Risk Factors and clinical features of deterioration of COVID-19 Patients in Zhejiang, China: a single-centered, retrospective study

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Research article

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Abstract

Background

A severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection swept through Wuhan and spread across China and overseas from December 2019. To identify predictors associated with disease progression, we evaluate clinical risk factors of exacerbation of SARS-CoV2 infection.

Method

a retrospective analysis was used for PCR-confirmed COVID-19 (coronavirus disease 2019) diagnosed hospitalized cases between January 19, 2019 and February 19, 2020 in Zhejiang, China. We systematically analyzed the clinical characteristics of the patients and predictors of clinical deterioration.

Result

100 patients with COVID-19 were included, with median age of 54 years. Among them, 49 cases (49%) were severe and critical cases. Age (P=0.0001), gender (P=0.0031), BMI (P=0.0339), hypertension (P<0.0001), IL6 (P=0.0001), IL10 (P<0.0001), T lymphocyte count (P=0.0001), B lymphocyte count (P=0.0001), White blood cell count (P=0.0002), d2 dimer (P=0.005), PCT (P=0.0039), CRP (P<0.0001), AST (P=0.0484) and artificial liver therapy (P=0.0148), glucocorticoid therapy (P<0.0001) were associated with the severity of the disease. Age and overweigh were independent risk factors for disease severity.

Conclusion

Deterioration among covid-19 infected patients occurred rapidly after hospital admission, it is necessary to pay attention to these patients. In our cohort, we found that several factors resulted in increased severity. Among these factors, Early detection and reversal of these indicators may reduce the progression of the disease. In addition, early treatment with low doses of glucocorticoids and necessary liver therapy may help reduce mortality in critically ill patients.

Introduction

In December 2019, a new type of coronavirus disease (COVID-19) occurred in Wuhan, China, which was caused by a novel enveloped RNA betacoronavirus 2[1]. Due to its phylogenetic similarity to severe acute respiratory syndrome coronavirus (SARS-CoV), COVID-19 was also named SARS-CoV-2 [2]. The SARS-CoV-2 infection has become a public health emergency of international concern and has spread to cities in China and more than dozens of other countries. Up to 1 pm 19 February 2020, a total 74280 cases were confirmed infection of COVID-19 in China with a total of 2008 deaths occurred[3]. The latest mortality was approximately 2.3%[4]. The disease is highly contagious, which can be transmitted from person to person and lead to clusters transmission in families[5]. However, its origin and pathogenesis are not yet clear. Clinical manifestations of COVID-19 range from asymptomatic to severe acute respiratory syndrome[1]. Due to these unknown factors, there is currently no specific treatment for COVID-

19, the risk of death for severely ill patients is greatly increased. Early warning of severe cases can reduce mortality. In this paper, a retrospective analysis was used for inpatients diagnosed with COVID-19 in Hangzhou of Zhejiang, China over the period from January 19, 2019 to February 19, 2020, to explore relevant factors that may predict the risk factors for disease severity.

Method

Study Design and Participants

We included in the study all patients diagnosed with COVID-19 who were admitted to the first affiliated hospital of Zhejiang university school of medicine between January 19, 2020 and February 19, 2020. This study was approved by the ethics review committee of the first affiliated hospital of Zhejiang university, and conforms to the code of ethics of Helsinki declaration 2013.

The degree of severity of COVID-19 (severe vs nonsevere) at admission were assessed using the latest guidelines of COVID-19 infection ordained by national health commission of China[6]. As mentioned, patients could be classified into four types: mild, ordinary, severe, and critical illness. Mild cases include patients with mild clinical symptoms and no signs of pneumonia on imaging. Ordinary cases are patients with fever, respiratory symptoms, and image manifestation of pneumonia. Severe cases are those who meet one of the following criteria: respiratory rate ≥ 30 bpm; arterial oxygen saturation (SaO2) ≦ 93% at rest; partial pressure of oxygen (PaO2)/oxygen absorption concentration (FiO2) ≦ 300mmmhg. Critical illness cases are patients who satisfy any of the following criteria: respiratory failure and mechanical ventilation required, occurrence of shock, and complicated with other organ failure requires intensive care unit. Mild and ordinary cases were recognized as non-severe cases, while severe and critical illness cases were defined as severe cases in this study.

