Sakarya Tıp Dergisi
Sakarya Med J

E-ISSN: 4146-409X
Yayıncı / Publisher: Sakarya Üniversitesi

Cilt/Vol. 14, Sayı/No. 1, 11-19, 2024
DOI: http://doi.org/10.31832/smj.1030208

Research Article/ Araştırma Makalesi

Predictive Factors for Severe and Critical Coronavirus Disease-19 in Young Adults

Aslı Vatan[1]*, Hüseyin Doğuş Okan[1], Aylin Çalıca Utku[1], Gökcen Gürkök Budak[1], Ertuğrul Güçlü[1], Elif Köse[2], Aziz Öğütlü[1], Oğuz Karabay[1]

[1] Sakarya University Faculty of Medicine, Infectious Diseases, Sakarya, Türkiye
asli_oner@hotmail.com
okanhd@hotmail.com
aylindoctor@hotmail.com
gokcenbudak@gmail.com
eguclu@sakarya.edu.tr
aogutlu@sakarya.edu.tr
okarabay@sakarya.edu.tr

[2] Department of Public Health, Sakarya University Training and Research Hospital, Sakarya, Türkiye
elifyldzkose@hotmail.com

*Corresponding Author

Received Date:
29.12.2021
Accepted Date:
30.05.2023
Available Online Date:
15.03.2024

Purpose: Advanced age is associated with a poor prognosis in Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The present study investigated the predictive factors for disease severity in young adults.

Method: Our study is a descriptive cross-sectional study. A total of 399 patients with SARS-CoV-2 aged under 60 who had been hospitalized at our hospital were retrospectively evaluated. Patients were stratified into mild, moderate, severe, and critical groups according to their respiratory rate, SpO2, and PaO2/FiO2 levels. The relationship between the signs and symptoms on hospital admission and the disease severity was evaluated.

Results: The patients were classified as mild (n:112), moderate (n:192), severe and critical (n:95) according to disease severity. The mean age was 44. 43 of 399 patients were followed in the intensive care unit, and 17 patients died. According to the binary logistic regression analysis, advanced age, hypertension, dyspnea on admission, elevated CRP, decreased lymphocyte and eosinophil count, multiple bilateral ground glass appearances, and consolidation independently predicted the severity of the disease.

Conclusion: The signs and symptoms should be evaluated in detail also in young patients with SARS-CoV-2. If risk factors are detected, they should be monitored more closely to predict a poor prognosis..

Keywords: SARS-CoV-2, Young adult, Prognostic factors

1.INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which has rapidly spread from Wuhan, China, to the whole world in 2019, has led to the SARS-CoV-2 pandemic.[1] Approximately 2.978.935 individuals have lost their lives due to SARS-CoV-2 until today.[2] Although the SARS-CoV-2-related mortality rate is lower than that determined in previous SARS-CoV (13%) and MERS-CoV (35%)-related cases of pneumonia, SARS-CoV-2 is more contagious.[3] SARS-CoV-2 was found to be more severe and fatal in the elderly with underlying comorbid conditions, although SARS-CoV-2 -related mortality is relatively lower in the general population.[4] On the other hand, a severe disease course has been frequently reported also in healthy young adults.[5] The present study aimed to investigate the predictors of severe disease in young adults under the age of 60 infected with SARS-CoV-2.

2. MATERIALS and METHODS

2.1.Patient Collection Data

Our study is a descriptive cross-sectional study. Sakarya University Training and Research Hospital is the medical center where SARS-CoV-2 patients have been followed since the emergence of the pandemic in the city of Sakarya, which has a population of over 1 million. The University Hospital has a bed capacity of approximately 750 patients. Our study is a single-center retrospective study. The predictive factors for disease severity were evaluated in 399 SARS-CoV-2 infected patients under the age of 60 years. Patients aged

Cite as: Vatan A, Okan HD, Utku Çalıca A, Budak Gürkök G, Güçlü E, Köse E, Öğütlü A, Karabay O. Predictive Factors for Severe and Critical Coronavirus Disease-19 in Young Adults. Sakarya Med J 2024; 14(1): 11-19 DOI: 10.31832/smj.1030208

between 18 and 60 years who had been followed up at Sakarya University Training and Research Hospital between 11 March and 30 July 2020 with proven SARS-CoV-2 infection through real-time protein chain reaction (RT-PCR) test were included in the study. The first case was enrolled to the study at 15 March. The baseline demographic, laboratory, and clinical characteristics were obtained from hospital database system. The hematological and biochemical test results on admission and the consequences of computed tomography (CT) of the thorax were evaluated.

