



Outcome, Severity, and Risk of Mortality in Patients with COVID-19 and Chronic Underlying Diseases: A Prospective Study

Amir Salimi^{1,2}, Mahmood Aghaziarati¹, Mohammad Qasem Roshanfekr Balalami¹, Nastaran Rastgoo¹, Fatemeh Taghizadeh¹, Zahra Pirastepoor¹, Zahra Bashiri Aghchekand¹, Zahra Arman Boroujeny¹ and Hamed Akhavadegan^{3,*}

¹Tehran University of Medical Sciences, Tehran, Iran

²Shahid Beheshti University of Medical Sciences, Tehran, Iran

³Department of Urology, Baharloo Hospital, Tehran University of Medical Sciences, Tehran, Iran

*Corresponding author: Department of Urology, Baharloo Hospital, Tehran University of Medical Sciences, Tehran, Iran. Email: h-akhavadegan@tums.ac.ir

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Abstract

Background: The novel coronavirus pandemic, severe acute respiratory syndrome CoV-2 (SARS CoV-2), has become a global threat and rapidly spread worldwide. The COVID-19 pandemic has posed a number of challenges, the most notable of which is the management of patients with chronic underlying diseases.

Objectives: The present study aimed to evaluate the risk of COVID-19 severity and mortality in patients with chronic underlying diseases.

Methods: In this retrospective cohort study, the data on the disease severity and mortality of confirmed COVID-19 patients admitted to Baharloo Hospital, Tehran, Iran, from February 2020 to March 2020 were analyzed and reported. Patients' characteristics, including age, gender, and underlying diseases, were also considered.

Results: The study encompassed 1244 patients with the mean age of 53.29 years, among whom there were 573 patients with at least one co-existing chronic disease. Hypertension, diabetes mellitus (DM), and ischemic heart disease (IHD) were the most common co-existing chronic diseases. The findings revealed that underlying diseases were significantly associated with disease mortality and severity.

Conclusions: The findings showed that patients with comorbidities were significantly at higher risk of death and severe forms of COVID-19. In this regard, patients with underlying diseases should be of concern.

Keywords: SARS-CoV-2, COVID-19, Diabetes, Cardiovascular Disease, Disease Severity, Mortality

1. Background

In December 2019, a group of pneumonia-like illnesses with unknown origin was identified in Wuhan, Hubei province, China (1). A novel coronavirus (2019-nCoV), named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was recognized as an organism in charge of the concerned diseases (2). The World Health Organization (WHO) called the disease caused by SARS-CoV-2 Coronavirus disease-2019 (COVID-19) (3). The virus spread globally and caused an ongoing pandemic quickly. By November 23, SARS-CoV-2 infected about 60 million people and killed above 1.4 million infected individuals (4).

A wide range of COVID-19 clinical manifestations, from symptom-free to death, has been introduced in previous studies (5, 6). Researchers from different countries are reporting newer symptoms continuously (7-9). Many in-

fectured individuals are supposed to be symptom-free (9); however, the most common symptoms are mild upper airway inflammation, including fever, dry cough, loss of smell, taste accompanied with fatigue, and muscle soreness (5, 10). Thrombosis occurs in some patients manifesting as CVA or MI (11). Other symptoms are less common (10, 12, 13). COVID-19 has been associated with various mortality rates worldwide, ranging from 0.17 to 1.7% (14). Heterogeneous mortality rates are attributed to age, gender, and comorbidities (15-18).

Individuals with underlying comorbidities present higher mortality rates and suffer from more severe symptoms, and longer hospital and ICU stay (19, 20). In this regard, diabetes mellitus (DM), hypertension, obesity, cardiovascular disorders, cancer, and chronic lung diseases are the most common comorbidities (6, 21-25). Moreover,

COVID-19 patients are at an increased risk of developing cardiovascular disorders and thromboembolism (26, 27). In the US, black ethnicity represents a higher mortality rate considering race as a prognostic factor (28).

In Iran, as a country with high infection and mortality rates, there is no comprehensive evaluation of risk factors among a large sample.

2. Objectives

The present study aimed to evaluate the disease outcomes and severity according to different chronic underlying diseases in Iranian tertiary hospital cases.

3. Methods

3.1. Study Design and Participants

This retrospective cohort study included patients diagnosed with COVID-19, who were admitted to Baharloo Hospital, Tehran, Iran, from February 2020 to March 2020. In Baharloo Hospital, the patients were triaged mainly based on the WHO's case definition (29, 30); however, imaging criteria were also evaluated, as proposed by European Centre for Disease Control (ECDC), and physicians ordered chest computed tomography (CT) for probable cases (30, 31). Inclusion criteria were confirmed case of COVID-19, patients with available medical records, and those with informed consent. The COVID-19 diagnosis was confirmed by a positive SARS-CoV-2 RT-PCR using throat and nose swab from the upper respiratory tract sample or was clinically diagnosed based on lung imaging findings, especially chest CT scan ground glass pathognomonic features consistent with coronavirus pneumonia (31-33) when RT-PCR tests were not available. The admission criteria were as follows: (1) oxygen saturation (SO₂) < 93% without supplementary oxygen, and (2) observing the COVID-19 symptoms on the patient's CT scan (i.e., the involvement of more than half of the lungs). However, we admitted patients with comorbidities if they had severe symptoms and signs of COVID-19 on their chest CT scan but not reduced SO₂ levels.

3.2. Ethical Approvals, Registrations, and Patient Consents

All study procedures were approved by the Ethics Committee of the Tehran University of Medical Sciences (Code: IR.TUMS.VCR.REC.1399.209). The written informed consent form was obtained from all participants or their proxies.

3.3. Data Collection

Epidemiological, demographic characteristics, and the treatment and clinical outcomes of these patients were extracted from their medical records. Collected data included information about previous medical conditions, underlying diseases, ICU admission, and complications at the time of discharge and death.