Data Collection

Collecting data for the following parameters from electronic medical records: demography, underlying medical comorbidities, clinical symptoms and signs, laboratory findings, treatment measures, laboratory findings consisted of IL6, IL10, lymphocyte subsets count, White blood cell count, d2 dimer, PCT, CRP, and AST. Underlying medical comorbidities mainly includes hypertension, diabetes and coronary heart disease. Treatment measures included receipt of antivirus, ambroxole, glucocorticoids, and artificial liver therapy.

Laboratory Confirmation

All included cases were collected of respiratory tract samples such as nasopharyngeal, sputum, swab or throat swab samples daily. Using the COVID-19 nucleic acid detection kits (Shanghai bio-germ Medical Technology Co Ltd), We detected the SARS-CoV-2 viral RNA by polymerase chain reaction analysis in

accordance with the manufacturer's protocol. The diagnosis was confirmed by the criteria recommended by the National Institute for Viral Disease Control and Prevention (China). A virus cycle threshold (CT) value less than 37 was defined as positive, and a CT-value greater than 40 was defined as negative. A CT-value between 37 and 40 required to be confirmed by retesting.

Statistics Analyses

Continuous variables were presented as median (IQR) and compared by Kruskal-Wallis test between non-severe group and severe group. Categorical variables were presented as number (%) and compared by Chi-square (χ^2) test or Fisher's exact test. The Kaplan-Meier (Product-limit) method was used to evaluate the time periods from glucocorticoids and artificial liver therapy to different clinical outcomes between the two groups. All statistical analyses were performed with the SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). The significance level of the hypothesis tests was set at 0.05 (two-sided).

Patient And Public Participation

This was a retrospective cohort study in which patients were not involved in study design, the setting of the study questions, or the direct measurement of the results. And patients were not asked to advise on the interpretation or writing of the results

Result

Patient characteristics on admission

Of 100 hospitalized COVID-19 patients between January 19, 2019 and February 19, 2020, 49 (49%) patients were critically ill. The demographic and clinical characteristics are shown in Table 1. The median age was 54 years. The age (median) of the severe group was significantly higher than that of the non-severe group (61 [51–70] vs 50 [36–58]; P = 0.0001]). 63% of the patients were older than 50 years of age. A total of 63% were male. In the severe group, the proportion of males was higher than that of females, which was statistical difference (77.6% vs 49%; P = 0.0031). Overweight (BMI (Body Mass Index)≥24) was more common in both group of COVID-19 patients. BMI was significantly higher in severely ill group (24.44 (23.28–27.01) vs 24 (21.53–25.51); P = 0.0339). Underlying medical conditions such as hypertension (37%) and diabetes mellitus (11%) were the most common coexisting illness among COVID-19 patients. Moreover, the presence of hypertension was more common among patients with severe disease (57.1% vs 17.6; P < 0.0001). Fever was present in 71% of our patients and no statistical difference between the two groups. In our cases, the vast majority of patients (98%) had obvious pulmonary CT lesions. Especially in severe patients, pulmonary CT had lesions of different degrees on admission, including patchy, nodular ground glass shadows and interstitial abnormalities.

Table 1
Clinical Characteristics of 100 Patients With COV-SARS2 Infection

Characteristic	Total (N = 100)	Non-Severity (n = 51)	Severity (n = 49)	*P* Value*
Demographics, n (%)				
Age, median (IQR), y	54 (42–64)	50 (36–58)	61 (51–70)	0.0001
≥ 55	23(23)	5(9.8)	17(34.7)	0.0027
≥ 50	63(63)	26(51)	37(75.5)	0.0111
Male sex	63 (63)	25 (49)	38 (77.6)	0.0031
BMI	24.27 (22.14–25.97)	24.01 (21.53–25.51)	24.44 (23.28–27.01)	0.0339
Mainly underlying conditions, n (%)				
Hypertension	37 (37)	9 (17.6)	28 (57.1)	< 0.0001
Diabetes mellitus	11 (11)	3 (5.9)	8 (16.3)	0.3574
Cardiac disease	4 (4)	1 (2)	3 (6)	0.118
Fever on admission-°C				
< 37.5 °C	29(29)	19(37.3)	10(20.4)	0.0635
Fever during hospitalization				
Median highest temperature (IQR)	38.25 (37.5–39)	38.2 (37.6–39)	38.3 (37.5–39)	0.9669
Radiologic findings on admission				
chest CT — no./total no. (%)				
Normal	2(2)	2(3.9)	0	0.4952
Initial laboratory findings, median (IQR)				
WBC, 109/L	6.4 (4.1–10.8)	5.15 (3.9–7.6)	9.1 (5.5–13.6)	0.0002
d-dimer	452.5 (240-857.5)	339 (172–836)	604 (408–953)	0.005