The study was performed in accordance with the ethical considerations of the Helsinki Declarations. The Ethics Committee of Sakarya University School of Medicine approved this study. (Approval number is: 71522473/050.01.04/530)

2.2. Definitions

The diagnosis of SARS-CoV-2 was made based on the current guideline of the World Health Organization (WHO).[6] The patients were allocated to three groups according to the disease severity: mild, moderate, severe, or critical.[7] Disease severity was comprehensively assessed by systemic symptoms (e.g., fever, pulmonary manifestations), physical examinations of lungs, and radiological imaging.The mild disease was described as; mild symptoms and no radiological evidence of pneumonia on thorax CT. The moderate disease was characterized as fever, mild respiratory signs or symptoms, and radiological evidence of pneumonia on CT. Severe disease was defined as severe dyspnea, respiratory rate ≥30/minute, finger oxygen saturation ≤93%, PaO2/FiO2 ratio <300, and lung infiltrates >50% of the lung field within 24–48 h. Patients with respiratory failure who required ICU monitoring and treatment, septic shock, or multiple organ failure were defined as 'critically ill'.

2.3. Statistical Analysis

The compliance of numerical variables obtained from patient groups to normal distribution was examined by visual and analytical methods, and non-normally distributed parameters were defined by specifying the median and interquartile distribution and categorical variables by specifying percentage and number. Mann-Whitney U test was used for continuous variables that were not distributed normally, and the Kruskal Wallis test was used when there were more than two variables. Post hoc analyzes were performed in the analyzes comparing more than two groups.

Ordinal logistic regression was performed to predict the severity of the disease in three patient groups. For good fit in regression analysis, the nagelkerke value has been studied. A test of parallel lines was conducted.

The situations where the P value is less than 0.05 will be evaluated as statistically significant results. SPSS 20.0 program was used while evaluating the study data.

3. RESULTS

3.1. Clinical Characteristics

A total of 399 patients (190 females) were included in the study. The mean age of the patients was 44. The patients were allocated to three groups according to the disease severity: mild, moderate, severe, and critical. Of the 399 patients, 112 (28%) had mild, 192 (49%) had moderate, and 95 (23%) had severe and critical illness. The disease severity increased with age ($p<0.001$). Table 1 shows the clinical characteristics and comorbidities at the time of admission. Severe disease was more common among males. Cough, fatigue, and fever were the most common symptoms on admission. Dyspnea was more common in the severe illness group compared to the mild and moderate groups

(p<0.005). At least one comorbidity was detected in 98 patients. The frequency of hypertension and diabetes increased with the disease severity (p<0.005).

3.2. Laboratory Data

The laboratory parameters have been presented in Table 2.

Alanine aminotransferase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), creatine phosphokinase, C -reactive protein (CRP), serum ferritin, plasma random glucose, and the D-dimer levels at the time of admission were higher in patients with severe illness compared to those in the mild and the moderate illness groups (p<0.001). The monocyte, lymphocyte, and eosin-

Table 1.

