ORIGINAL ARTICLE

Risk Factors and Prognosis; An Effort to Predict the Severity of COVID-19

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Abstract

Background: Up to this time, screening for people infected with coronavirus disease 2019 (COVID-19) relies on clinical symptoms. As a result, our study focused on establishing a relationship between clinical manifestations, risk factors, and the prognosis of COVID-19 for prompt intervention.

Methods: This cross-sectional study was performed on patients with positive COVID-19 tests in Shiraz, Iran, from 2020 through 2021. Patients were randomly selected from those registered as COVID-19 positive in various family clinics affiliated with Shiraz University of Medical Sciences Health Centers. A telephone interview was conducted to gather necessary data about the clinical symptoms of 401 patients, their risk factors, and their prognosis of the disease in two weeks.

Results: Body pain, followed by fever, were the most reported symptoms. Except for dyspnea that was related to hospitalization, no relation was found between initial clinical symptoms and hospitalization or 2-week recovery. We observed a statistically significant difference between different blood groups of patients concerning their rate of hospitalization and recovery after two weeks. A significant relationship between hypertension and hospitalization was seen.

Conclusion: Body pain, fever, certain demographic aspects (such as older age), and comorbidities like hypertension showed strong associations with the severity and prognosis of COVID-19. Our results add to the growing body of evidence suggesting blood type may play a role in the prognosis of COVID-19.

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Introduction

Coronavirus disease 2019 (COVID-19) is an airborne viral disease caused by a novel coronavirus belonging to the Coronaviridae family, severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2). The susceptibility and vulnerability of human beings towards SARS-CoV-2 turned it into a serious pandemic.[1, 2] Screening for infected people heavily relies on clinical signs and symptoms. Further, identifying the risk factors and prognostic indices for this disease is essential to recognize and isolate individuals in a shorter time to break the chain of infection.[3] Determining the patients with poor prognoses based on the risk factors could be of great significance in prioritizing them for hospital admission.[4] Studies have identified various risk factors with different coefficients correlating the adverse outcomes of COVID-19. These include age over 60 years, smoking, critical comorbidities, diabetes, high Troponin-I levels, leukocytosis, and neutrophilia.[3-7] The relationship between these risk factors and the prognosis of COVID-19 has been discussed below.

A total of 60 predictors of disease severity have been found until now, of which seven are highly correlated, 40 are moderately correlated, and 13 are less correlated. Highly correlated factors are

age, C-reactive protein, D-dimer, albumin, body temperature, Sequential Organ Failure Assessment (SOFA) score, and diabetes.[5] Many comorbidities, such as diabetes mellitus and hypertension, have been shown to worsen the patient's condition and the severity of their symptoms.[8-11] Other comorbidities, such as chronic obstructive pulmonary disease (COPD), play a significant role in disease severity, intensive care unit (ICU) admission, mortality, the need for mechanical ventilation via intubation, and disease progression in patients with COVID-19.[12] Moreover, severe asthma has also been directly linked to COVID-19-related mortality.[13] Further, chronic kidney disease (CKD) has also been shown to be associated with increased mortality.[6, 12] Cerebrovascular disease is likely to increase the severity of symptoms and risk of death in COVID-19 patients.[6, 12, 14 (Ref 15 ??)]

Signs of increased liver damage, especially abnormal aspartate transaminase (AST) levels, are strongly linked with the risk of death from COVID-19.[16] Liver-associated disorders are also thought to make the prognosis worse by changing blood albumin levels.[17] Examining the connection between malignancies and COVID-19 revealed that COVID-19 is associated with higher hospitalization rates and severe outcomes in cancer patients.[18, 19]

There is also a significant relationship between air pollution and SARS-CoV-2 infection, as more severe symptoms of COVID-19 have been noticed in smokers.[20, 21] Overweight and obese individuals, regardless of age, require more mechanical ventilation and admission to intensive or semi-intensive care units than normal-weight individuals.[10, 22] It turns out that obesity, air pollution, and smoking-related risk factors are associated with the underlying pathophysiology of the renin-angiotensin system in SARS-CoV-2 infection.[23] The vitamin D level is also one of the factors determining the severity of the disease in patients with COVID-19. Previous research found that patients with a poor prognosis had significantly lower serum levels of vitamin D than patients with a good prognosis.[24, 25]