Abbreviation: IQR, inter quartile range; BMI, body mass index; WBC, white blood count; ALT, aspartate aminotransferase; AST, alanine aminotransferase; CRP, c-reactive protein; PCT, procalcitonin; IL, interleukin; TNF-a, tumor necrosis factor a; IFN, interferon; Th, T helper cells; Ts, T suppressor cells; Tc, cytotoxic T cells; ALC, absolute lymphocyte count; NK cells, natural killer cells.

*, Chi-square (χ^2) test or Fisher's exact test was used with $P < 0.05$ as significant

Characteristic	Total (N = 100)	Non-Severity (n = 51)	Severity (n = 49)	*P* Value*
ALT	22 (15-40.5)	20 (13–41)	24 (15–40)	0.2801
AST	20.5 (16, 34)	20 (16, 29)	25 (18, 42)	0.0484
CRP	24.665 (7.785–47.6)	10.9 (3.8–27.9)	39.78 (17.3–58.9)	0.0001
PCT	0.06 (0.03–0.1)	0.04 (0.03–0.07)	0.07 (0.04–0.15)	0.0039
IL2	0.95 (0.855–1.82)	0.95 (0.78–1.83)	0.95 (0.95–1.81)	0.5534
IL6	20.425 (8.78–56.04)	12.52 (6.42, 30.46)	38.22 (16.2-81.71)	0.0001
IL10	4.775 (2.91–8.03)	3.45 (2.16, 5.82)	6.93 (4.35–9.63)	< 0.0001
TNF-a	17.98 (10.945–59.085)	23.29 (12.2, 65.49)	12.22 (10.77–36.44)	0.1658
IFN-r	10.06(5.12–33.56)	11.4 (4.92, 39.71)	9.82 (5.19–28.57)	0.6943
Th/Ts cells	1.35 (1-1.97)	1.52 (1.1, 1.83)	1.265 (0.865–2.005)	0.4524
ALC	703 (402–1119)	1119 (620, 1554)	543.5 (367.5-810.5)	0.0002
Total T cells	348 (233–775)	752 (305, 1178)	276.5 (167.5–440)	0.0001
Th/induced T cells	176 (79–431)	376 (176–618)	115 (60.5-214.5)	< 0.0001
Ts/Tc	132 (77–278)	265 (137–443)	89.5 (69-140.5)	< 0.0001
B cells	115 (70–211)	167 (91–213)	93.5 (54.5-163.5)	0.0189
NK cells	105 (64–183)	154 (70–207)	101 (61.5-155.5)	0.1201

Abbreviation: IQR, inter quartile range; BMI, body mass index; WBC, white blood count; ALT, aspartate aminotransferase; AST, alanine aminotransferase; CRP, c-reactive protein; PCT, procalcitonin; IL, interleukin; TNF-a, tumor necrosis factor a; IFN, interferon; Th, T helper cells; Ts, T suppressor cells; Tc, cytotoxic T cells; ALC, absolute lymphocyte count; NK cells, natural killer cells.

*, Chi-square (χ^2) test or Fisher's exact test was used with $P < 0.05$ as significant

Laboratory Findings

Among laboratory indicators at admission, the white blood cell count (P = 0.0002), d-dimer (P = 0. 005), C-reactive protein (P < 0.0001), Procalcitonin (P = 0.0039) and Alanine aminotransferase (P < 0.0484) in non-severe group were significantly lower than those in severe group. In our study, we mainly detected the expression of cytokines and immune cell subsets in patients with COVID-19 infection. We found that the expressions of IL6 in severe patients was significantly higher than that in non-severe group (P = 0.0001), while the expressions of IL10 of severe patients was significantly lower than that of the other group (P < 0.0001). And the total number of T cells (P < 0.0001), B cells (P = 0.0189), absolute number of lymphocytes (P = 0.0002), Th/induced T cells (P < 0.0001) and Ts/Tc cells (P < 0.0001) were significantly lower than those in nonsevere cases.