Clinical characteristics and comorbidities of SARS-COV-2 patients

Variables	All (n=399)	Disease Severity			p
		Mild (n=112)	Moderate (n=192)	Severe (n=95)	
Age (years)	44 (36-54)	37 (28-46)1)2)	44 (38-53)2)	52 (45-57)	<0.001
Sex					0.025
Male	209 (52.4)	57 (50.9)	91 (47.4)2)	61 (64.2)	
Female	190 (47.6	55 (49.1)	101 (52.6)	34 (35.8)	
Smoking	12 (3)	1 (0.9)	7 (3.6)	4 (4.2)	-
Symptoms					
Fever(>38 C)	166 (41.6)	39 (34.8)	82 (42.7)	45 (47.4)	0.172
Cough	262 (65.7)	68 (60.7)	134 (69.8)	60 (63.2)	0.231
Shortness of breath	120 (30.1)	18 (16.1)2)	46 (24) 2)	56 (58.9)	<0.001
Sputum production	9 (2.3)	-	2 (1)	7 (7.4)	-
Myalgia	158 (39.6)	38 (33.9)	85 (44.3)	35 (36.8)	0.169
Headache	56 (14)	14 (12.5)	31 (16.1)	11 (11.6)	0.496
Diarrhea	34 (8.5)	4 (3.6)	20 (10.4)	10 (10.5)	0.087
Loss of appetite	41 (10.3)	10 (8.9)	23 (12)	8 (8.4)	0.555
Loss of taste	47 (11.8)	12 (10.7)	27 (14.1)	8 (8.4)	0.347
Loss of smelling	51 (12.8)	13 (11.6)	28 (14.6)	10 (10.5)	0.568
Comorbidities					
At least one comorbidty	98 (24.6)	6 (5.4) 1)2)	40 (20.8) 2)	52 (54.7)	<0.001
Hypertension	54 (13.5)	4 (3.6)1)2)	26 (13.5) 2)	24 (25.3)	<0.001
Diabetes	48 (12)	3 (2.7)1)2)	23 (12) 2)	22 (23.2)	<0.001
Chronic kidney failure	11 (2.8)	1 (0.9)	3 (1.6)	7 (7.4)	-
Malignancy	10 (2.5)	-	1 (0.5)	9 (9.5)	-
Asthma	8 (2)	-	3 (1.6)	5 (5.3)	-
Coronary artery disease	9 (2.3)	1 (0.9)	4 (2.1)	4 (4.2)	-
COPD	8 (2)	1 (0.9)	1 (0.5)	6 (6.3)	-
Covid 19 patient in family	132 (33.1)	35 (31.3)	66 (34.4)	31 (32.6)	0.851

Note: Data are median (IQR) or n (%). P value denotes the comparison among mild, moderate and severe illness group. [1)] and [2)] signify $P < 0.05$ for post-hoc comparison.
[1)]Refers to comparison between the moderate group and the mild group.
[2)]Refers to comparison between the severe group and the moderate group or the mild group.
IQR, interquartile range; COPD, chronic obstructive pulmonary disease.

ophil counts were low in the severe illness group (p<0.005).

3.3. Radiological Data

Thorax computed tomography (CT) findings have been presented in Table 3.

Ground glass appearance was detected in 340 patients. Lung involvement was not seen in 59 patients (14.8%). The rate of multiple ground glass appearances and the presence of consolidation increased as the disease severity increased (p<0.001). The absence of ground glass appearance and focal involvement in a single lobe was more common in the mild and moderate illness group (p<0.001).

3.4. Predictive Factors

According to the binary logistic regression analysis, advanced age, hypertension, dyspnea on admission, elevated CRP, reduced lymphocyte and eosinophil count, multiple ground glass appearances, and consolidation independently predicted the disease severity (Table 4).

4. DISCUSSION

In our study, the rate of severe illness was 23%, similar to a previous study.[8] In that study, the presence of fever and anorexia on admission was shown to predict severe illness. In our study, severe illness was found to be 2,74-fold greater among symptoms on admission in patients with dyspnea. In a recent study, the development of dyspnea was found to be related to delayed admission to the hospital and delayed treatment.[5] This condition may be associated with a poor prognosis, although not evaluated in our study. This was suggested to be related to dyspnea being more common among patients who present to the hospital late. In a study supporting this, the time from onset to dyspnea was 5.0 days, 7.0 days to hospital admission, and 8.0 days to ARDS.8 Furthermore, dyspnea can predict a poor prognosis as it can be related to lung involvement.

