Benign Clinical and Epidemiological Outcomes-Associated Factors of COVID-19 from a Solved Epidemic with a Low Case Fatality Rate

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Research Article

Keywords: Coronavirus disease-19 (COVID-19), clinical outcome, epidemiological outcome, clinical characteristics, antiviral treatment

Posted Date: November 12th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-104036/v1>

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Abstract

Background: Since December 2019, COVID-19 has been confirmed in more than 18.8 million patients and leads to 0.70 million deaths worldwide. The mortality and disease severity predictors of COVID-19 have been investigated in many studies. However, they are based on early or partial datasets from high epidemic areas. Here, we retrospectively investigate benign clinical and epidemiological outcomes-associated factors from a solved epidemic in a low epidemic area.

Methods: All 98 laboratory-confirmed COVID-19 patients in a local epidemic (Zhuhai, China) from January 17, 2020 to March 10, 2020 were enrolled. Data were updated until all patients having final outcomes.

Results: Patients were all hospitalized. The case fatality rate was 1.0%. There were no local secondary infection cases. The median age was 46.3 years. Underlying diseases were found in 33.7% patients. The severe/critical rate was 19.4%. The mean period from disease onset to admission was 4.4 days. Compared with serious/critical cases, mild/common cases on admission were much younger, lacked comorbidities and normal in functions of vital organs and indicators of secondary bacterial infections. The lymphocyte counts in serious/critical cases began to be significantly lower 3 days before their identification dates. The absence of lymphopenia before the eighth day from disease onset can exclude the possibility of 78.5% to be serious/critical ill. Most patients (88.8%) received antiviral treatments. Early antiviral treatment significantly shortened the viral RNA-negative conversion time. The delayed antiviral treatment was associated with critical patients.

Conclusions: Younger age, lack of aging-related diseases and early hospitalization of all patients to conduct antiviral treatment and prevention of secondary epidemic were the important benign clinical and epidemiological outcomes-associated factors of COVID-19. In combating COVID-19, the active intervention strategies are crucial in low epidemic areas and the continuous monitoring of lymphocytes may be useful to sort patients reasonably in high epidemic areas.

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused an ongoing pandemic of coronavirus disease-2019 (COVID-19) since December 2019. As of November 4, 2020, COVID-19 has been worldwide confirmed in more than 48.0 million individuals with case fatality rate of 3.0% [1]. SARS-CoV-2 has strong affinity to human respiratory receptors [2], which is in concordance with its fast respiratory transmission from person to person [3]. Concordantly, the severe patients of COVID-19 usually require costly intensive care and some of them evolve into adult respiratory distress syndrome with high mortality ignoring mechanical ventilation or extracorporeal membrane oxygenation [4].

As the increasing number of confirmed cases, the clinical features of COVID-19 have well documented in the literature [5–7], which help us understand the epidemiological, clinical, laboratory and radiological characteristics of this disease. Some studies have paid attention to the mortality predictors [8–12]. The

age of more than 65 years, pre-existing underlying diseases, the presence of secondary bacterial infections and the rises in blood inflammatory indicators are predictors of fatal outcomes. In addition, some studies have shown that patients with severe infection are more likely to have diabetes, renal disease, and chronic pulmonary disease and have higher white blood cell counts, lower lymphocyte counts, and increased C-reactive protein [13–15]. The intensive care unit admission is predicted by raises in leukocyte count, alanine aminotransferase, aspartate transaminase, lactate dehydrogenase and procalcitonin [16]. However, these predictors are mainly summarized from high epidemic areas, usually from partial epidemic datasets in the early stage. The proposed models are indeed thought to be poorly reported, at high risk of bias, and their reported performance is probably optimistic [8].

The case fatality rate of COVID-19 significantly varies as the local intensity of epidemic. The case fatality rate is 6.6% in a high epidemic province, but only 0.8% in the rest provinces in China (updated on November 4, 2020), suggesting that there may be significant differences in mortality and disease severity predictors between high and low epidemic areas. On the other hand, a solved or complete epidemic, especially with a low case fatality rate and few secondary infection cases, may provide novel clues to reduce the deaths and secondary epidemic in high or new epidemic areas. For these reasons, we further investigated the benign clinical and epidemiological outcomes-associated factors of COVID-19 from a solved epidemic of 98 patients with one death and no local secondary infection cases.