Treatment And Clinical Outcomes

The treatment and clinical outcomes of COVID-19 patients are shown in Table 2. All 100 patients received antiviral treatment including Lopinavir/ritonavir, Interferon-α, darunavir/cobicistat, Favipiravir and Arbidol. The median time from symptom onset to antiviral regiments use was 7 (4-9.5) days. There was no significant difference between the non-severe and severe group. And the median time from antiviral regiments use to the COVID-19 virus RNA negative for the first time was 9 (5–14) days. Moreover, the time in the non-severe group was significantly shorter than that in the severe group (6 (4–12) vs 9 (7–15); P = 0.0142). The median time from antiviral treatment to duration of virus negative was 10 (6–15) days, and the time of nonsevere group was significantly shorter than that of the severe group (7 (4–13) vs 12 (9–18); P = 0.0006). In addition, our patients received supportive symptomatic treatments, including glucocorticoid, ambroxole, antibiotic, artificial liver therapy.The glucocorticoid was given to 80 (80%) patients and the proportion was significantly higher in the severe group than that in the non-severe group (98% vs 64.7%; P < 0.0001). Meanwhile the maximum dosage of glucocorticoids in the severe group was significantly higher than that in the non-severe group (40[40–80] vs 40 [0–40]; P = 0.0001). Compared with the nonsevere group, the severe group had higher rate of antibiotic treatment (44.9% vs 3.9%; P < .0001). In the retrospective analysis, we found that the clinical outcome of our patients was ideal. No patients died and 86% of the patients recovered and were discharged from the hospital. The discharge rate of the non-severe group was significantly higher than that of the severe group (96.1% vs 75.5%; P = 0.003). The ICU admission rate was 23%, which was higher in the severe group (42.9%vs 3.9%; P < 0.0001).

Table 2

Comparison of treatment responses and clinical outcomes between non-severe and severe group

Variable	Total (N = 100)	Non-Severity (n = 51)	Severity (n = 49)	P Value
Treatments n (%)				
Antivirus treatment	100(100)	51(100)	49(100)	
median (IQR), days				
Time from illness onset to Antivirus start	7 (4-9.5)	6 (3–9)	7 (5–10)	0.2948
Glucocorticoid treatment n (%)	81(81)	33(64.7)	48(98)	< 0.0001
Maximum dosage	80 (20–80)	80 (0–40)	80 (40–80)	0.0001
(equivalent methylprednisolone), median (IQR), mg/d				
Artificial liver support n (%)	9(9)	1(2)	8(16.3)	0.0148
Antibiotic treatment n (%)	24(24)	2(3.9)	22(44.9)	< 0.0001
median (IQR), days				
*AT to first virologic conversion	9 (5–14)	6 (4–12)	9 (7–15)	0.0142
AT to stable virologic conversion	10 (6–15)	7 (4–13)	12 (9–18)	0.0006
AT to radiologic recovery	7 (4, 10)	7 (5, 11)	6.5 (4- 9.5)	0.3162
AT to temperature recovery	5 (2–8)	3 (2–7)	6.5 (2–9)	0.0903
Clinical outcomes, n (%)				
Discharge from hospital	86 (86)	49 (96.1)	37(75.5)	0.0030
#ICU admission	23 (23)	2 (3.9)	21(42.9)	< 0.0001
Death	0	0	0	0

**Abbreviation: ***AT, Antiviral therapy onset; ICU, intensive care unit;

Risk Factors For Covid-19 Severe Illness

Using a multivariate logistic regression analysis, we conducted to identify risk factors associated with exacerbation of COVID-19 infection (Table 3). Age, BMI were recognized as predictors (independent

factors) of severe illness. However gender, hypertension, IL6, T lymphocyte cell, B lymphocyte cell, glucocorticoid treatment and artificial liver support were not recognized as independent factors.