In many studies, advanced age was reported to predict mortality independently in SARS-CoV-2 patients.[9] Although the patients included in our study were below 60 years of age; the disease severity was found to increase 1.05- fold with each year. The increase in the disease severity with growing age also in young patients was shown to be related to pathophysiological changes, such as changes to the immune cell repertoire, the epigenome, the NAD+ levels, inflammasome activity, biological clocks, and covalent modifications of human and viral proteins.[10] Decreased airway viral clearance and decreased protective barrier functions also lead to disease progression.[11]

In the logistic regression analysis, elevated CRP and lymphopenia predicted the disease severity in young patients. Similarly, lymphopenia was shown to be the strongest predictor of severe disease in healthy young individuals diagnosed with COVID-19.5 The primary pathophysiological mechanism of severe SARS-CoV-2 infection is cytokine storm-related tissue and organ damage. Many studies indicate that pro-inflammatory cytokine release induces lymphopenia in viral infections.[12] In addition, the release of inflammatory cytokines like IL-1, IFN-γ, and IL-6 leads to lymphopenia by inhibiting T cell proliferation.[13] CRP is an inflammatory marker that also increases in acute systemic inflammatory syndromes triggered by viral infections. Similar to our study, CRP elevation was shown to predict severe illness development in SARS-CoV-2 patients.[14] Elevated CRP resulting from SARS-CoV-2-related pro-inflammatory cytokine release and increased inflammatory response is suggested to be associated with a poor prognosis and death.[14,15]

Table 2.

Laboratory findings on admission of SARS-COV-2 patients

Variables	All (n=399)	Disease Severity			p
		Mild (n=112)	Moderate (n=192)	Severe (n=95)	
Laboratory findings [1)]					
ALT <50 (µ/l)	28 (19-40)	22(16-31) [1)2)]	28 (19-41)	32(25-51)	<0.001
AST <40 (µ/l)	28 (22-38.25)	24 (19-31)[1)2)]	28(23-36) [2)]	36(26-55)	<0.001
Total bilirubin (µmol/l)	0.5 (0.3-0.6)	0.45 (0.3-0.6) [2)]	0.5 (0.3-0.6)	0.5 (0.4-0.7)	0.056
Blood glucose(mmol/l)	106 (95-123)	98 (93-107) [1)2)]	108 (96-124) [2)]	117(104-144)	<0.001
CK(U/L)	88 (58-151)	82 (54-121) [2)]	87 (61-168)	104 (63-195)	0.046
LDH(U/L)	244 (197-319)	208(178-241) [1)2)]	247(202-305) [2)]	339(244-414)	<0.001
Na(mEq/L)	138 (135-140)	139(136-140) [2)]	138(136-140) [2)]	136(134-138)	<0.001
K(mEq/L)	4.1 (3.8-4.4)	4.1 (3.9-4.4)	4.1 (3.8-4.3)	4.1 (3.7-4.4)	0.474
C-reactive protein (mg/l)	13.4 (4-51)	5 (3-14.5) [1)2)]	12.5 (5-42) [2)]	62(19-119)	<0.001
D-Dimer(mg/dl)	301(167.7-564)	241(110-411) [1)2)]	301(185-538) [2)]	457(234-826)	<0.001
Ferritin(µ/l)	127 (44-328)	68 (20.2-153) [1)2)]	125 (47-290) [2)]	313 (105-871)	<0.001
INR	1.1 (1-1.16)	1.07 (1-1.1) [2)]	1.1 (1-1.1) [2)]	1.1 (1-1.2)	0.005
Lactat(mmol/L)	1.7 (1.3-2.2)	1.7 (1.3-2.1) [2)]	1.6 (1.12-2.1) [2)]	1.9(1.6-2.5)	0.001
White blood cell count (×109/l)	5.6 (4.5-7.2)	6.01 (4.83-7) [1)]	5.2(4.3-6.5) [2)]	6.1 (4.6-8)	0.001
Haemoglobin (g/l)	13.3 (12.2-14.3)	13.3(12.4-14.5)	13.3(12.3-14.4) [2)]	13(11.1-14.1)	0.029
Platelet count (×109/l)	192 (161-245)	208(166-253) [1)]	184(158-222)	189(153-302)	0.029
Neutrophil count (×109/l)	3.5(2.6-4.8)	3.55 (2.6-4.9) [2)]	3.2 (2.4-4.4) 2)	4.3(3-5.8)	<0.001
Lymphocyte count (×109/l)	1.4 (1.05-2)	1.84 (1.3-2.4) [1)2)]	1.5 (1.1-1.8) [2)]	1.1 (0.7-1.4)	<0.001
Eosionophil					
(×109/l)	0.01(0.002-0.05)	0.03 (0.003-0.1) [1)2)]	0.01 (0.001-0.04)	0.008 (0.003-0.02)	<0.001
Monosit(×109/l)	0.4 (0.3-0.5)	0.4 (0.3-0.6) [1)2)]	0.37 (0.3-0.5)	0.3 (0.2-0.5)	0.001
MPV(fl)	9 (8.2-9.8)	8.8 (8.2-9.88)	9.05(8-9.8)	8.9 (8.1-9.9)	0.678
PCT	0.1 (0.1-0.2)	0.17 (0.1-0.2) [1)2)]	0.1 (0.1-0.19)	0.1(0.1-0.2)	<0.001
RDW	15.3 (13.9-16.4)	15.3(15.7-16.4)	15.2(13.1-16)	15.4(14.3-16.4)	0.403
PDW	17.8 (16.8-18.9)	17.7(16.6-18.6) [2)]	17.7(16.6-18.7) [2)]	18.1(17.3-19.1)	0.014
Prognosis					
Recovery	382 (95.7)	112	192(99.5)	78 (82.1)	<0.001
Exitus	17 (4.3)	-	-	17 (17.9)	-
ICU hospitalization	43 (10.8)	-	2 (1)	41 (43.2)	<0.001