Methods

Study design and patients

This single-center retrospective observational study was conducted in the Fifth Affiliated Hospital of Sun Yat-sen University, a designated hospital for COVID-19 in Zhuhai, Guangdong province, China. All 98 laboratory-confirmed COVID-19 patients in the local epidemic were hospitalized from 17 January 2020 to 10 March 2020.

Data collection

The epidemiological, demographical and clinical data, laboratory examination results, imaging reports and treatment regimens of all patients were extracted from the electronic medical records. The data collected were examined by two doctors, and the third researcher was responsible for determining whether there was a difference between the two doctors' explanations. The main symptoms, laboratory results and chest computed tomography (CT) findings on admission and the final clinical classification were conducted based on entire disease course unless mentioned elsewhere.

Laboratory confirmation

Laboratory confirmation of SARS-CoV-2 infection was performed at the Chinese Center for Disease Prevention and Control. SARS-CoV2 RNA in the nasal and pharyngeal swab specimens was detected using real-time RT-PCR assays [6]. All patients were confirmed before admission.

Definitions

According to guideline of diagnosis and treatment of COVID-19 issued by National Health Commission of China [17], those patients were clinically classified into 4 types. Mild type: mild clinical symptoms, no evidence of pneumonia on imaging. Common type: fever, respiratory tract and other symptoms. The imaging examination shows pneumonia. Serious type: Meet any of the following conditions: 1) Shortness of breath, respiratory rate > 30 times / min; 2) In resting state, oxygen saturation $\leq 93\%$; 3. Partial pressure of oxygen/fraction of inspiration $O_2 \leq 300$ mmHg. Critical type: meet one of the following conditions: 1) Respiratory failure, requiring mechanical ventilation; 2) Shock; 3) Combined with other organ failure, need intensive care unit (ICU) monitoring treatment.

Treatments

Most adult patients received antiviral treatment with lopinavir and ritonavir (400 mg twice daily and 100 mg twice daily for 14 days, respectively), arbidol (200 mg three times daily for 7-14 days) and/or chloroquine (500 mg once or twice daily for 7 days). Severe patients or patients with more than 50% progression in pneumonia within 48 hours were treated with corticosteroid (40-80 mg/day) and gamma globulin (15-20 g/day) for 3-5 days. Quinolones, macrolides or antifungal drugs were administered if there were co-infections with bacteria or fungus.

Statistical analysis

When the data were normally distributed, the continuous variables were expressed as mean $\pm$ standard deviation (SD) and compared using student's t test and Pearson correlation analysis. When the data were non-normally distributed, the variables were expressed as median (interquartile range, IQR) and compared using Mann-Whitney U test and Spearman correlation analysis. The classification variables were expressed as number (%) and compared by χ^2 test or Fisher's exact test. Histogram was used to describe the proportion of patients in different groups whose indicators were lower than normal. Line charts and scatter charts were used to describe the mean of various indicators in different groups. $P < 0.05$ was considered statistically significant. All data were analyzed using SPSS (version 23.0) software.

Results

Clinical and epidemiological outcomes

All 98 laboratory-confirmed COVID-19 patients, either Hebei citizens or Hebei visitors, in this local epidemic were hospitalized and included in our analysis. Data were continuously updated until all patients having final clinical outcomes (recovery or death). The epidemic had a benign epidemiological outcome without local secondary infection cases in health workers and local citizens. These patients, including 5 children (under 14 years old) and 15 elderly persons (over 65 years old), had benign clinical outcomes with a case fatality rate of 1.0% (1/98) (Table S1). Out of 98 cases, 13 (13.3%) and 6 (6.1%) belonged to serious and critical types, respectively. The serious/critical rate was 19.4% (19/98). All 6

(6.1%) critical patients were admitted to the intensive care unit and 3 (3.1%) of them underwent mechanical ventilation. Only a 78-years-old man with hypertension, coronary heart disease and diabetes died of adult respiratory distress syndrome. The rest of patients were successfully cured and discharged from hospital. The mean period from disease onset to admission was 4.4 days. The average length of hospitalization was 21.1 days. The mean period of the first viral RNA negative conversion was 8.2 days. The rate of re-positive viral RNA was 18.4%.