In general, age significantly determines the clinical features and prognosis of COVID-19. The prognosis is significantly worse in patients over 60 years of age.[26] In men, especially the old, disease severity is significantly higher, and the prognosis is poor.[26, 27] In some studies, the proportion of shortness of breath in male patients was significantly higher than in female patients.[28, 29] In May et al.'s study, the chest pain and shortness of breath ratio was significantly higher in patients with severe disease than in patients with mild symptoms. The ratio of nasal congestion, sore throat, olfactory, and taste dysfunction was significantly higher in children than in adult patients. Asymptomatic patients were also significantly younger than symptomatic patients.[28]

A systemic review conducted by Li et al. emphasized the fact that factors such as fever, dyspnea, certain hematological changes: lymphocytopenia, thrombocytopenia, leukocytosis, and biochemical indices like C-reactive protein, procalcitonin, lactose dehydrogenase, aspartate aminotransferase, alanine aminotransferase, creatinine kinase, and creatinine levels significantly differed between the groups of severe and non-severe COVID-19 patients. Further, they also stated an increased likelihood of mortality and fewer chances of discharge in severe COVID-19 patients.[30, 31]

A cohort study by Li et al. found that those who died of COVID-19 were significantly older than the survivors. For both survivors and deceased, chest computerized tomography (CT) scores did not differ in the first period but subsequently diverged. COVID-19 mortality has been found to increase uniformly, with chest CT scores.[32] Zieleskiewicz et al. showed that lung ultrasound scores were also significantly associated with pneumonia severity assessed by chest CT and clinical features.[33] Patients' chest CT scans can distinguish between mild and severe COVID-19 progression.[34,35]

Regarding the correlation between prognosis and viral load of SARS-CoV-2, viral load was not noticeably associated with ICU admission, length of oxygen support, and overall survival. Also, the risk of viral shedding is higher in patients with fewer symptoms.[36]

Methods

Background and Target Population

This cross-sectional study was performed on COVID-19 patients in Shiraz from 2020 through 2021. Cochran's formula calculated a sample size of 385 cases, considering statistical significance when P=0.05. Anticipating some attrition in the follow-ups, we decided to recruit a minimum of 400 cases. In the present study, we studied patients diagnosed with COVID-19 by a positive polymerase chain reaction (PCR) test. Then, 401 people registered as COVID-19 positive in family clinics affiliated with Shiraz University of Medical Sciences (Enghelab and Valfajr Health Centers) were randomly chosen.

The Medical Ethics Committee of Shiraz University of Medical Sciences approved this study; therefore, we were granted permission to access the COVID-19 registry of Iranian Ministry of Health and Medical Education of for patient selection. We used the cluster random sampling method for choosing our cases, as it was impossible to study the whole population subgroup. A phone interview was conducted with each patient after they were selected. Before the interview, the nature and goals of the study were explained to the patients, and verbal consent

was obtained to begin the interview. Patients' early symptoms, such as fever, chills, sore throat, body aches, headache, dry cough, dyspnea, anosmia, loss of sense of taste, diarrhea, vomiting, and contact with an infected person, were also recorded. The severity and outcome of the disease were determined by indices such as indicators of death, hospitalization, and duration of hospitalization, and patients were asked to monitor the improvement, duration, and absence of clinical symptoms at two-week intervals from the onset of the disease. In the case of partial improvement, they were asked to inform us if any symptoms persisted in this interval of two weeks.

Inclusion and Exclusion Criteria

To be included in the study, patients needed to be registered in the COVID registry of the Ministry of Health and have only been diagnosed through PCR tests. Patients with incomplete information in the registry were excluded from the study.

Statistical Analysis

The statistical analysis was conducted using SPSS software for Windows version 25 (IBM Crop, Armonk, NY). A mean±standard deviation (SD) was used to describe quantitative data, whereas percentage and frequency were used to describe qualitative data. Also, the Chi-Square test was used to analyze and compare qualitative data. A statistical significance was considered when P=0.05.

Results

In the present study, the data of 401 patients with COVID-19 disease, whose positive results were confirmed by performing a PCR test, were recorded [214 males (53.36)]. Table 1 shows information about the age, sex, blood groups, signs, symptoms of participants, and the history of contact with COVID-19 patients. It is pertinent to mention that 55 patients had not mentioned their blood type and did not cooperate to have it checked. No significant association was established between having contact with a COVID-19-positive patient and recovery (220 patients) after 14 days, hospitalization, or death. Among the symptoms felt by the patients, body pain followed by fever were the most commonly recorded [190 (47.38%) and 187 (46.63%) patients, respectively]. In contrast, vomiting and diarrhea were the lowest recorded symptoms [18 (4.48%) and 39 (9.72%) patients, respectively]. Furthermore, 22 patients (5.48%) required hospitalization following infection, and only one death was reported (Table 1).