3.4. Grading Criteria for COVID-19

The COVID-19 severity was classified according to the interim guidelines proposed by the WHO. The patients were classified into four categories (namely mild, moderate, severe, and critical) based on the patients' symptoms, laboratory results, and imaging findings at admission. Patients with slight clinical symptoms without imaging finding and those with fever or respiratory symptoms were considered as mild and moderate cases, respectively. Patients with respiratory distress and a respiratory rate > 30 times per minute, and fingertip blood oxygen saturation < 93% at rest were considered as severe cases. Patients were regarded as critical cases if they met one of the following prerequisites: shock, respiratory failure requiring mechanical ventilation, and other organ failure requiring ICU treatment.

3.5. Statistical Analysis

We calculated the number and percentage for the categorical variables and used chi-squared test to evaluate differences in categorical variables between the groups. Moreover, mean and standard deviation (SD) were presented for the numerical variables. Kolmogorov-Smirnov test was used to determine the normal distribution of numerical variables. We used parametric tests to evaluate the differences in the variables with normal distribution between the research groups. In contrast, we used non-parametric tests for variables with non-normal distribution. Statistical analysis was conducted using IBM SPSS software version 24 (IBM Corporation, Armonk, NY). Statistical significance was set as $P < 0.05$.

4. Results

In this study, 1244 patients with a mean age of 53.29 ± 17.61 years were randomly selected and enrolled in the study. Out of the 1244 patients, there were 549 (44.1%) females and 695 (55.9%) males. Moreover, 731 (58.8%) cases were SARS-CoV-2 RT-PCR positive, and 513 (41.2%) patients were negative. Our data showed that 573 (46.1%) of patients had at least one comorbid condition, among which hypertension (24.6%), DM (22.1%), and ischemic heart disease (IHD) (11.8%) were the most common underlying diseases in

these patients. On the other hand, 671 patients (53.9%) were healthy. [Figure 1](#) shows the prevalence of underlying diseases in COVID-19 patients. The participants' demographic characteristics, RT-PCR test result, and habitual history regarding their underlying diseases are presented in [Table 1](#). We prescribed hydroxychloroquine and oseltamivir, lopinavir/ritonavir, naproxen and ribavirin as single or combination regimens for patients. Hypertension, dyslipidemia, and thyroidal diseases were significantly more common among females than males ($P < 0.05$). On the other hand, ESRD and DM were significantly more common among males ($P < 0.05$). In general, underlying diseases were significantly more common among females compared to males (50.1 vs. 42.9%; $P = 0.007$). The COVID-19 patients with an underlying disease were significantly younger compared to those with no underlying disease (62.05 vs. 45.82; $P < 0.001$). Mean body mass index (BMI) was not significantly different in those with and without underlying diseases ($P = 0.063$). The COVID-19 patients with no underlying disease significantly had a more positive RT-PCR test compared to those with underlying diseases (64.2 vs. 52.4%; $P < 0.001$). Smoking, drug abuse, and alcohol consumption were not significantly different among the individuals with and without underlying diseases ($P = 0.472$).

[Table 2](#) shows the severity of COVID-19 and mortality regarding the underlying diseases. Patients with underlying cardiac diseases, DM, hypertension, dyslipidemia, ESRD, neurological diseases, and psychological diseases experienced more severe types of COVID-19 compared to those without these diseases ($P < 0.05$). The mortality rate was significantly higher in those with cardiac diseases, pulmonary diseases, hypertension, DM, and ESRD ($P < 0.05$). After adjusting for age and gender, only DM (OR = 1.56, $P = 0.045$) and cardiac diseases (OR = 1.88, $P = 0.01$) were independent risk factors for mortality in the COVID-19 patients.

5. Discussion

The present retrospective cohort study on 1244 COVID-19 cases provides information about the COVID-19 disease and its outbreak in Iran. Our findings suggested that around 57.8 % of individuals infected with COVID-19 had a severe disease; hence, a majority of cases needed to be hospitalized. As the Baharloo Hospital is a referral center in Tehran, a similar trend in the general population can be concluded. In our study population, there were 573 patients with at least one kind of co-existing chronic disease. The mean age of the patients was 53.29 years, indicating that individuals of all ages are susceptible to the virus. Male patients were more frequent than females, which is consistent with other studies ([6, 15](#)). This difference can be attributed to their different lifestyles, especially smoking.

Cai indicated that smoking could increase angiotensin-converting enzyme 2 (ACE2) expression in the respiratory system ([34](#)). ACE2 is proved to be a receptor for SARS-CoV-2 ([31](#)). Moreover, the X chromosome and sex hormone play a critical role in innate and adaptive immunity, which can expose susceptible females to less infection ([35](#)).

The clinical diagnosis and CT scan results consistent with COVID-19 were used for patient admission. The CT scan results had greater sensitivity than the RT-PCR test. Our RT-PCR results were only positive in 58.8% of cases admitted to our center. The low rate of positive tests can be attributed to several reasons. First, the complicated sampling technique and the type of sample taken by the medical staff's limited expertise and the overwhelming condition during the outbreak could have affected the accuracy of the samples sent to the PCR laboratory. Second, the number of samples and tests from each patient could have influenced the RT-PCR test's sensitivity ([36](#)). Under this condition, the hospitals should not focus on the findings of the RT-PCR test to diagnose and treat the COVID-19 patients. Medical examination, including signs and symptoms, low oxygen saturation, and pulmonary involvement pattern in CT scan, was deemed adequate to support and treat patients, especially during the epidemic ([37](#)).