Benign outcomes-associated factors in demographic and clinical characteristics

The demographic and epidemiological characteristics of 98 COVID-19 patients were shown in Table S1. Mean age was 46.3 years and 45 (45.9%) were male. When patients were stratified by the disease severity, the mean age of mild/common cases (43.2 years) was significantly younger than that of serious/critical cases (59.3 years) ($P < 0.001$) (Table S1), suggesting that the younger age was a benign clinical outcome-associated factor. To confirm it, the mean age in 4 different clinical types and the occurrence of serious/critical cases in different age groups were compared (Fig. 1). The less severity the cases, the younger the mean of age was (Fig. 1A). The younger the group, the lower the proportion of patients with severe illnesses was (Fig. 1B). The freeness of comorbidities seemed to be another benign clinical outcome-associated factor (Table S1). It was obvious, however, that the disease severity was associated with aging-related diseases, such as hypertension and diabetes. Only 3 cases had a history of respiratory disease, 2 of them had pulmonary tuberculosis. Fever, cough and sore throat were the three most common symptoms, accounting for 57.1%, 39.8% and 9.2% respectively. Nonetheless, the common symptoms along as the gender, smoking history and exposure manners did not show any associations with the disease severity (Table S1).

Benign outcomes-associated factors in Laboratory findings

Laboratory and chest CT scan findings on admission were shown in Table S2. Blood routine examination showed that the decreases in eosinophil, lymphocyte and platelet counts were significantly associated with the serious/critical patients. The lymphopenia ($< 1.0 \times 10^9/L$) occurred more frequently in serious/critical cases (Fig. 2A). Furthermore, the counts of lymphocyte (Fig. 2B), cluster of differentiation (CD) 3+ (Fig. 2C), CD3 + CD4+ (Fig. 2D) and CD3 + CD8+ (Fig. 2E) T lymphocytes and eosinophil (Fig. 2F) significantly decreased in serious/critical patients. Moreover, when compared the data before the identification date (an average of 7.8 days from disease onset) in serious/critical patients and the reference date (the eighth day) in mild/common cases, we found that the lymphocyte counts in serious/critical cases began to be significantly lower 3 days before their identification dates (Fig. 3). As for mild/common patients, the predictive sensitivity, predictive specificity, positive predictive value and negative predictive value of the absence of lymphopenia before the eighth day from disease onset were 78.5% (62/79), 89.5% (17/19), 96.9% (62/64) and 50.0% (17/34), respectively. Simultaneously, bacterial infection indicators, C-reactive protein and procalcitonin, were elevated in a portion of serious/critical patients. Moreover, the decreases in serum albumin and increases in serum γ -globulin, total bilirubin, lactate dehydrogenase and D-dimer were significantly associated with the disease severity (Table S2), suggesting that admission of all patients before the occurrences of obvious dyspnea, substantial

changes of vital organs and secondary bacterial infections were the major benign outcome-associated factors. To our surprise, lung-related structure and function indicators, partial pressure of oxygen and chest CT scan except for partial pressure of carbon dioxide, did not change more obviously in serious/critical cases on admission.

Benign outcomes-associated factors in treatments

The general data about treatments of antivirals, antibiotics and corticosteroids were shown in Table S1. Chloroquine, arbidol and lopinavir/ritonavir were the major antivirals used in this local epidemic. Some patients used two or three antivirals simultaneously or sequentially. Among the different clinical types, the rates of antiviral treatment were similar (Fig. 4A), but the average delayed time of antiviral treatment from disease onset in critical cases was significantly longer than that in serious cases (Fig. 4B), which was in concordance with the longer time for viral RNA-negative conversion of critical patients (Fig. 4C). The influences of antiviral treatment on clinical outcome indicators were shown in Table 1. The antiviral treatment within 3 days from disease onset significantly shortened the time of viral RNA-negative conversion. Although it was not statistically significant, the rate of re-positive viral RNA was relatively lower in those patients who received antivirals. To our surprise, the hospitalization time was significantly longer in antivirals-treated patients, probably because there was a tendency to give antivirals to the relatively severe patients in each clinical type. Similar tendencies explained that antibiotics and corticosteroids elongated the time of viral RNA-negative conversion or were associated with a higher serious/critical rate. Thus, antiviral treatment was ascertained to be an important benign clinical outcome-associated factor. Simultaneously, the treatments of antibiotics and corticosteroids might be also contributable to the benign clinical outcome of serious/critical cases due to the low case fatality rate (1.0%) in spite of the higher serious/critical rate (19.4%).

