiman, O., Al-Aithan, A.M., Al-Raddadi, R., Ragab, A., Balkhy, H.H., Al Harthy, A., Deeb, A.M., Al Mutairi, H., Al-Dawood, A., Merson, L., Hayden, F.G., Fowler, R.A., 2018. Corticosteroid therapy for critically ill patients with middle east respiratory syndrome. Am. J. Respir. Crit. Care Med. 197, 757–767. https://doi.org/10.1164/rccm.201706-1172OC.

Atsumi, K., Saito, Y., Kuse, N., Kobayashi, K., Tanaka, T., Kashiwada, T., Inomata, M., Kokuho, N., Hayashi, H., Kamio, K., Fujita, K., Abe, S., Azuma, A., Kubota, K., Gemma, A., 2018. Prognostic factors in the acute exacerbation of idiopathic pulmonary fibrosis: a retrospective single-center study. Intern. Med. 57, 655–661. https://doi.org/10.2169/internalmedicine.9331-17.

Bradley, B.T., Bryan, A., 2019. Emerging respiratory infections: the infectious disease pathology of SARS, MERS, pandemic influenza, and Legionella. Semin. Diagn. Pathol. 36, 152–159. https://doi.org/10.1053/j.semdp.2019.04.006.

Channappanavar, R., Zhao, J., Perlman, S., 2014. T cell-mediated immune response to respiratory coronaviruses. Immunol. Res. 59, 118–128. https://doi.org/10.1007/s12026-014-8534-z.

Ding, Y., Wang, H., Shen, H., Li, Z., Geng, J., Han, H., Cai, J., Li, X., Kang, W., Weng, D., Lu, Y., Wu, D., He, L., Yao, K., 2003. The clinical pathology of severe acute