The prevalence of the population and the approximate number of individuals with chronic medical disorders provide planning details and have implications for allocating health care services. The occurrence of a pre-existing chronic condition is identified as a potential risk factor for the increased severity of SARS-CoV-2 infection. Our findings indicated that patients with chronic underlying disease experienced more severe forms of COVID-19. Moreover, the mortality rate tends to be higher in these patients. This finding of the present research was compatible with other studies ([7, 38, 39](#)). Surprisingly, there was no correlation between pulmonary disease and COVID-19 severity; this can be due to the small number of patients with pulmonary diseases. Mertz et al. demonstrated that in patients with comorbidities, the risk of death from influenza was significantly higher than the risk in individuals with no comorbidities ([40](#)). Since SARS-CoV-2 is a recently discovered pathogen, there is no pre-existing immunity to SARS-CoV-2 in human population. To date, there is no definite treatment to stop or minimize the spread of this virus. These complexities make the disease more dangerous for susceptible members of the population, including those with immune disorders, co-existing morbidity, and elders. In a systematic review by Javanmardi et al., the most prevalent underlying conditions in hospitalized patients with COVID-19 were hypertension, cardiovascular disease, diabetes, kidney disease, smoking, and COPD ([17](#)). Among the aforementioned comorbidities, cardiovascular disease

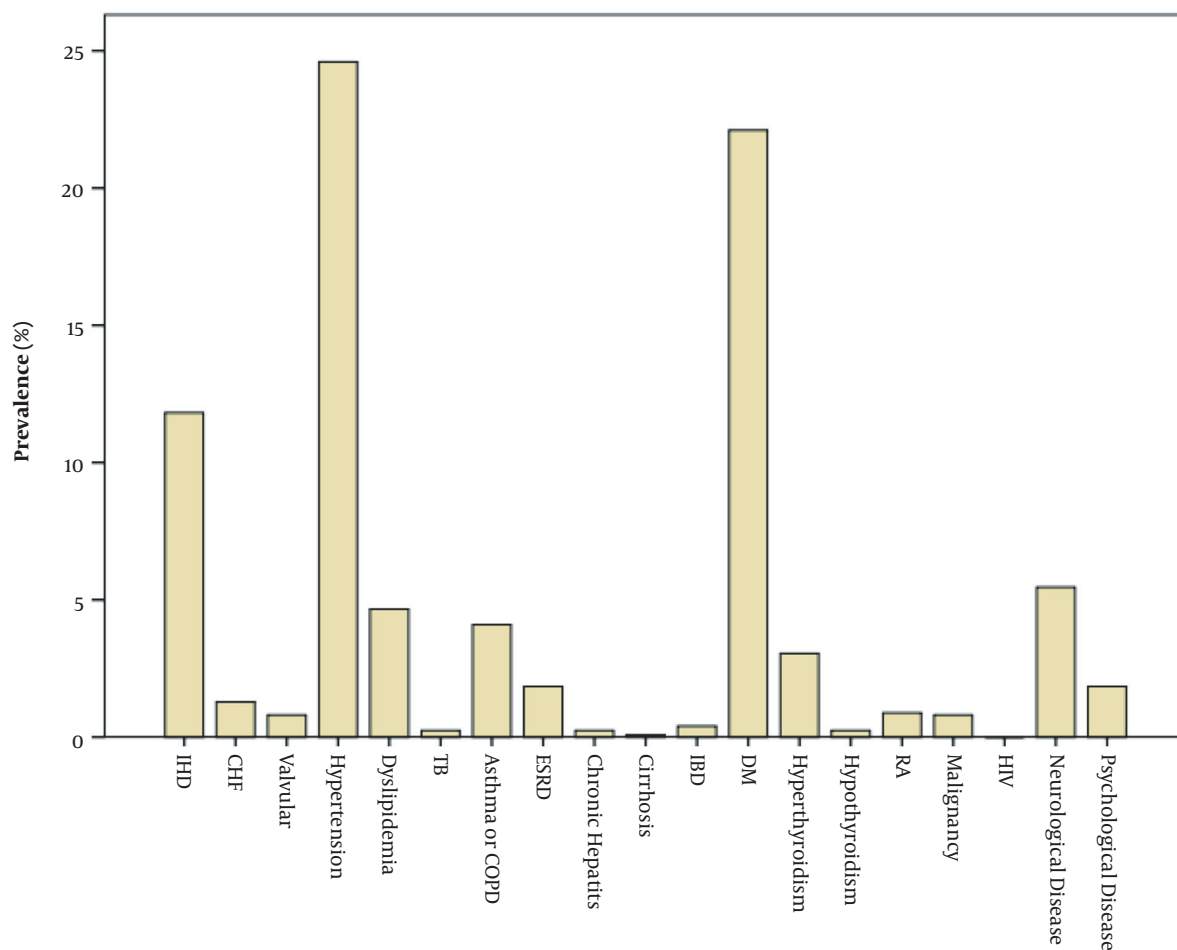


Figure 1. Prevalence of underlying diseases in COVID-19 patients

Table 1. Participants' Demographic Characteristics of Regarding Underlying Diseases ^a

Variables	Cardiac Diseases	Pulmonary Diseases	Hypertension	DM	Dyslipidemia	Thyroid Disease	ESRD	Neurological Diseases	Psychiatric Diseases	Other	No Underlying Diseases
Gender											
Female	61 (38.1)	27 (50)	163 (53.3)	135 (49.1)	34 (58.6)	25 (61)	3 (13)	35 (51.5)	14 (60.9)	15 (55.6)	274 (40.8)
Male	99 (61.9)	27 (50)	143 (46.7)	140 (50.9)	24 (41.4)	16 (39)	20 (87)	33 (48.5)	9 (39.1)	12 (44.4)	397 (59.2)
Age (y) [mean (%)]	67.78 (12.93)	64.02 (15.35)	66.57 (12.7)	62.27 (14.18)	64.84 (13.61)	51.73 (15.5)	70.52 (13.47)	64.01 (18.69)	49.09 (15.68)	58 (16.15)	45.82 (15.73)
BMI [mean (%)]	27.16 (3.98)	27.24 (3.79)	29.11 (21.02)	27.78 (6.94)	28.3 (4.41)	29 (4.3)	28.66 (4.67)	26.42 (3.57)	27.34 (3.51)	27.28 (4.37)	29.26 (38.94)
PCR											
Positive	84 (52.5)	24 (44.4)	165 (53.9)	159 (57.8)	34 (58.6)	15 (36.6)	13 (56.5)	28 (41.2)	4 (17.4)	8 (29.6)	431 (64.2)
Negative	76 (47.5)	30 (55.6)	141 (46.1)	116 (42.2)	24 (41.4)	26 (63.4)	10 (43.5)	40 (58.8)	19 (82.6)	19 (70.4)	240 (35.8)
Smoking, alcohol consumption, or drug abuse	19 (18.6)	9 (22.5)	19 (9.8)	22 (12.6)	7 (16.3)	2 (6.5)	4 (26.7)	5 (11.1)	4 (22.2)	3 (15)	41 (14)

^a Values are expressed as No. (%) unless otherwise indicated.