Table 1
Influences of treatments on the clinical outcomes

	Serous/critical rate (%)	RNA (-) conversion (days)	RNA re-(+) rate (%)	Hospitalization (days)
Antivirals				
+ (87)	17(19.5%)	8.41 ± 0.50	15(17.2%)	21.6 ± 0.87*
- (11)	2(18.2%)	6.55 ± 0.95	3(27.3%)	17.3 ± 2.16
≤ 3 days (32)	4(12.5%)	7.06 ± 0.81*	5(15.6%)	21.3 ± 1.39
> 3 days (35)	13(23.6%)	9.20 ± 0.62	10(18.2%)	21.7 ± 1.11
Antibiotics				
+ (71)	18(25.4%)*	8.69 ± 0.56*	10(14.1%)	21.6 ± 0.98
- (27)	1(3.70%)	6.93 ± 0.75	8(29.6%)	19.8 ± 1.43
≤ 3 days (30)	6(20.0%)	8.10 ± 0.71	6(20.0%)	22.4 ± 1.49
> 3 days (41)	12(29.3%)	9.12 ± 0.83	4(9.80%)	21.0 ± 1.31
Corticosteroids				
+ (15)	10(66.7%)**	9.67 ± 1.84	2(13.3%)	20.5 ± 1.64
- (83)	9(10.8%)	7.94 ± 0.43	16(19.7%)	21.2 ± 0.92
Data are shown in n (%) or mean ± standard deviation; Severe case, serious/critical types of patients; * $P < 0.05$, ** $P < 0.01$, compared with the datum in the next line.				

Discussion

COVID-19 has evolved into a pandemic worldwide. It led to around 0.56 million deaths with case fatality rate of 4.4% [1]. Unfortunately, there is a lack of standardized and convincing general solutions to stop the pandemic or for clinicians to reduce the deaths in clinical practice. It may be helpful to find some effective solutions by careful retrospection of solved epidemics with a low case fatality rate and no local secondary infection cases. Compared with Hebei province, China, Zhuhai is a low epidemic area. The local epidemic began in early January and disappeared with a final case fatality rate of 1.0% and no local secondary infection cases at the end of March, 2020. Therefore, this local epidemic was suitable for the analysis of benign clinical and epidemiological outcomes-associated factors. By retrospection of this resolved epidemic episode, we found that younger age, lack of aging-related diseases, admission of all patients before the occurrences of obvious dyspnea, substantial changes of vital organs, and secondary bacterial infections and early antiviral treatment were the major benign clinical and epidemiological outcomes-associated factors. Among these associated factors, early hospitalization seemed to be the most important one. It provided chances to conduct early antiviral treatment, antibacterial and antifungal

treatments in times, reasonable care and anxiety treatment. Therefore the above findings might be of many implications in combating COVID-19.

The clinical outcomes-associated factors of COVID-19 based on death cases have been broadly studied [8–12]. The fatal outcomes are correlated with the age of more than 65 years, pre-existing underlying diseases, the presence of secondary infections and the rises in blood inflammatory indicators. The disease severity is correlated with underlying diseases such as diabetes, renal disease, and chronic pulmonary disease and abnormality of higher white blood cell counts, lower lymphocyte counts, and increased C-reactive protein [13–15]. Based on a solved epidemic in this study, we also found that the age and underlying comorbidities were the major factors associated with the disease severity. The younger the mean age of the patients, the lower the chance of severe illnesses was. Moreover, the underlying comorbidities were mainly aging-related diseases such as hypertension and diabetes. Thus, age seemed to be the key disease severity-associated factor. The mean age in our dataset was 46.3 years, which is much younger than that reported from China (47–55 years), Italy (65 years), Germany (65 years) and United States of America (65.5 years) [18–21]. By careful retrospection of the reports from a high epidemic area in China, the mean age was 42 years between January 16 and January 29, 2020 and 50–55 years between January 20 and February 14, 2020 [22,23], suggesting that the shift to the elders is the important contributing factor for the high case fatality in high epidemic area in China. Therefore, it is ascertained that younger age is the benign clinical outcome-associated factor of the epidemic episode in Zhuhai, China. The prevention of the elders from COVID-19 and the providing a priority to reasonable medication and care for elder patients may sharply reduce the deaths in high epidemic areas.