Note: Data are median (IQR) or n (%). P value denotes the comparison among mild, moderate and severe illness group. [1)] and [2)]Signify P < 0.05 for post-hoc comparison.
[1)] Refers to comparison between the moderate group and the mild group.
[2)] Refers to comparison between the severe group and the moderate group or the mild group.

ALT, alanine transaminase; AST, aspartate transaminase; CK, creatine kinase; LDH, Lactate dehydrogenase; Na, sodium; K, potassium; INR, international normalized ratio; MPV, mean platelet volüme; PCT, plateletcrit; RDW, Red Cell Distribution Width; PDW, platelet distribution width; ICU, intensive care unit; IQR, interquartile range.

Table 3.

Chest CT findings on admission of SARS-COV-2 patients

Variables	All (n=399)	Disease Severity			p
		Mild (n=112)	Moderate (n=192)	Severe (n=95)	
Chest CT findings					
Ground glass appearance	340 (85.2)	60 (53.6) 1)2)	188 (97.9)	92 (96.8)	<0.001
Single lobe focal ground glass	44 (11.0)	24 (21.4) 1)2)	12 (6.3)	8 (8.4)	<0.001
Multiple unilateral glass	13 (3.3)	5 (4.5)	7 (3.6)	1 (1.1)	-
Multiple bilateral glass	301 (75.4)	49 (43.8) 1)	167 (87.0)	85 (89.5)	<0.001
Consolidation	127 (31.8)	17 (15.2) 1)2)	58 (30.2) 2)	52 (54.7)	<0.001
Pleural effusion	9 (2.3)	2 (1.8)	1 (0.5)	6 (6.3)	-
Peripheral lung involvement	283 (70.9)	59 (52.7) 1)2)	155 (80.7)	69 (72.6)	<0.001

Note: Data are median (IQR) or n (%). P value denotes the comparison among mild, moderate and severe illness group. 1) and 2)Signify P < 0.05 for post-hoc comparison.
1) Refers to comparison between the moderate group and the mild group.
2)Refers to comparison between the severe group and the moderate group or the mild group.

Table 4.

Results of ordinal logistic regression model using three levels of severity as response