Table 2. Severity and Mortality of Underlying Diseases ^a

Underlying Diseases	Severity			Mortality			
	Mild	Moderate	Severe	P-Value	Yes	No	P-Value
Cardiac disease				0.001			0.001
Yes	93 (66.3)	23 (16.4)	24 (17.1)		35 (21.9)	125 (78.1)	
No	744 (84.3)	91 (10.3)	48 (5.4)		72 (6.6)	1012 (93.4)	
Pulmonary disease				0.798			0.036
Yes	38 (82.6)	4 (8.7)	4 (8.7)		9 (16.7)	45 (83.3)	
No	799 (81.8)	110 (11.3)	68 (7)		98 (8.2)	1092 (91.8)	
Hypertension				0.001			0.001
Yes	188 (69.2)	51 (19)	30 (11.2)		44 (14.4)	262 (85.6)	
No	649 (86.1)	63 (8.4)	42 (5.6)		63 (6.7)	875 (93.3)	
DM				0.001			0.001
Yes	172 (72)	43 (18)	24 (10)		41 (14.9)	234 (85.1)	
No	665 (84.8)	71 (9.1)	48 (6.1)		66 (6.8)	93 (93.2)	
Dyslipidemia				0.029			0.109
Yes	42 (80.8)	10 (19.2)	-		2 (3.4)	56 (96.6)	
No	795 (81.9)	104 (10.7)	72 (7.4)		105 (8.9)	1081 (91.1)	
Thyroidal disease				0.524			0.476
Yes	33 (84.6)	5 (12.8)	1 (2.6)		4 (9.8)	37 (90.2)	
No	804 (81.7)	109 (11.1)	71 (7.2)		103 (8.6)	1100 (91.4)	
ESRD				0.001			0.041
Yes	12 (52.2)	7 (30.4)	4 (17.4)		5 (21.7)	18 (78.3)	
No	825 (82.5)	107 (10.7)	68 (6.8)		102 (8.4)	1119 (91.6)	
Neurological disease				0.001			0.223
Yes	41 (65.1)	15 (23.8)	7 (11.1)		8 (11.8)	60 (88.2)	
No	796 (82.9)	99 (10.3)	65 (6.8)		99 (8.4)	1077 (91.6)	
Psychological disease				0.001			0.603
Yes	11 (52.4)	8 (38.1)	2 (9.5)		2 (8.7)	21 (91.3)	
No	826 (82.4)	106 (10.6)	70 (7)		105 (8.6)	1116 (91.4)	
Other				0.288			0.197
Yes	17 (70.8)	5 (20.8)	2 (8.3)		4 (14.8)	23 (85.2)	
No	820 (82.1)	109 (10.9)	70 (7)		103 (8.5)	1114 (91.5)	

^a Values are expressed as No. (%).

was the most frequent and put patients at higher mortality rates. This might be due to increasing pro-inflammatory cytokines contributing to poorer immune function (41). In our study, hypertension, DM, and IHD were the three most common co-existing chronic diseases and had a significant impact on the disease severity and its mortality rate.

The mechanism underlying comorbid chronic diseases and the COVID-19 severity is poorly understood. However, for patients with cardiovascular diseases, ACE2, which

mediates the SARS-CoV-2 to the lung, is also expressed in the cardiovascular system and can directly affect the cardiac function (42). Drug-induced cardiotoxicity is another mechanism exposing patients with cardiovascular disease at a higher risk of severe forms of COVID-19 (43). Moreover, immunohistochemistry has demonstrated that SARS-CoV-2 antigen accumulates in renal tubules with severe acute tubular necrosis, however, without indication of glomerular pathology or infiltration of tubulointersti-

tial lymphocytes (44). SARS-CoV-2 infection can cause a cytokine storm, which releases high levels of various cytokines and chemokines, including IL-2, IL-7, and IL-10 and hurts patients' tissues (45). Yang et al. showed that ACE2 is also expressed in pancreatic islet cells targeted by the virus (46). Furthermore, ACE2 knockout mice have compromised B-cell pancreatic activity, implying a potential link between infection with SARS-CoV-2 and diabetes (47). Finally, through a compromised immune system, multiple chronic comorbidities, including hypertension, cardiovascular disease, chronic kidney disease, and diabetes, make the affected organs and tissues susceptible to the virus (48).

To the best of our knowledge, this study with large sample size is among the first reports in Iran. While the sample size in this study is a major advantage, more detailed information on patients, especially clinical outcomes, was not available at the time of review. Notably, this can limit the results of this data. However, the data provides information about the epidemiological characteristics of the COVID-19 cases in Tehran, Iran. Further research in outpatient, primary care, or community settings will provide a comprehensive understanding of clinical diagnosis, risk factors, and the scale of clinical severity under the same condition.

Further attempts should be made to resolve the afore limitation. Rapid, accurate, and practicable diagnostic tests are essential, however diagnostics selection is based on physicians' clinical logic. Monitoring the disease and its epidemiological features, including virulence, host tolerance, transmissibility, and pathogenicity, requires careful national surveillance. At the national, regional, and global levels, efforts and interventions need to be made to interrupt the disease transmission chain.