Table 3
Multivariate Logistic Regression Analysis of Risk Factors for disease severity from SARS-COV2 Virus in 100 Hospitalized Patients

Variable	Odds Ratio (95% Confidence Interval)	P Value
Age	1.064 (1.007–1.124)	.**027**
BMI	1.240(1.006–1.528)	.**044**
IL6	1.005(0.995–1.015)	.307
T cells	1.003(0.995–1.011)	.424
B cells	1.005(0.997–1.014)	.196
Artificial liver support	0.985(0.073–13.211)	.0.99

Discussion

In December 2019, a new infectious disease, the COVID-19, swept through Wuhan and quickly spread to all Chinese cities and dozens of countries overseas. The infectious disease is highly infectious, which could occur human-to-human transmission among close contacts and spreads over a wide area[7, 8]. However, its source is not fully clear, and the lack of specific treatment drugs which may cause the patient's symptoms to progress from mild to severe, or even death. Previous studies reported that the fatality rate among hospitalized COVID-19 patients was about 2.3%, which was much lower than those of SARS and Middle East Respiratory Syndrome (MERS) infected patients[4, 9]. For such patients, we need to strengthen vigilance, and give symptomatic support treatment early to reduce the occurrence of severe diseases.

In our retrospective cohort study, we included100 COVID-19 patients from a single clinical center in Hangzhou, Zhejiang province. Our result showed that age and BMI were independent risk factor of severe illness. The median age was 54 years. 63% of the patients were older than 50 years, which was consistent with multiple reported literature[10, 11]. Severe patients were much older than nonsevere ones and may be relate to lower immunity response and higher frequency of underlying conditions, which were not good for a self-limited recovery after virus infection. In addition, we discovered that overweight (BMI≥24) was an important risk factor of severity in COVID-19 patients. Compared with the BMI value of severe patients,nonsevere cases was lower. And there was significant differences between the two groups (P = 0.0339).

Like H7N9, the most common symptoms of COVID-19 patients were fever and cough[5, 12]. However, there were still 26% COVID-19 patients, who were admitted to our hospital with normal temperature. Once these patients were ignored, more people might be infected. It was similar to previous reports[13].

Coexisting disorder such as hypertension and diabetes mellitus were associated with severe illnesses. The proportions of hypertension and diabetes mellitus in severe illnesses were higher than those in non-severe cases. Furthermore, hypertension was significantly different between the two groups ($P < 0.0001$). This was consistent with H7N9 Patients[14]. In addition, we also found that Laboratory parameters and supplementary treatment in single variable analysis identified as risk factors for severe illnesses including the white blood cell count, d-dimer, C-reactive protein, procalcitonin, alanine aminotransferase, IL6, IL10, the total number of T cells, B cell, absolute number of lymphocytes, TH/induced T cells, TS/ Tc cells and the need for antibiotic treatment, glucocorticoid and artificial liver therapy, but these risk factors did not reach our criteria of our multivariate analysis.

Previous studies found that inflammatory factor storm was one of the important factors for severe illness and even death of H7N9, SARS-CoV, MERS- CoV. The mechanism may be related to the overexpression of inflammatory factors and chemokines, which can lead to acute lung injury and ARDS[1, 15, 16]. In our retrospective study, we also found a significant increase in cytokine IL6 in the severe patients. Therefore, for patients with the gradual increase expression of such inflammatory factors, early low-dose glucocorticoid and artificial liver treatment may alleviate the progress of the disease and reduce the risk of death. The effectiveness and necessity of glucocorticoid use has been controversial in novel coronavirus infections. Large doses of glucocorticoids may cause significant side effects such as lymphocytopenia and femoral head necrosis[17]. In our cohort, the rates of treatments with glucocorticoid and artificial liver in the severe group were greater than those in the non-severe group, and there were statistical differences. However, there were no statistically difference in treatment effect between the two groups (the days from treatment initiation to virus clearance) (supplementary Fig. 1–2), which may be related to our small sample size. Further research on larger samples is in progress. Our study found that the number of immune cells in most patients with mild disease is normal. The decrease of T lymphocyte, B lymphocyte and absolute Lymphocyte count are positively correlated with the severity of the disease. Therefore, early detection of related immune indicators may provide us with the ability to predict the severe tendency. Furthmore, we need more samples to confirm whether these factors are the severity of the disease.