respiratory syndrome (SARS): a report from China. J. Pathol. 200, 282–289. https://doi.org/10.1002/path.1440.
Fang, Y., Zhang, H., 2020. Sensitivity of chest CT for COVID-19: comparison to RT-PCR. Radiology 200432. https://doi.org/10.1148/radiol.2020200432.
Heymann, D.L., Shindo, N., 2020. COVID-19: what is next for public health? Lancet 395, 542–545. https://doi.org/10.1016/s0140-6736(20)30374-3.
Huang, P., Liu, T., 2020. Use of chest CT in combination with negative RT-PCR assay for the 2019 novel coronavirus but high clinical suspicion. Radiology 295, 22–23. https://doi.org/10.1148/radiol.2020200330.
Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., Gao, H., Guo, L., Xie, J., Wang, G., Jiang, R., Gao, Z., Jin, Q., Wang, J., Cao, B., 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395, 497–506. https://doi.org/10.1016/s0140-6736(20)30183-5.
Lamontagne, F., Briel, M., Guyatt, G.H., Cook, D.J., Bhatnagar, N., Meade, M., 2010. Corticosteroid therapy for acute lung injury, acute respiratory distress syndrome, and severe pneumonia: a meta-analysis of randomized controlled trials. J. Crit. Care 25, 420–435. https://doi.org/10.1016/j.jcrc.2009.08.009.
Lee, D.T., Wing, Y.K., Leung, H.C., Sung, J.J., Ng, Y.K., Yiu, G.C., Chen, R.Y., Chiu, H.F., 2004a. Factors associated with psychosis among patients with severe acute respiratory syndrome: a case-control study. Clin. Infect. Dis. 39, 1247–1249. https://doi.org/10.1086/424016.
Lee, N., Allen Chan, K.C., Hui, D.S., Ng, E.K., Wu, A., Chiu, R.W., Wong, V.W., Chan, P.K., Wong, K.T., Wong, E., Cockram, C.S., Tam, J.S., Sung, J.J., Lo, Y.M., 2004b. Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. J. Clin. Virol. 31, 304–309. https://doi.org/10.1016/j.jcv.2004.07.006.
Li, Y.M., Wang, S.X., Gao, H.S., Wang, J.G., Wei, C.S., Chen, L.M., Hui, W.L., Yuan, S.L., Jiao, Z.S., Yang, Z., Su, B., 2004. [Factors of avascular necrosis of femoral head and osteoporosis in SARS patients' convalescence]. Zhonghua Yi Xue Za Zhi 84, 1348–1353.
Li, C., Yang, P., Zhang, Y., Sun, Y., Wang, W., Zou, Z., Xing, L., Chen, Z., Tang, C., Guo, F., Deng, J., Zhao, Y., Yan, Y., Tang, J., Wang, X., Jiang, C., 2012. Corticosteroid treatment ameliorates acute lung injury induced by 2009 swine origin influenza A (H1N1) virus in mice. PLoS One 7, e44110. https://doi.org/10.1371/journal.pone.0044110.
Louie, J.K., Acosta, M., Winter, K., Jean, C., Gavali, S., Schechter, R., Vugia, D., Harriman, K., Matyas, B., Glaser, C.A., Samuel, M.C., Rosenberg, J., Talarico, J., Hatch, D., 2009. Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. JAMA 302, 1896–1902. https://doi.org/10.1001/jama.2009.1583.
Mauad, T., Hajjar, L.A., Callegari, G.D., da Silva, L.F., Schout, D., Galas, F.R., Alves, V.A., Malheiros, D.M., Auler Jr., J.O., Ferreira, A.F., Borsato, M.R., Bezerra, S.M., Gutierrez, P.S., Caldini, E.T., Pasqualucci, C.A., Dolhnikoff, M., Saldiva, P.H., 2010. Lung pathology in fatal novel human influenza A (H1N1) infection. Am. J. Respir. Crit. Care Med. 181, 72–79. https://doi.org/10.1164/rccm.200909-1420OC.
Min, C.K., Cheon, S., Ha, N.Y., Sohn, K.M., Kim, Y., Aigerim, A., Shin, H.M., Choi, J.Y., Inn, K.S., Kim, J.H., Moon, J.Y., Choi, M.S., Cho, N.H., Kim, Y.S., 2016. Comparative and kinetic analysis of viral shedding and immunological responses in MERS patients representing a broad spectrum of disease severity. Sci. Rep. 6, 25359. https://doi.org/10.1038/srep25359.
National Health Commission of the People's Republic of China, 2020. New Coronavirus Infected Pneumonia Diagnosis and Treatment Plan (7th Trial Version)(National Health Office Medical Letter [2020] No.184) [Internet] [Accessed on 28 Mar, 2020] Available from: http://www.nhc.gov.cn/xcs/zhengcwj/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml.
Ni, Y.N., Chen, G., Sun, J., Liang, B.M., Liang, Z.A., 2019. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. Crit Care 23, 99. https://doi.org/10.1186/s13054-019-2395-8.
Ottolini, M., Blanco, J., Porter, D., Peterson, L., Curtis, S., Prince, G., 2003. Combination anti-inflammatory and antiviral therapy of influenza in a cotton rat model. Pediatr. Pulmonol. 36, 290–294. https://doi.org/10.1002/ppul.10320.
Pan, F., Ye, T., 2020. Time course of lung changes at Chest CT during recovery from coronavirus disease 2019 (COVID-19). Radiology 295, 715–721. https://doi.org/10.1148/radiol.2020200370.
Peiris, J.S., Yuen, K.Y., Osterhaus, A.D., Stöhr, K., 2003. The severe acute respiratory syndrome. N. Engl. J. Med. 349, 2431–2441. https://doi.org/10.1056/NEJMra032498.
Perlman, S., Dandekar, A.A., 2005. Immunopathogenesis of coronavirus infections: implications for SARS. Nat. Rev. Immunol. 5, 917–927. https://doi.org/10.1038/nri1732.
Perlman, S., Netland, J., 2009. Coronaviruses post-SARS: update on replication and pathogenesis. Nat. Rev. Microbiol. 7, 439–450. https://doi.org/10.1038/nrmicro2147.
Qin, C., Zhou, L., Hu, Z., Zhang, S., Yang, S., Tao, Y., Xie, C., Ma, K., Shang, K., Wang, W., Tian, D.S., 2020. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin. Infect. Dis. https://doi.org/10.1093/cid/ciaa248.
Russell, C.D., Millar, J.E., Baillie, J.K., 2020. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 395, 473–475. https://doi.org/10.1016/s0140-6736(20)30317-2.