Symptomatic patients' symptoms were reported to be up to 60 days, with a mean of 11.58 days

Table 1: Demographic and clinical characteristics of participants

	Number (%)
Total	401 (100)
Sex	
Male	214 (53.36)
Female	187 (46.64)
History of contact with COVID-19* patients	
Yes	279 (69.57)
No	122 (30.43)
Blood groups	
O	124 (30.92)
A	108 (26.93)
B	69 (17.20)
AB	45 (11.22)
Total	346 (86.28)
Signs and symptoms	
Fever	187 (46.63)
Chills	174 (43.39)
Sore throat	136 (33.91)
Body pain	190 (47.38)
Headache	117 (29.17)
Cough	135 (33.66)
Shortness of breath	73 (18.20)
Anosmia	105 (26.18)
Loss of taste (ageusia)	68 (16.95)
Diarrhea	39 (9.72)
Vomiting	18 (4.48)
Disease result after 2 weeks follow up	
Hospitalization	22 (5.48)
Death	1(0.24)
Complete Recovery	325 (81)

*Coronavirus Disease 2019

(11.58±7.18). However, in hospitalized patients, the duration of hospitalization was reported to be at least two days and up to 40 days (mean: 0.41±2.70).

We observed a significant difference between different blood groups of patients with respect to their rate of hospitalization and recovery after two weeks, with a statistical significance of P<0.001. Also, the highest and lowest improvements after 14 days were observed in individuals with blood groups O (99 patients) and AB (37 patients), respectively. Additionally, a significant relationship was observed between blood groups and hospitalization rates, with the lowest and highest hospitalization rates belonging to blood groups AB (two patients) and A (seven patients), respectively (P<0.001). Examination of the initial symptoms and the outcome of the disease after two weeks from the onset of the disease (in terms of complete recovery, hospitalization, and death) showed a statistically significant relationship between fever and complete recoveryof those who recovered two weeks after the onset of the disease. 165 patients (50.76%) did not have a fever versus 160 patients who had a fever with a statistical significance of P=0.0310. Still, no significant association was observed between fever and hospitalization or death (P=0.100 and P=0.028). None of the other symptoms were significantly associated with complete recovery after two weeks.

Table 2: Signs and Symptoms of Disease and Prognosis after 2 Weeks in Patients with COVID-19*(Coronavirus Disease 2019)

Sign and Symptoms		Improvement		Admission		Death	
		Number(%)	P value	Number(%)	P value	Number(%)	P value
Total patients		**325**		**22**		**1**	
Fever	Yes	160 (49.23)	0.0310	14 (63.63)	0.100	1 (100)	0.284
	No	165 (50.76)		8 (36.36)		0 (0)	
Chills	Yes	148 (45.53)	0.0728	12 (54.54)	0.277	0 (0)	0.380
	No	177 (54.46)		10 (45.45)		1 (100)	
Sore throat	Yes	116 (35.69)	0.120	9 (40.90)	0.476	1 (100)	0.476
	No	209 (64.30)		13 (59.09)		0 (0)	
Pain Body	Yes	161(49.53)	0.0736	13 (59.09)	0.291	1 (100)	0.291
	No	164 (50.46)		9 (40.90)		0 (0)	
Headache	Yes	92 (28.30)	0.428	10 (45.45)	0.0840	0 (0)	0.520
	No	233 (71.69)		12 (54.54)		1 (100)	
Cough	Yes	108 (33.23)	0.703	11 (50)	0.094	0 (0)	0.475
	No	217 (66.76)		11 (50)		1(100)	
Shortness of breathing	Yes	57 (17.5)	0.474	12 (54.54)	< 0.001	0 (0)	0.629
	No	268 (76.5)		10 (45.45)		1 (100)	
Loss of smell	Yes	86 (26.46)	0.794	3 (13.63)	0.168	0 (0)	0.550
	No	239 (73.53)		19 (86.36)		1 (100)	
Loss of taste	Yes	53 (16.30)	0.473	2 (9.09)	0.312	0 (0)	0.650
	No	272 (83.69)		20 (90.90)		1 (100)	
Diarrhea	Yes	30 (9.2)	0.489	4 (18.18)	0.168	0 (0)	0.742
	No	295 (90.7)		18 (81.81)		1 (100)	
Vomiting	Yes	16 (2.76)	0.385	1 (4.54)	1	0 (0)	0.828
	No	309 (95.07)		21 (95.45)		1 (100)	