There are several limitations to be considered when interpreting the findings. First, our study is a single-center study of COVID19 risk factors for critically ill patients in a hospital. Furthermore, when screening confirmed cases, the vast majority of lower respiratory tract specimens were used, but there were still a few patients who collected pharyngeal swab specimens, and their false negative rate may lead to the lack of included patients. Finally, the number of children under 18 years in our sample was small, so no specific conclusions could be drawn for adolescents.

In Conclusion

Patients with SARS-CoV2-infected are more likely to progress to critical illness. Although its case fatality rate is lower than that of other novel coronavirus infections (SARS and MERS), it has a highly infectious and wide range of spread. In particular, at present, many overseas countries have become the new hard-

hit areas that need attention. In our analysis, we found that basic diseases and multiple laboratory indicators were associated with disease progression. And age and BMI may be independent risk factors for COVID19 intensification. Therefore, it is important to actively evaluate the severity of the newly diagnosed patients' condition to provide individualized diagnosis and treatment and evaluate the prognosis.

Declarations

Contributors.

PY and XY contributed equally to this article. KJX and LJL conceptualized the paper. CD analyzed the data, with input from JFS, KJX, YFC, CD, QN, YTL, XZ, JL.PY and XY wrote the initial draft with all authors providing critical feedback and edits to subsequent revisions. All authors approved the final draft of the manuscript. L-LJ is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Potential conflicts of interest.

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References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, et al: **Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China**. *Lancet* 2020.
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8):727–33.

3. **WHO**. 2019 **nCoV situation report**. **Available from**:**https**://**www**.**who**.**int**/**docs**/**default**-source/coronaviruse/**situation-reports**/**20200204**-**sitrep**-**15**-**ncov**.**pdf**?**sfvrsn**=**88fe8ad6_2**. In.
4. Wu Z, McGoogan JM: **Characteristics of and Important Lessons From the Coronavirus Disease 2019** (**COVID**-**19**) **Outbreak in China**: **Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention**. *JAMA* 2020.
5. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, et al: **Clinical Characteristics of Coronavirus Disease 2019 in China**. *N Engl J Med* 2020.
6. Clinical. **management of 2019 nCoV guidelines by National Health Commission of the People Republic of China**. **Available from**: [http://www.nhc.gov.cn/yzygj/s7652m/202003/a31191442e29474b98bfed5579d5af95.shtml].
7. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, et al: **Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia**. *N Engl J Med* 2020.
8. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507–13.
9. Deng SQ, Peng HJ. **Characteristics of and Public Health Responses to the Coronavirus Disease 2019 Outbreak in China**. *J Clin Med* 2020, 9(2).
10. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, Akdis CA, Gao YD: **Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan**, **China**. *Allergy* 2020.
11. Jiang F, Deng L, Zhang L, Cai Y, Cheung CW, Xia Z. **Review of the Clinical Characteristics of Coronavirus Disease 2019 (COVID-19)**. *J Gen Intern Med* 2020.
12. Gao HN, Lu HZ, Cao B, Du B, Shang H, Gan JH, Lu SH, Yang YD, Fang Q, Shen YZ, et al. Clinical findings in 111 cases of influenza A (H7N9) virus infection. N Engl J Med. 2013;368(24):2277–85.
13. Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X, Ma H, Chen W, Lin Y, Zheng Y, et al: **Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China**. *Sci China Life Sci* 2020.
14. Wang C, Yu H, Horby PW, Cao B, Wu P, Yang S, Gao H, Li H, Tsang TK, Liao Q, et al. Comparison of patients hospitalized with influenza A subtypes H7N9, H5N1, and 2009 pandemic H1N1. Clin Infect Dis. 2014;58(8):1095–103.
15. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017;39(5):529–39.
16. Yu M, Wang Q, Qi W, Zhang K, Liu J, Tao P, Ge S, Liao M, Ning Z. Expression of inflammation-related genes in the lung of BALB/c mice response to H7N9 influenza A virus with different pathogenicity. Med Microbiol Immunol. 2016;205(5):501–9.
17. Panesar NS. What caused lymphopenia in SARS and how reliable is the lymphokine status in glucocorticoid-treated patients? Med Hypotheses. 2008;71(2):298–301.