Variables	Esti-mate	Std. Error	Wald	OR	p	95% Confidence Interval	
						Lower Bound	Upper Bound
Age (years)	.049	.013	14.7	1.05	<0.001	1.024	1.076
C-reactive protein (mg/l)	.016	.003	23.072	1.016	0	1.009	1.022
INR	.451	.270	2.784	0.637	0.095	.375	1.082
Lactate	.178	.094	3.565	1.195	0.059	0.993	1.438
Lymphocyte count (× 10^9 per L)	-.366	.146	6.312	1.6	0.012	.521	0.923
Eosionophil count (× 10^9 per L)	-2.608	1.259	4.288	14	0.038	0.006	0.870
Haemoglobin (g/L)	-.117	.075	2.395	1.25	0.122	.768	1.032
White blood cell count (× 10^9 per L)	.004	.035	.016	1.004	0.9	.938	1.076
Female sex (vs male)	.109	.26	.176	1.115	0.675	0.67	1.858
Fever (temperature ≥38°C)	-.296	.238	1.547	1.4	0.214	.467	1.186
Ground-glass opacity	-3.184	.508	39.278	24.3	<0.001	0.015	0.112
Consolidation	-.851	.260	10.721	2.34	0.001	0.257	.711
Multiple bilateral pulmonary infiltration	-1.006	.310	10.518	3.3	0.001	0.199	.672
Hypertension	-,782	,346	5,100	2.18	0.024	0,232	,902
Diarhea	-,788	,409	3,705	2.5	0.054	0,204	1,015
Shortness of breath	-1,010	,269	14,043	2.74	<0.001	0,215	,618
Cough	,207	,252	,673	1,230	0.412	,750	2,016

OR, odds ratio.

Lung damage develops as a result of cytokine release from pneumocytes and cytokine storm as a result of binding of SARS-CoV-2 to ACE-2 receptors in alveolar epithelial cells.[16] Hence, the findings of CT of the thorax are crucial in diagnosing SARS-CoV-2 and predicting the disease severity. The Chinese Medical Association Radiology Branch divided CT findings into four categories, and bilateral patchy ground glass appearance was reported to be typical for early-stage lung involvement. The presence of consolidation due to the accumulation of exudate in the alveoli and the interstitial space is observed in stages two and three.[17] In our study, the disease severity was found to be 24,39-fold greater among patients with ground glass appearance and 2.34-fold greater among patients with consolidation.

Similarly, while consolidation was reported in patients with severe and advanced stage illness in a study, the mortality rate was said to be higher in patients with consolidation.[18,19] The presence of consolidation is suggested to be related to increased viral load and related necrotizing bronchitis and widespread alveolar damage.[20] The patients who had consolidation on hospital admission are thought to have presented late, so they should be monitored closely.

ACE-2 receptors on which SARS-CoV-2 binds are known to be also found in the cardiovascular system.[21] Many studies have been conducted investigating the influence of hypertension on SARS-CoV-2 due to the role of ACE-2 in the pathogenesis of hypertension.[22] Increased cytokine release and inflammatory changes found in the pathophysiology of hypertension may partially explain the poor prognosis in hypertensive patients with SARS-CoV-2.[23] Studies investigating the relationship between hypertension and SARS-CoV-2 prognosis have yielded different results. In a meta-analysis evaluating 30 studies, hypertension was associated with severe SARS-CoV-2 and increased mortality.[24] In a study including 44672 patients, hypertension was shown to be related to increased mortality, independent of age.[25] In another study analyzing more than 17 million patient records, hypertension was reported not to increase mortality significantly but lead to a mild risk increase. This increased risk was associated with hypertension being more common in advanced age.[26] In our study, the disease was found to be 2.18-fold more severe among hypertensive patients independent of age and other variables. In conclusion, the present study has revealed the predictive factors for severe SARS-CoV-2 development in patients under 60. It is recommended that patients who present to the hospital with these symptoms be monitored more closely.

Acknowledgements: Authors acknowledge that the copyright of this paper is transferred to the property of your journal. Nobody else contributed to the study by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content but did not meet the criteria for authorship. This research received no grant from any funding agency in public, commercial or not-for-profit sectors.

Conflict of Interest

The Authors declare that there is no conflict of interest

Author Contributions

A.V. planned the methodology, built the hypothesis of the article, and wrote the manuscript; H.D.O. and A.C.U. were responsible for data management and reporting collected data; G.G.B. provided access to crucial research components (personnel,

equipment, environment), and E.G and O.K. were responsible for the Ethical Approval process; E.K and A.O. were responsible for the statistical interpretation and conclusion of the results and reviewed the article scientifically, besides its spelling and grammar, before submission.