The commonest laboratory change is lymphopenia [6,24,25], which is similar to other viral infections [26,27]. Indeed, compared with mild/common ones, the serious/critical patients had significantly lower lymphocyte counts in this study. The lymphocyte counts in serious/critical cases began to be significantly lower 3 days before their identification dates. The absence of lymphopenia before the eighth day from disease onset can exclude the possibility of 78.5% to be serious/critical ill. These findings are helpful to reduce the pressure of the medical system by sorting patients reasonably in high epidemic areas. Except for clinical types-sorting dyspnea, those serious/critical patients on admission are more likely to have abnormalities in other vital organ functions, coagulation and secondary bacterial infections [11,28–30]. These abnormalities indeed frequently occurred in this study. However, compared with reports from high epidemic and high case fatality areas [6,22,31], the overall symptoms (fever and cough) and laboratory changes of our patients were mild on admission, especially in the lung functions. The average time of our dataset from disease onset to admission was 4.4 days, and to diagnosis was 7.8 days, implying that most serious/critical patients were diagnosed after admission. Indeed, there were only 2 patients including the dead case had dyspnea on admission. In contrast, the average time for admission was 7.0 days in high epidemic and high case fatality rate area [31]. Therefore, laboratory data told us that early admission of all patients was the important benign clinical outcome-associated factor in this study. Patients in hospital may obtain benefits from early or in time treatments, reasonable care and anxiety remission.

The treatments of COVID-19 mainly consist of maximal supportive care and antiviral agents. Though antivirals are worldwide expected, there are no approved antiviral agents up to now. However, some drugs including chloroquine, arbidol, remdesivir and lopinavir/ritonavir have shown aspiring effects on reduction of deaths [32–36]. In this study, most patients (88.8%) completed antiviral regimen without obvious side effects, and the early antiviral treatment started within 3 days from disease onset significantly shortened the time of viral RNA-negative conversion, which was in concordance with early antiviral treatment contributing to alleviate the severity and improve the prognosis of patients [33], and no benefit was observed with lopinavir/ritonavir treatment beyond standard care in serious/critical patients [34]. The average delayed time of antiviral treatment in critical cases was significantly longer than that of serious cases, suggesting that early antiviral treatment might play a role in preventing from the serious-to-critical progression, perhaps were correlated with the low case fatality rate (1.0%) in spite of the higher serious/critical rate (19.4%) in our dataset. Regretfully, antibiotics and corticosteroids were not found to be benign clinical outcome-associated factors. However, secondary bacterial infections and inflammatory factor storms play important roles in respiratory failure [32,37]. Some physicians believe that a portion of patients die of fulminant myocarditis [38,39]. Therefore, most serious/critical patients received the treatments of antibiotics and corticosteroids might be contributable to the benign clinical outcomes in this epidemic episode.

Since massive migration is considered to promote the early spread of COVID-19 in China and China's practices with isolation of patients and quarantine of persons with close contacts [41,42], the early admissions of all patients and widespread antiviral therapy might be contributable for the benign epidemiological outcome of this local epidemic episode. Early admissions might be helpful for the prevention of community infection. Early and widespread antiviral therapy might be one of the reasons of no health worker infection since early antiviral therapy shortened the time of viral RNA-negative conversion. Nonetheless, to control this pandemic of COVID-19, there are many uncertainties [42]. Frankly, some of associated factors concluded by rough comparison with published literature need to be confirmed in the future. We here reported them only as new clues for combating COVID-19. In addition, it is uncertain whether our successful experience is effective in high epidemic areas since the major death-contributable factor there is the lack of enough facilities to meet the needs of so many patients. However, the continuous monitoring of lymphocytes may be useful reduce the pressure of the medical system by sorting patients reasonably in high epidemic areas. We also strongly suggest that the conducts of early isolation and general antiviral therapy to mild or young patients who are suite for most current potential antivirals by any means are imperative to reduce the deaths by preventing old or fragile persons from infection in high epidemic areas.