In conclusion, the present findings demonstrate the remarkable impact of chronic underlying diseases on the risk of mortality and disease severity in patients with COVID-19, as previously stated in other reports. Hence, it is recommended to take prevention strategies more seriously. Regarding medical care services, it is also important to pay particular attention to patients with underlying diseases. As COVID-19 is known to be a global health threat, more comprehensive investigations are still suggested.

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Footnotes

Authors' Contribution: Study concept and design: Amir Salimi, Hamed Akhaviadegan, Mahmood Aghaziarati, Mohammad Ghasem Roshanfekr Balalami, Nastaran Rastgoo; Acquisition of data: Fatemeh Taghizadeh, Zahra Pirastepoor, Zahra Bashiri Aghchekand, Amir Salimi; Analysis and interpretation of data: Amir Salimi, Zahra Arman Boroujeny; Drafting of the manuscript: Amir Salimi, Mahmood Aghaziarati, Mohammad Ghasem Roshanfekr Balalami, Nastaran Rastgoo; Critical revision of the manuscript for important intellectual content: Amir Salimi, Hamed Akhaviadegan; Statistical analysis: Amir Salimi, Zahra Arman Boroujeny; Study supervision: Hamed Akhaviadegan.

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References

1. Nishiura H, Jung SM, Linton NM, Kinoshita R, Yang Y, Hayashi K, et al. The Extent of Transmission of Novel Coronavirus in Wuhan, China, 2020. *J Clin Med*. 2020;9(2). doi: [10.3390/jcm9020330](https://doi.org/10.3390/jcm9020330). [PubMed: 31991628]. [PubMed Central: PMC7073674].
2. She J, Jiang J, Ye L, Hu L, Bai C, Song Y. 2019 novel coronavirus of pneumonia in Wuhan, China: emerging attack and management strategies. *Clin Transl Med*. 2020;9(1):19. doi: [10.1186/s40169-020-00271-z](https://doi.org/10.1186/s40169-020-00271-z). [PubMed: 32078069]. [PubMed Central: PMC7033263].
3. World Health Organization. *Naming the coronavirus disease (COVID-19) and the virus that causes it*. Geneva, Switzerland: World Health Organization; 2020. Available from: [https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-\(covid-2019\)-and-the-virus-that-causes-it](https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it).
4. Worldometer. *COVID-19 CORONAVIRUS PANDEMIC*. United States of America: Worldometer; 2020, [updated March 06, 2022]. Available from: <https://www.worldometers.info/coronavirus/>.
5. Firouzabadi FD, Firouzabadi MD, Ghalehbaghi B, Jahandideh H, Roomiani M, Goudarzi S. Have the symptoms of patients with COVID-19 changed over time during hospitalization? *Med Hypotheses*. 2020;143:110067. doi: [10.1016/j.mehy.2020.110067](https://doi.org/10.1016/j.mehy.2020.110067). [PubMed: 32634735]. [PubMed Central: PMC7328546].
6. 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(8):727-33. doi: [10.1056/NEJMoa2001017](https://doi.org/10.1056/NEJMoa2001017). [PubMed: 31978945]. [PubMed Central: PMC7092803].
7. Pathak SK, Pandey S, Pandey A, Salunke AA, Thivari P, Ratna HVK, et al. Focus on uncommon symptoms of COVID-19: Potential reason for spread of infection. *Diabetes Metab Syndr*. 2020;14(6):1873-4.