Shieh, W.J., Blau, D.M., Denison, A.M., Deleon-Carnes, M., Adem, P., Bhatnagar, J., Sumner, J., Liu, L., Patel, M., Batten, B., Greer, P., Jones, T., Smith, C., Bartlett, J., Montague, J., White, E., Rollin, D., Gao, R., Seales, C., Jost, H., Metcalfe, M., Goldsmith, C.S., Humphrey, C., Schmitz, A., Drew, C., Paddock, C., Uyeki, T.M., Zaki, S.R., 2010. 2009 pandemic influenza A (H1N1): pathology and pathogenesis of 100 fatal cases in the United States. Am. J. Pathol. 177, 166–175. https://doi.org/10.2353/ajpath.2010.100115.
Stockman, L.J., Bellamy, R., Garner, P., 2006. SARS: systematic review of treatment effects. PLoS Med. 3, e343. https://doi.org/10.1371/journal.pmed.0030343.
Tagami, T., Matsui, H., Horiguchi, H., Fushimi, K., Yasunaga, H., 2015. Low-dose corticosteroid use and mortality in severe community-acquired pneumonia patients. Eur. Respir. J. 45, 463–472. https://doi.org/10.1183/09031936.00081514.
Talbot, H.K., 2017. Influenza in older adults. Infect. Dis. Clin. North Am. 31, 757–766. https://doi.org/10.1016/j.idc.2017.07.005.
Tang, B.M., Craig, J.C., Eslick, G.D., Seppelt, I., McLean, A.S., 2009. Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis. Crit. Care Med. 37, 1594–1603. https://doi.org/10.1097/CCM.0b013e31819fb507.
Valiathan, R., Ashman, M., Asthana, D., 2016. Effects of ageing on the immune system: infants to elderly. Scand. J. Immunol. 83, 255–266. https://doi.org/10.1111/sji.12413.
Wong, C.K., Lam, C.W., Wu, A.K., Ip, W.K., Lee, N.L., Chan, I.H., Lit, L.C., Hui, D.S., Chan, M.H., Chung, S.S., Sung, J.J., 2004. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin. Exp. Immunol. 136, 95–103. https://doi.org/10.1111/j.1365-2249.2004.02415.x.
World Health Organization, 2020. Clinical Management of Severe Acute Respiratory Infection When Novel Coronavirus (nCoV) Infection Is Suspected [Internet] [Accessed on 28 Jan, 2020] Available from: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novelcoronavirus-(ncov)-infection-is-suspected.
Wu, C., Chen, X., Cai, Y., Xia, J., Zhou, X., Xu, S., Huang, H., Zhang, L., Zhou, X., Du, C., Zhang, Y., Song, J., Wang, S., Chao, Y., Yang, Z., Xu, J., Zhou, X., Chen, D., Xiong, W., Xu, L., Zhou, F., Jiang, J., Bai, C., Zheng, J., Song, Y., 2020a. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern. Med. https://doi.org/10.1001/jamainternmed.2020.0994.
Wu, J.T., Leung, K., Leung, G.M., 2020b. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. Lancet 395, 689–697. https://doi.org/10.1016/s0140-6736(20)30260-9.
Xiao, J.Z., Ma, L., Gao, J., Yang, Z.J., Xing, X.Y., Zhao, H.C., Jiao, J.S., Li, G.W., 2004. [Glucocorticoid-induced diabetes in severe acute respiratory syndrome: the impact of high dosage and duration of methylprednisolone therapy]. Zhonghua Nei Ke Za Zhi 43, 179–182.
Xie, X., Zhong, Z., 2020. Chest CT for typical 2019-nCoV pneumonia: relationship to negative RT-PCR testing. Radiology 200343. https://doi.org/10.1148/radiol.2020200343.
Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., Liu, S., Zhao, P., Liu, H., Zhu, L., Tai, Y., Bai, C., Gao, T., Song, J., Xia, P., Dong, J., Zhao, J., Wang, F.S., 2020. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir. Med. 8, 420–422. https://doi.org/10.1016/s2213-2600(20)30076-x.
Yang, S.Q., Qu, J.X., Wang, C., Yu, X.M., Liu, Y.M., Cao, B., 2014. Influenza pneumonia among adolescents and adults: a concurrent comparison between influenza A (H1N1) pdm09 and A (H3N2) in the post-pandemic period. Clin. Respir. J. 8, 185–191. https://doi.org/10.1111/crj.12056.
Yao, X.H., Li, T.Y., He, Z.C., Ping, Y.F., Liu, H.W., Yu, S.C., Mou, H.M., Wang, L.H., Zhang, H.R., Fu, W.J., Luo, T., Liu, F., Guo, Q.N., Chen, C., Xiao, H.L., Guo, H.T., Lin, S., Xiang, D.F., Shi, Y., Pan, G.Q., Li, Q.R., Huang, X., Cui, Y., Liu, X.Z., Tang, W., Pan, P.F., Huang, X.Q., Ding, Y.Q., Bian, X.W., 2020. [A pathological report of three COVID-19 cases by minimal invasive autopsies]. Zhonghua Bing Li Xue Za Zhi 49, 411–417. https://doi.org/10.3760/cma.j.cn112151-20200312-00193.
Ye, Z., Zhang, Y., Wang, Y., Huang, Z., Song, B., 2020. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. Eur. Radiol. 1–9. https://doi.org/10.1007/s00330-020-06801-0.
Yu, X., Zhang, X., Zhao, B., Wang, J., Zhu, Z., Teng, Z., Shao, J., Shen, J., Gao, Y., Yuan, Z., Wu, F., 2011. Intensive cytokine induction in pandemic H1N1 influenza virus infection accompanied by robust production of IL-10 and IL-6. PLoS One 6, e28680. https://doi.org/10.1371/journal.pone.0028680.
Zhao, Y., Zhang, Y.H., Denney, L., Young, D., Powell, T.J., Peng, Y.C., Li, N., Yan, H.P., Wang, D.Y., Shu, Y.L., Kendrick, Y., McMichael, A.J., Ho, L.P., Dong, T., 2012. High levels of virus-specific CD4+ T cells predict severe pandemic influenza A virus infection. Am. J. Respir. Crit. Care Med. 186, 1292–1297. https://doi.org/10.1164/rccm.201207-1245OC.
Zhou, M., Zhang, X., Qu, J., 2020a. Coronavirus disease 2019 (COVID-19): a clinical update. Front. Med. 14, 126–135. https://doi.org/10.1007/s11684-020-0767-8.
Zhou, W., Liu, Y., Tian, D., Wang, C., Wang, S., Cheng, J., Hu, M., Fang, M., Gao, Y., 2020b. Potential benefits of precise corticosteroids therapy for severe 2019-nCoV pneumonia. Signal Transduct. Target. Ther. 5, 18. https://doi.org/10.1038/s41392-020-0127-9.