Conclusions

Based on a resolved epidemic, younger age, lack of aging-related diseases and early hospitalization of all patients to realize early antiviral treatment, maximal supportive care and prevention of secondary epidemic were the important benign clinical and epidemiological outcomes-associated factors of COVID-19. These results support that the active intervention strategies in combating COVID-19 are crucial,

especially at early stage of the epidemic or in low epidemic areas. The serious/critical patients of COVID-19 can be at least 3 days in advance predicted by lymphopenia. In contrast, the absence of lymphopenia before the eighth day from disease onset can exclude the possibility of 78.5% to be serious/critical ill. These findings are helpful to reduce the pressure of the medical system by sorting patients reasonably in high epidemic areas.

Abbreviation

SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease-2019; CT, computed tomography; ICU, intensive care unit; SD, standard deviation; IQR, interquartile range; CD, cluster of differentiation.

Declarations

Ethics and consent to participate

This study was approved by the ethics committee of the Fifth Affiliated Hospital of Sun Yat-sen University. The ethics committee also authorized us to waive written informed consent because only clinical data of hospitalized patients with emerging infectious disease were used, and no sample collections and interventions in the diagnosis and treatment were conducted in this respective study.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interest

The authors declare that they have no competing interest.

Funding

This work was supported by COVID-19 special fund 2020 from Science and technology Bureau of Zhuhai, Guangdong Province, China. The funding source did not have a role in collection, analysis and interpretation of data.

Authors' contributions

XMP is the guarantor of the article. XMP, GH and JL brought the concept; PYH, LJO and BJZ collected the data; XMP, GH and LJO made the statistical analysis and wrote the paper; All co-authors approved the

final version of the paper.

Acknowledgements

We thank all the front-line medical staffs in the Fifth Affiliated Hospital, Sun Yat-Sen University for their bravery and efforts in combating COVID-19.

References

1. Johns Hopkins University. COVID-19 dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). 2020. <https://coronavirus.jhu.edu/map.html> (accessed November 4, 2020).
2. Xu X, Chen P, Wang J, Wang J, Feng J, Zhou H, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Sci China Life Sci.* 2020;63:457-60.
3. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person to-person transmission: a study of a family cluster. *Lancet.* 2020;395:514-23.
4. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. *Lancet Respir Med.* 2020;8:475-81.
5. Wu B, Lei ZY, Wu KL, He JR, Cao HJ, Fu J, et al. Compare the epidemiological and clinical features of imported and local COVID-19 cases in Hainan, China. *Infect Dis Poverty.* 2020;9:143.
6. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020;382:1708-20.
7. Zhao XY, Xu XX, Yin HS, Hu QM, Xiong T, Tang YY, et al. Clinical characteristics of patients with 2019 coronavirus disease in a non-Wuhan area of Hubei Province, China: a retrospective study. *BMC Infect Dis.* 2020;20:311.
8. Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E, et al. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. *BMJ.* 2020; 69:m1328.
9. Tian W, Jiang W, Yao J, Nicholson CJ, Li RH, Sigurslid HH, et al. Predictors of mortality in hospitalized COVID-19 patients: A systematic review and meta-analysis. *J Med Virol.* 2020; 10.1002/jmv.26050.
10. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med.* 2020;46:846-8.
11. Zhang SY, Lian JS, Hu JH, Zhang XL, Lu YF, Cai H, et al. Clinical characteristics of different subtypes and risk factors for the severity of illness in patients with COVID-19 in Zhejiang, China. *Infect Dis Poverty.* 2020;9:85.