- doi: [10.1016/j.dsx.2020.09.017](https://doi.org/10.1016/j.dsx.2020.09.017). [PubMed: [32998094](https://pubmed.ncbi.nlm.nih.gov/32998094/)]. [PubMed Central: [PMC7493791](https://pubmed.ncbi.nlm.nih.gov/PMC7493791/)].
8. Shojaei F, Habibi Z, Goudarzi S, Firouzabadi FD, Montazerin SM, Najafi H, et al. COVID-19: A double threat to takotsubo cardiomyopathy and spontaneous coronary artery dissection? *Med Hypotheses*. 2021;**146**:110410. doi: [10.1016/j.mehy.2020.110410](https://doi.org/10.1016/j.mehy.2020.110410). [PubMed: [33267999](https://pubmed.ncbi.nlm.nih.gov/33267999/)]. [PubMed Central: [PMC7680528](https://pubmed.ncbi.nlm.nih.gov/PMC7680528/)].
 9. Jalali A, Karimi Alavijeh E, Alinia Gerdroudbari E, Babaniamansour S. Incidentally Diagnosed COVID-19 in the Emergency Department: A Case Series. *Case Reports in Clinical Practice*. 2021;**5**(1):15–8. doi: [10.18502/crcp.v5i1.6238](https://doi.org/10.18502/crcp.v5i1.6238).
 10. Doo FX, Kassim G, Lefton DR, Patterson S, Pham H, Belani P. Rare presentations of COVID-19: PRES-like leukoencephalopathy and carotid thrombosis. *Clin Imaging*. 2021;**69**:94–101. doi: [10.1016/j.clinimag.2020.07.007](https://doi.org/10.1016/j.clinimag.2020.07.007). [PubMed: [32707411](https://pubmed.ncbi.nlm.nih.gov/32707411/)]. [PubMed Central: [PMC7365057](https://pubmed.ncbi.nlm.nih.gov/PMC7365057/)].
 11. Chi G, Lee JJ, Jamil A, Gunnam V, Najafi H, Memar Montazerin S, et al. Venous Thromboembolism among Hospitalized Patients with COVID-19 Undergoing Thromboprophylaxis: A Systematic Review and Meta-Analysis. *J Clin Med*. 2020;**9**(8). doi: [10.3390/jcm9082489](https://doi.org/10.3390/jcm9082489). [PubMed: [32756383](https://pubmed.ncbi.nlm.nih.gov/32756383/)]. [PubMed Central: [PMC7463975](https://pubmed.ncbi.nlm.nih.gov/PMC7463975/)].
 12. Goudarzi S, Dehghani Firouzabadi F, Dehghani Firouzabadi M, Rezaei N. Cutaneous lesions and COVID-19: Cystic painful lesion in a case with positive SARS-CoV-2. *Dermatol Ther*. 2020;**33**(6). e14266. doi: [10.1111/dth.14266](https://doi.org/10.1111/dth.14266). [PubMed: [32882081](https://pubmed.ncbi.nlm.nih.gov/32882081/)].
 13. Dehghani Firouzabadi M, Goudarzi S, Dehghani Firouzabadi F, Moosaie F. Complete heart block and itchy rash in a patient with COVID-19. *Caspian J Intern Med*. 2020;**11**(Suppl 1):569–71. doi: [10.22088/cjim.11.0.569](https://doi.org/10.22088/cjim.11.0.569). [PubMed: [33425278](https://pubmed.ncbi.nlm.nih.gov/33425278/)]. [PubMed Central: [PMC7780868](https://pubmed.ncbi.nlm.nih.gov/PMC7780868/)].
 14. Meyerowitz-Katz G, Merone L. A systematic review and meta-analysis of published research data on COVID-19 infection fatality rates. *Int J Infect Dis*. 2020;**101**:138–48. doi: [10.1016/j.ijid.2020.09.1464](https://doi.org/10.1016/j.ijid.2020.09.1464). [PubMed: [33007452](https://pubmed.ncbi.nlm.nih.gov/33007452/)]. [PubMed Central: [PMC7524446](https://pubmed.ncbi.nlm.nih.gov/PMC7524446/)].
 15. Omori R, Matsuyama R, Nakata Y. The age distribution of mortality from novel coronavirus disease (COVID-19) suggests no large difference of susceptibility by age. *Sci Rep*. 2020;**10**(1):16642. doi: [10.1038/s41598-020-73777-8](https://doi.org/10.1038/s41598-020-73777-8). [PubMed: [33024235](https://pubmed.ncbi.nlm.nih.gov/33024235/)]. [PubMed Central: [PMC7538918](https://pubmed.ncbi.nlm.nih.gov/PMC7538918/)].
 16. Joe W, Kumar A, Rajpal S, Mishra US, Subramanian SV. Equal risk, unequal burden? Gender differentials in COVID-19 mortality in India. *J Glob Health Sci*. 2020;**2**(1). doi: [10.35500/jghs.2020.2.e17](https://doi.org/10.35500/jghs.2020.2.e17).
 17. Javanmardi F, Keshavarzi A, Akbari A, Emami A, Pirbonyeh N. Prevalence of underlying diseases in died cases of COVID-19: A systematic review and meta-analysis. *PLoS One*. 2020;**15**(10). e0241265. doi: [10.1371/journal.pone.0241265](https://doi.org/10.1371/journal.pone.0241265). [PubMed: [33095835](https://pubmed.ncbi.nlm.nih.gov/33095835/)]. [PubMed Central: [PMC7584167](https://pubmed.ncbi.nlm.nih.gov/PMC7584167/)].
 18. Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, et al. Comorbidity and its Impact on Patients with COVID-19. *SN Compr Clin Med*. 2020;**2**(8):1069–76. doi: [10.1007/s42399-020-00363-4](https://doi.org/10.1007/s42399-020-00363-4). [PubMed: [32838147](https://pubmed.ncbi.nlm.nih.gov/32838147/)]. [PubMed Central: [PMC7314621](https://pubmed.ncbi.nlm.nih.gov/PMC7314621/)].
 19. Luo L, Fu M, Li Y, Hu S, Luo J, Chen Z, et al. The potential association between common comorbidities and severity and mortality of coronavirus disease 2019: A pooled analysis. *Clin Cardiol*. 2020;**43**(12):1478–93. doi: [10.1002/clc.23465](https://doi.org/10.1002/clc.23465). [PubMed: [33026120](https://pubmed.ncbi.nlm.nih.gov/33026120/)]. [PubMed Central: [PMC7675427](https://pubmed.ncbi.nlm.nih.gov/PMC7675427/)].
 20. Rees EM, Nightingale ES, Jafari Y, Waterlow NR, Clifford S, B. Pearson CA, et al. COVID-19 length of hospital stay: a systematic review and data synthesis. *BMC Med*. 2020;**18**(1):270. doi: [10.1186/s12916-020-01726-3](https://doi.org/10.1186/s12916-020-01726-3). [PubMed: [32878619](https://pubmed.ncbi.nlm.nih.gov/32878619/)]. [PubMed Central: [PMC7467845](https://pubmed.ncbi.nlm.nih.gov/PMC7467845/)].
 21. Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. *Lancet Diabetes Endocrinol*. 2020;**8**(9):782–92. doi: [10.1016/S2213-8587\(20\)30238-2](https://doi.org/10.1016/S2213-8587(20)30238-2). [PubMed: [32687793](https://pubmed.ncbi.nlm.nih.gov/32687793/)]. [PubMed Central: [PMC7367664](https://pubmed.ncbi.nlm.nih.gov/PMC7367664/)].