*Chi-Square Tests

Table 3: Underlying Conditions and Prognosis of Patients after 2 Weeks in Patients with COVID-19*(Coronavirus disease 2019)

Underlying Risk Factors		Death N (P value)		Admission N (P value)		Improvement (P value)	
		Number (%)	P value	Number (%)	P value	Number (%)	P value
Total patients		1		22		325	
Diabetes	Yes	0 (0)	0.745	4 (18.18)	0.151	34 (10.46)	0.163
	No	1 (100)		18 (81.81)		291 (89.53)	
Hypertension	Yes	1 (100)	0.010	6 (27.27)	0.042	44 (13.53)	0.693
	No	0 (0)		16 (72.72)		281 (86.46)	
Malignancy	Yes	0 (0)	0.920	0 (0)	0.627	4 (1.23)	0.33
	No	1 (100)		22 (100)		321 (98.76)	
Underlying Lung disease	Yes	0 (0)	0.837	4 (18.18)	0.0004	11 (3.38)	0.200
	No	1 (100)		18 (81.81)		314 (96.61)	
Pregnancy	Yes	0 (0)	0.902	0 (0)	0.551	5 (1.53)	0.884
	No	1 (100)		22 (100)		320 (98.46)	
Age over 60	Yes	1 (100)	0.002	8 (36.36)	<0.001	31 (9.53)	0.546
	No	0 (0)		14 (63.63)		294 (90.46)	

*Chi-Square Tests

Dyspnea was directly related to the hospitalization rate). Of those admitted to COVID-19, 12 (54.54%) patients had shortness of breath with a statistical significance of P<0.001, but no association was observed between dyspnea and death (P=0.62) (Table 2).

Among the underlying diseases, diabetes was not found to be significantly associated with recovery after 14 days (P=0.163) or the rate of hospitalization (P=0.151) (Table 3).

Hypertension was significantly associated with hospitalization and death rates. Two weeks after the onset of COVID-19 disease, 16 (72.72%) patients with a history of hypertension were admitted (P=0.042), and one person with a history of hypertension died (P=0.01). Underlying lung diseases were significantly associated with hospitalization (P=0.0004), as 18 (81.81%) people with underlying lung diseases hospitalized during the two weeks after the onset of COVID-19 disease. Also, age over 60 years had a direct relationship with hospitalization and death following COVID-19 infection (P<0.001 and P=0.002, respectively). Further, suffering from a malignant disease did not increase the chances of hospitalization (P=0.627). All risk factors had a significant relationship with the rate of hospitalization (P<0.001), except for malignancies, which had no significant relationship with the recovery time after 14 days or the rate of hospitalization (P=0.126). Moreover, in the hospitalized patients, age over 60 years was directly related to the duration of symptoms and the rate and duration of hospital stay (P<0.001). There was also a significant relationship between age over 60 years and mortality rate and hospitalization (P<0.0026 and P<0.001, respectively). Of those over 60, who devel. But no significant relationship was observed with recovery after 14 days (P=0.546) (Table 3).

Discussion

The World Health Organization (WHO) has emphasized that one of the most important questions to address regarding the COVID-19 pandemic is understanding the disease severity risk factors. In line with this pursuit, the current study aimed to find risk factors that could predict the severity of COVID-19 infection. The blood group had a significant relationship with recovery and hospitalization among the evaluated risk factors. Also, age over 60 is related to mortality, symptom duration, and hospitalization. Body pain and fever were the most commonly reported symptoms, but only shortness of breath increased the risk of hospitalization. Fever was related to an improvement rate after two weeks. In other words, the number of recovered patients who did not have a fever was higher. Hypertension and pulmonary disease increase the chance of hospitalization.

The results of the present study suggested no positive relation between diabetes mellitus, one of the most prevalent comorbidities of SARS-CoV-19, and the rate of hospitalization or recovery rate after 14 days of testing positive. But a meta-analysis conducted by Wu et al. revealed a significant association between DM and COVID-19 severity. Their study also showed that COVID-19-positive diabetic patients had a 2.95-fold higher risk of fatality than those without DM.[37] This finding can be r justified by the prompt diagnosis and management of patients with DM and COVID-19 due to the previous concerns and alarms raised by experts or by the small sample size of the current study.