12. Du RH, Liang LR, Yang CQ, Wang W, Cao TZ, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur Respir J*. 2020;55:2000524.
13. Bhargava A, Fukushima EA, Levine M, Zhao W, Tanveer F, Szpunar SM, Saravolatz L. Predictors for Severe COVID-19 Infection. *Clin Infect Dis*. 2020;ciaa674.
14. Wang D, Li R, Wang J, Jiang Q, Gao C, Yang J, et al. Correlation analysis between disease severity and clinical and biochemical characteristics of 143 cases of COVID-19 in Wuhan, China: a descriptive study. *BMC Infect Dis*. 2020;20:519.
15. Ji D, Zhang D, Xu J, Chen Z, Yang T, Zhao P, et al. Prediction for Progression Risk in Patients with COVID-19 Pneumonia: the CALL Score. *Clin Infect Dis*. 2020;ciaa414.
16. Zhang JJY, Lee KS, Ang LW, Leo YS, Young BE. Risk Factors of Severe Disease and Efficacy of Treatment in Patients Infected with COVID-19: A Systematic Review, Meta-Analysis and Meta-Regression Analysis. *Clin Infect Dis*. 2020;ciaa576.
17. National Health Commission of the People's Republic of China. Diagnosis and treatment of pneumonia caused by novel coronavirus (trial version 7). Available at: <http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml>.
18. Aggarwal S, Garcia-Telles N, Aggarwal G, Lavie C, Lippi G, Henry BM. Clinical features, laboratory characteristics, and outcomes of patients hospitalized with coronavirus disease 2019 (COVID-19): Early report from the United States. *Diagnosis (Berl)*. 2020;7:91-6.
19. Porcheddu R, Serra C, Kelvin D, Kelvin N, Rubino S. Similarity in Case Fatality Rates (CFR) of COVID-19/SARS-COV-2 in Italy and China. *J Infect Dev Ctries*. 2020;14:125-8.
20. Ciceri F, Castagna A, Rovere-Querini P, De Cobelli F, Ruggeri A, Galli L, et al. Early predictors of clinical outcomes of COVID-19 outbreak in Milan, Italy. *Clin Immunol*. 2020;217:108509.
21. Dreher M, Kersten A, Bickenbach J, Balfanz P, Hartmann B, Cornelissen C, et al. The Characteristics of 50 Hospitalized COVID-19 Patients With and Without ARDS. *Dtsch Arztebl Int*. 2020;117:271-8.
22. Li R, Tian J, Yang F, Lv L, Yu J, Sun G, et al. Clinical characteristics of 225 patients with COVID-19 in a tertiary Hospital near Wuhan, China. *J Clin Virol*. 2020;127:104363.
23. Zhang G, Hu C, Luo L, Fang F, Chen Y, Li J, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. *J Clin Virol*. 2020;127:104364.
24. Liu J, Li S, Liu J, Liang B, Wang X, Wang H, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. *EBioMedicine*. 2020;55:102763.
25. Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang YQ, et al. [Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study](#). *Signal Transduct Target Ther*. 2020;5:33.
26. Chan MH, Wong VW, Wong CK, Chan PKS, Chu CM, Hui DSC, et al. Serum LD1 isoenzyme and blood lymphocyte subsets as prognostic indicators for severe acute respiratory syndrome. *J Intern Med*. 2004;255:512-8.