 22. Shibata S, Arima H, Asayama K, Hoshida S, Ichihara A, Ishimitsu T, et al. Hypertension and related diseases in the era of COVID-19: a report from the Japanese Society of Hypertension Task Force on COVID-19. *Hypertens Res*. 2020;**43**(10):1028–46. doi: [10.1038/s41440-020-0515-0](https://doi.org/10.1038/s41440-020-0515-0). [PubMed: [32737423](https://pubmed.ncbi.nlm.nih.gov/32737423/)]. [PubMed Central: [PMC7393334](https://pubmed.ncbi.nlm.nih.gov/PMC7393334/)].
 23. Mahase E. Covid-19: Why are age and obesity risk factors for serious disease? *BMJ*. 2020;**371**:m4130. doi: [10.1136/bmj.m4130](https://doi.org/10.1136/bmj.m4130). [PubMed: [33106243](https://pubmed.ncbi.nlm.nih.gov/33106243/)].
 24. Moris D, Tsilimigras DI, Schizas D. Cancer and COVID-19. *Lancet*. 2020;**396**(10257):1066. doi: [10.1016/S0140-6736\(20\)32069-9](https://doi.org/10.1016/S0140-6736(20)32069-9). [PubMed: [33038962](https://pubmed.ncbi.nlm.nih.gov/33038962/)]. [PubMed Central: [PMC7544492](https://pubmed.ncbi.nlm.nih.gov/PMC7544492/)].
 25. Schultze A, Walker AJ, MacKenna B, Morton CE, Bhaskaran K, Brown JP, et al. Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: an observational cohort study using the OpenSAFELY platform. *Lancet Respir Med*. 2020;**8**(11):1106–20. doi: [10.1016/S2213-2600\(20\)30415-X](https://doi.org/10.1016/S2213-2600(20)30415-X). [PubMed: [32979987](https://pubmed.ncbi.nlm.nih.gov/32979987/)]. [PubMed Central: [PMC7515601](https://pubmed.ncbi.nlm.nih.gov/PMC7515601/)].
 26. Kermani-Alghoraishi M, Ghahramani R. A Review of Venous Thromboembolism Phenomena in COVID-19 Patients. *Curr Probl Cardiol*. 2021;**46**(3):100692. doi: [10.1016/j.cpcardiol.2020.100692](https://doi.org/10.1016/j.cpcardiol.2020.100692). [PubMed: [32994052](https://pubmed.ncbi.nlm.nih.gov/32994052/)]. [PubMed Central: [PMC7452823](https://pubmed.ncbi.nlm.nih.gov/PMC7452823/)].
 27. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. *Nat Rev Cardiol*. 2020;**17**(9):543–58. doi: [10.1038/s41569-020-0413-9](https://doi.org/10.1038/s41569-020-0413-9). [PubMed: [32690910](https://pubmed.ncbi.nlm.nih.gov/32690910/)]. [PubMed Central: [PMC7370876](https://pubmed.ncbi.nlm.nih.gov/PMC7370876/)].
 28. Golestaneh L, Neugarten J, Fisher M, Billett HH, Gil MR, Johns T, et al. The association of race and COVID-19 mortality. *EClinicalMedicine*. 2020;**25**:100455. doi: [10.1016/j.eclinm.2020.100455](https://doi.org/10.1016/j.eclinm.2020.100455). [PubMed: [32838233](https://pubmed.ncbi.nlm.nih.gov/32838233/)]. [PubMed Central: [PMC7361093](https://pubmed.ncbi.nlm.nih.gov/PMC7361093/)].
 29. Public health surveillance for COVID-19. *WHO COVID-19: Case definition*. Geneva, Switzerland: World Health Organization; 2020.
 30. Abdolrahimzadeh Fard H, Borazjani R, Sabetian G, Shayan Z, Boland Parvaz S, Abbasi HR, et al. Establishment of a novel triage system for SARS-CoV-2 among trauma victims in trauma centers with limited facilities. *Trauma Surg Acute Care Open*. 2021;**6**(1). e000726. doi: [10.1136/tsaco-2021-000726](https://doi.org/10.1136/tsaco-2021-000726). [PubMed: [34222675](https://pubmed.ncbi.nlm.nih.gov/34222675/)]. [PubMed Central: [PMC8212155](https://pubmed.ncbi.nlm.nih.gov/PMC8212155/)].
 31. European Centre for Disease Prevention and Control. *Case definition for coronavirus disease 2019 (COVID-19), as of 3 December 2020*. Stockholm, Sweden: European Centre for Disease Prevention and Control; 2020. [updated 3 December 2020]. Available from: <https://www.ecdc.europa.eu/en/covid-19/surveillance/case-definition>.
 32. Abdolrahimzadeh Fard H, Mahmudi-Azer S, Sefidbakht S, Iranpour P, Bolandparvaz S, Abbasi HR, et al. Evaluation of Chest CT Scan as a Screening and Diagnostic Tool in Trauma Patients with Coronavirus Disease 2019 (COVID-19): A Cross-Sectional Study. *Emerg Med Int*. 2021;**2021**:4188178. doi: [10.1155/2021/4188178](https://doi.org/10.1155/2021/4188178). [PubMed: [34327023](https://pubmed.ncbi.nlm.nih.gov/34327023/)]. [PubMed Central: [PMC8245252](https://pubmed.ncbi.nlm.nih.gov/PMC8245252/)].
 33. Jalali A, Karimialavijeh E, Babaniamansour P, Aliniagerdroudbari E, Babaniamansour S. Predicting the 30-day Adverse Outcomes of Non-Critical New-Onset COVID-19 Patients in Emergency Departments based on their Lung CT Scan Findings; A Pilot Study for Derivation an Emergency Scoring Tool. *Front. Emerg. Med*. 2021. doi: [10.18502/fem.v5i4.6691](https://doi.org/10.18502/fem.v5i4.6691).
 34. Cai G. Bulk and Single-Cell Transcriptomics Identify Tobacco-Use Disparity in Lung Gene Expression of ACE2, the Receptor of 2019-nCoV. *Preprints*. 2020;**3**(1). doi: [10.20944/preprints202002.0051.v3](https://doi.org/10.20944/preprints202002.0051.v3).
 35. Jaillon S, Berthenet K, Garlanda C. Sexual Dimorphism in Innate Immunity. *Clin Rev Allergy Immunol*. 2019;**56**(3):308–21. doi: [10.1007/s12016-017-8648-x](https://doi.org/10.1007/s12016-017-8648-x). [PubMed: [28963611](https://pubmed.ncbi.nlm.nih.gov/28963611/)].
 36. Wang Y, Kang H, Liu X, Tong Z. Combination of RT-qPCR testing and clinical features for diagnosis of COVID-19 facilitates management of SARS-CoV-2 outbreak. *J Med Virol*. 2020;**92**(6):538–9. doi: [10.1002/jmv.25721](https://doi.org/10.1002/jmv.25721). [PubMed: [32096564](https://pubmed.ncbi.nlm.nih.gov/32096564/)]. [PubMed Central: [PMC7233289](https://pubmed.ncbi.nlm.nih.gov/PMC7233289/)].