Further, hypertension and underlying lung diseases, both common comorbidities of COVID-19, were significantly associated with disease severity and hospitalization and death rates in the current study. In congruence with our results, Fang et al. also established a positive relationship between hypertension and underlying lung diseases and disease severity.[12] However, Williamson et al. found that people with hypertension are less likely to die in people who are 70 or older.[13]

Additionally, the Chinese Center for Disease Control and Prevention reported cardiovascular disease, hypertension, diabetes, and respiratory disease as associated with an increased mortality risk.[36] Moreover, a UK cross-sectional survey involving 16,749 COVID-19 hospitalized patients showed a higher risk of death for patients with pulmonary disease and malignancy.[38] Among the symptoms felt by the patients in the current study, body pain, followed by fever, was the highest recorded symptom, whereas vomiting and diarrhea were the lowest. In contrast with our findings, both Lim et al.[39] and Cheng et al.[40] reported fever as the most frequently recorded symptom patients felt upon admission.

A notable finding of the present study was the high rates of improvement observed in the type O blood group. Patients with the type AB blood group had longer symptoms, but their hospitalization rate was low. The risk of hospitalization was the highest among patients with the A blood group. Similar to our finding, Zietz et al. found non-O blood types slightly more predisposed to infection.[41] Significant studies add to evidence that people with type O or Rh− negative blood may be at slightly lower risk from the new coronavirus. Among 225,556 Canadians tested for the virus, the risk of COVID-19 diagnosis was 12% lower, and the risk for severe COVID-19 or death was 13% lower in people with blood group O versus those with A, AB, or B. People with Rh-negative blood from any blood group were also somewhat protected, particularly if they had O-negative blood.[42, 43]

The findings in the current study are also affected by several limitations. First, our study sample was comprised of a low number of participants. Second, some participants showed reluctance towards filling in the questionnaire details. Third data regarding people

who died of COVID-19 were inaccessible.

It can be inferred that comorbidities such as hypertension and underlying lung diseases are associated with increased risk of severe illness and death among COVID-19 patients. The results suggest that hypertension might be the most consistent comorbidity predicting disease severity, so future research should carefully consider the comparability of reporting cases, factors, and outcomes along the different stages of the natural history of COVID-19. This cross-sectional study showed that comorbidities significantly related to the severity and mortality rate of COVID-19.

Conclusion

In the current study, we highlighted signs and symptoms such as body pain, fever, older age, and comorbidities which showed strong epidemiological evidence of associations with the severity and prognosis of COVID-19. The absence of fever in patients with COVID-19 infection positively predicts recovery. Shortness of breath in COVID-19 infection is a risk factor for hospitalization and exacerbation of the disease. People with a history of hypertension and underlying lung disease were more likely to be hospitalized and experience more severe disease than those who did not. Furthermore, age over 60 is a risk factor for hospitalization and exacerbation of the disease. Our results add to the growing body of evidence suggesting blood type may play a role in COVID-19. People with blood type O are more likely to recover after two weeks than other blood types, and these people experience a milder COVID-19 disease. On the other hand, people with blood group A are more likely to be hospitalized and to experience more severe diseases than people with other blood group types. Further, well-designed prospective cohort studies and randomized controlled trials are warranted to explore the severity and prognosis of risk factors for COVID-19.

Limitations

We were unable to follow the patients for more than two weeks. Also, we could not involve all patients with COVID-19 in this study.

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Availability of Data and Materials

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' Contribution

Parisa Jooya: contributed to the conception and design of the research, wrote the proposal, collected and analyzed the data, wrote the article, and approved the final version. Neda Pouralimohamadi: contributed to the conception and design of the research, wrote the proposal, collected and analyzed the data, wrote the article, and approved the final version. Bisma Zulfiqar: wrote the proposal, analyzed the data, wrote the article, and approved the final version. Melika Arzhangzadeh: wrote the proposal, analyzed the data, wrote the article, and approved the final version. Seyed Amirhossein Shamszadeh: contributed to the conception and design of the research, data collection, and article writing and approved the final version. Behdad Tahayori: contributed to the conception and design of the research, wrote the proposal, collected the data, wrote the article, and approved the final version. All authors contributed to the article's review and editing, and they all approved the final version.

Ethics Approval and Consent to Participate

This study conforms to the Declaration of Helsinki regarding research involving human subjects and is approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (IR.SUMS.MED.REC.1399.482). All participants signed the written informed consents form.

Conflict of interest: None declared.

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