Ethical Statement

The study was performed in accordance with the ethical considerations of the Helsinki Declarations. The Ethics Committee of Sakarya University School of Medicine approved this study. (Approval number is: 71522473/050.01.04/530)

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020; 382:727–33.
2. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. Available at <https://covid19.who.int/> Accessed April 14, 2021.
3. Pormohammad A, Ghorbani S, Khatami A, Farzi R, Baradaran B, Turner DL, et al. Comparison of confirmed COVID-19 with SARS and MERS cases - Clinical characteristics, laboratory findings, radiographic signs and outcomes: A systematic review and meta-analysis. Rev Med Virol. 2020;30(4):e2112.
4. Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention. [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China]. Zhonghua Liu Xing Bing Xue Za Zhi. 2020;41(2):145-151.
5. Zhou C, Huang Z, Tan W, Li X, Yin W, Xiao Y, et al. Predictive factors of severe coronavirus disease 2019 in previously healthy young adults: a single-center, retrospective study. Respir Res. 2020 Jun 22;21(1):157.
6. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance.. Available at <https://apps.who.int/iris/handle/10665/330854.> Published January 28, 2020.
7. Lin L, Li TS. Interpretation of guidelines for the diagnosis and treatment of novel coronavirus (2019-nCoV) infection by the National Health Commission (trial version 5). Zhonghua Yi Xue Za Zhi. 2020;100:805–7.
8. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020 Mar 17;323(11):1061-1069.
9. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with SARS-COV-2 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 28;395(10229):1054-1062.
10. Mueller AL, McNamara MS, Sinclair DA. Why does SARS-COV-2 disproportionately affect older people? Aging (Albany NY). 2020;12:9959-81.
11. Liu K, Chen Y, Lin R, Han K. Clinical features of SARS-COV-2 in elderly patients: A comparison with young and middle-aged patients. J Infect. 2020;80:14-8.
12. Fathi N, Rezaei N. Lymphopenia in COVID-19: Therapeutic opportunities. Cell Biol Int. 2020;44:1792-97.
13. Jeffery LE, Burke F, Mura M, Zheng Y, Qureshi OS, Hewison M, et al. 1, 25-Dihydroxyvitamin D3 and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. The Journal of Immunology. 2009;183:5458–67.
14. Luo X, Zhou W, Yan X, Guo T, Wang B, Xia H,et al. Prognostic Value of C-Reactive Protein in Patients With Coronavirus 2019. Clin Infect Dis. 2020;71:2174-79..
15. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet, 2020;395:497–506.
16. Parasher A. COVID-19: Current understanding of its pathophysiology, clinical presentation and treatmentPostgraduate Medical Journal Published Online First: 25 September2020.
17. Yang Q, Liu Q, Xu H, Lu H, Liu S, Li H. Imaging of coronavirus disease 2019: A Chinese expert consensus statement. Eur J Radiol. 2020;127:109008.
18. Li K, Wu J, Wu F, Guo D, Chen L, Fang Z et al. The clinical and chest CT features associated with severe and critical SARS-COV-2 pneumonia. Invest Radiol.2020 ;55:327-31.
19. Yuan M, Yin W, Tao Z Tan W, Hu Y. Association of radiologic findings with mortality of patients infected with 2019 novel coronavirus in Wuhan, China. PLoS One. 2020;19:15.
20. Koo HJ, Lim S, Choe J, Choi SH, Sung H, Do KH.. Radiographic and CT features of viral pneumonia. Radiographics. 2018;38:719–39.
21. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203:631–7.
22. Drummond GR, Vinh A, Guzik TJ, Sobey CG. Immune mechanisms of hypertension. Nat Rev Immunol. 2019;19:517–32.
23. Huang S, Wang J, Liu F, Liu J, Cao G, Yang C, et al. COVID-19 patients with hypertension have more severe disease: a multicenter retrospective observational study. Hypertens Res. 2020;43:824-31.
24. Pranata R, Lim MA, Huang I, Raharjo SB, Lukito AA.

Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: a systematic review, meta-analysis and meta-regression. J Renin Angiotensin Aldosterone Syst. 2020 Apr;21(2):1470320320926899.

25. The Novel Coronavirus Pneumonia Emergency Response Epidemiology T. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) — China, 2020. China CDC Weekly. 2020;2:113–22.
26. Williamson E, Walker AJ, Bhaskaran KJ, Bacon S, Bates C, Morton CE, et al. Open SAFELY: factors associated with COVID19-related hospital death in the linked electronic health records of 17 million adult NHS patients. Nature. 2020;584:430-36.