37. Al-Tawfiq JA, Memish ZA. Diagnosis of SARS-CoV-2 infection based on CT scan vs RT-PCR: reflecting on experience from MERS-CoV. *J Hosp Infect.* 2020;**105**(2):154–5. doi: [10.1016/j.jhin.2020.03.001](https://doi.org/10.1016/j.jhin.2020.03.001). [PubMed: [32147407](https://pubmed.ncbi.nlm.nih.gov/32147407/)]. [PubMed Central: [PMC7124270](https://pubmed.ncbi.nlm.nih.gov/PMC7124270/)].
38. Meshkat S, Salimi A, Joshaghanian A, Sedighi S, Sedighi S, Aghamollaii V. Chronic neurological diseases and COVID-19: Associations and considerations. *Transl Neurosci.* 2020;**11**(1):294–301. doi: [10.1515/tnsci-2020-0141](https://doi.org/10.1515/tnsci-2020-0141). [PubMed: [33335769](https://pubmed.ncbi.nlm.nih.gov/33335769/)]. [PubMed Central: [PMC7712023](https://pubmed.ncbi.nlm.nih.gov/PMC7712023/)].
39. Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. *BMJ.* 2020;**368**:m1198. doi: [10.1136/bmj.m1198](https://doi.org/10.1136/bmj.m1198). [PubMed: [32217618](https://pubmed.ncbi.nlm.nih.gov/32217618/)].
40. Mertz D, Kim TH, Johnstone J, Lam PP, Science M, Kuster SP, et al. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. *BMJ.* 2013;**347**:f5061. doi: [10.1136/bmj.f5061](https://doi.org/10.1136/bmj.f5061). [PubMed: [23974637](https://pubmed.ncbi.nlm.nih.gov/23974637/)]. [PubMed Central: [PMC3805492](https://pubmed.ncbi.nlm.nih.gov/PMC3805492/)].
41. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol.* 2020;**17**(5):259–60. doi: [10.1038/s41569-020-0360-5](https://doi.org/10.1038/s41569-020-0360-5). [PubMed: [32139904](https://pubmed.ncbi.nlm.nih.gov/32139904/)]. [PubMed Central: [PMC7095524](https://pubmed.ncbi.nlm.nih.gov/PMC7095524/)].
42. Wang X, Fang X, Cai Z, Wu X, Gao X, Min J, et al. Comorbid Chronic Diseases and Acute Organ Injuries Are Strongly Correlated with Disease Severity and Mortality among COVID-19 Patients: A Systemic Review and Meta-Analysis. *Research (Wash D C).* 2020;**2020**:2402961. doi: [10.34133/2020/2402961](https://doi.org/10.34133/2020/2402961). [PubMed: [32377638](https://pubmed.ncbi.nlm.nih.gov/32377638/)]. [PubMed Central: [PMC7187729](https://pubmed.ncbi.nlm.nih.gov/PMC7187729/)].
43. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* 2020;**30**(3):269–71. doi: [10.1038/s41422-020-0282-0](https://doi.org/10.1038/s41422-020-0282-0). [PubMed: [32020029](https://pubmed.ncbi.nlm.nih.gov/32020029/)]. [PubMed Central: [PMC7054408](https://pubmed.ncbi.nlm.nih.gov/PMC7054408/)].
44. Diao B, Wang C, Wang R, Feng Z, Zhang J, Yang H, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 infection. *Nat Commun.* 2021;**12**(1):2506. doi: [10.1038/s41467-021-22781-1](https://doi.org/10.1038/s41467-021-22781-1). [PubMed: [33947851](https://pubmed.ncbi.nlm.nih.gov/33947851/)]. [PubMed Central: [PMC8096808](https://pubmed.ncbi.nlm.nih.gov/PMC8096808/)].
45. Tay MZ, Poh CM, Renia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol.* 2020;**20**(6):363–74. doi: [10.1038/s41577-020-0311-8](https://doi.org/10.1038/s41577-020-0311-8). [PubMed: [32346093](https://pubmed.ncbi.nlm.nih.gov/32346093/)]. [PubMed Central: [PMC7187672](https://pubmed.ncbi.nlm.nih.gov/PMC7187672/)].
46. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol.* 2010;**47**(3):193–9. doi: [10.1007/s00592-009-0109-4](https://doi.org/10.1007/s00592-009-0109-4). [PubMed: [19333547](https://pubmed.ncbi.nlm.nih.gov/19333547/)]. [PubMed Central: [PMC7088164](https://pubmed.ncbi.nlm.nih.gov/PMC7088164/)].
47. Bernardi S, Tikellis C, Candido R, Tsorotes D, Pickering RJ, Bossi F, et al. ACE2 deficiency shifts energy metabolism towards glucose utilization. *Metabolism.* 2015;**64**(3):406–15. doi: [10.1016/j.metabol.2014.11.004](https://doi.org/10.1016/j.metabol.2014.11.004). [PubMed: [25484288](https://pubmed.ncbi.nlm.nih.gov/25484288/)].
48. Saghaideh A, Rezaei N. Immune-epidemiological parameters of the novel coronavirus - a perspective. *Expert Rev Clin Immunol.* 2020;**16**(5):465–70. doi: [10.1080/1744666X.2020.1750954](https://doi.org/10.1080/1744666X.2020.1750954). [PubMed: [32237901](https://pubmed.ncbi.nlm.nih.gov/32237901/)]. [PubMed Central: [PMC7157951](https://pubmed.ncbi.nlm.nih.gov/PMC7157951/)].