27. He Z, Zhao C, Dong Q, Zhuang H, Song S, Peng G, Dwyer DE. Effects of severe acute respiratory syndrome (SARS) coronavirus infection on peripheral blood lymphocytes and their subsets. *Int J Infect Dis.* 2005;9:323-30.
28. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. *Clin Chim Acta.* 2020;506:145-8.
29. Wang F, Nie J, Wang H, Zhao Q, Xiong Y, Deng L, et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. *J Infect Dis.* 2020;jiaa150.
30. Liu F, Xu A, Zhang Y, Xuan W, Yan T, Pan K, et al. Patients of COVID-19 may benefit from sustained Lopinavir-combined regimen and the increase of Eosinophil may predict the outcome of COVID-19 progression. *Int J Infect Dis.* 2020;95:183-91.
31. Chan KW, Wong VT, Tang SCW. COVID-19: An Update on the Epidemiological, Clinical, Preventive and Therapeutic Evidence and Guidelines of Integrative Chinese-Western Medicine for the Management of 2019 Novel Coronavirus Disease. *Am J Chin Med.* 2020;48:737-62.
32. Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, Richardson P. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis.* 2020;20:400-2.
33. Wu J, Li W, Shi X, Chen Z, Jiang B, Liu J, et al. Early antiviral treatment contributes to alleviate the severity and improve the prognosis of patients with novel coronavirus disease (COVID-19). *J Intern Med.* 2020;288:128-38.
34. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med.* 2020;382:1787-99.
35. Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. *J Crit Care.* 2020;57:279-83.
36. Ferner RE, Aronson JK. Remdesivir in covid-19. *BMJ.* 2020;369:m1610.
37. Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, et al. Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. *Clin Infect Dis.* 2020;ciaa530.
38. Irabien-Ortiz Á, Carreras-Mora J, Sionis A, Pàmies J, Montiel J, Tauron M. Fulminant myocarditis due to COVID-19. *Rev Esp Cardiol (Engl Ed).* 2020;73:503-4.
39. Fadel R, Morrison AR, Vahia A, Smith ZR, Chaudhry Z, Bhargava P, et al. Early Short Course Corticosteroids in Hospitalized Patients with COVID-19. *Clin Infect Dis.* 2020;ciaa601.
40. Song WY, Zang P, Ding ZX, Fang XY, Zhu LG, Zhu Y, et al. Massive migration promotes the early spread of COVID-19 in China: a study based on a scale-free network. *Infect Dis Poverty.* 2020;9:109.
41. Xu TL, Ao MY, Zhou X, Zhu WF, Nie HY, Fang JH, et al. China's practice to prevent and control COVID-19 in the context of large population movement. *Infect Dis Poverty.* 2020;9:115.
42. Lazzerini M, Putoto G. COVID-19 in Italy: momentous decisions and many uncertainties. *Lancet Glob Health.* 2020;8:e641-e642.

Figures

Figure 1

The mean age of different clinical types and the age distribution of COVID-19 patients. (A) Mean age of different clinical types of COVID-19 patients. * $P<0.05$, ** $P<0.01$. (B) Age distribution of COVID-19 patients.

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Figure 2

The lymphocyte and eosinophil counts and lymphocyte subsets in peripheral blood from different types of COVID-19 patients. (A) The occurrence of lymphopenia, (B) Lymphocyte counts, (C) CD3+T lymphocyte counts, (D) CD3+CD4+T lymphocyte counts, (E) CD3+CD8+T lymphocyte counts, and (F) eosinophil counts in different clinical types of COVID-19 patients. *P<0.05, **P<0.01.

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The lymphocyte and eosinophil counts and lymphocyte subsets in peripheral blood from different types of COVID-19 patients. (A) The occurrence of lymphopenia, (B) Lymphocyte counts, (C) CD3⁺T lymphocyte counts, (D) CD3⁺CD4⁺T lymphocyte counts, (E) CD3⁺CD8⁺T lymphocyte counts, and (F) eosinophil counts in different clinical types of COVID-19 patients. *P<0.05, **P<0.01.

Figure 3

Early kinetic differences of lymphocyte counts in mild/common and serious/critical patients of COVID-19. R/I date, reference date in mild/common patients/identification date in serious/critical patients. The reference date was set as the eighth day that was equivalent to the mean time (7.8 days) for those serious/critical patients to be identified from disease onset. Lymphocyte counts of mild/common (blue line) and serious/critical (red line) COVID-19 patients were analyzed at different time points before R/I date, respectively. Error bars, mean $\pm$ SD. * $P < 0.05$, ** $P < 0.01$. The upper dotted lines show the upper normal limit and the lower dotted lines show the lower normal limit of lymphocyte counts.

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A

(%) 87.5 88.9 92.3 83.3

B **C**

Figure 4

Antiviral therapy and time of SARS-Cov-2 RNA-negative conversion. (A) Rates of antiviral treatment, (B) Delayed time of antiviral therapy, and (C) Time of SARS-Cov-2 RNA-negative conversion in different clinical types of COVID-19 patients. *P<0.05.

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Antiviral therapy and time of SARS-Cov-2 RNA-negative conversion. (A) Rates of antiviral treatment, (B) Delayed time of antiviral therapy, and (C) Time of SARS-Cov-2 RNA-negative conversion in different clinical types of COVID-19 patients. *P<0.05.

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