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Original Article

Coronavirus Disease in Cardiovascular Patients: Clinical Characteristics and Final Prognosis

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Abstract

Background: Being infected with COVID-19 is a multifaceted syndrome that should be managed in the context of concurrent comorbidities. This study aimed to decipher the influence of cardiovascular diseases (CVDs) in the COVID-19 progression and its outcome.

Methods: From a cohort of 184 consecutive CVD patients diagnosed with COVID-19, 86 and 98 cases were placed in the non-severe and severe groups. The clinical, laboratory, and outcome data were compared between two divisions. A logistic regression model was further applied to determine parameters associated with disease severity and outcomes.

Results: Patients in the severe group had significantly a higher mean age and *body mass index (BMI)*. Of laboratory parameters, neutrophil/lymphocyte (N/L) ratio, *blood urea nitrogen*, serum creatinine, troponin I, and creatine kinase-myocardial band increased significantly in the severe group. Heart failure (HF) was the only CVD type that was associated with disease severity and outcome. The overall mortality rate among CVD patients was 24.5%, and patients with age over 75, dyspnea, and lower O_2 saturation at the admission time were at risk of an increased chance of death.

Conclusion: The mortality rate of COVID patients with underlying CVDs is high, and identifying the factors associated with disease progression is of great value. Obesity and advanced age put cardiovascular patients at the stake of severe disease and poorer outcomes. Dyspnea and hypoxia at the admission time, as well as the N/L ratio, were associated with disease severity and outcome, and chances are that they can be used as suitable predictors for recognizing those who need intensive management care.

Keywords: COVID-19, Cardiovascular disease, Heart failure, Coronary artery disease, Hypertension

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Introduction

First emerging in Wuhan, China, coronavirus – an enveloped, positive single-stranded RNA virus – progressively distributed all over the world and soon outlined a global pandemic, pronouncing drastic hazard to public health (1,2). Since then, (2021.07.20), 191 733 410 confirmed cases have been officially reported in more than 200 countries, along with 4 113 054 deaths. Most COVID-19 patients have mild illness and gradually recover after two weeks, but about 15%-20% of patients developing severe clinical course are facing deadly complications such as acute respiratory distress syndrome, acute kidney injury, shock, and acute cardiac injury (3). As the pandemic unfolds, the importance of identifying the relationship between underlying medical conditions and disease progression becomes more highlighted. One of the most challenging areas is that of cardiovascular disease (CVD) in which not only infection could directly affect the cardiovascular system but already-existing CVDs might make individuals

susceptible to the COVID-19 infection and an elevated risk for adverse outcomes as well (1,2, 4). In fact, a mutual interaction has been proposed between the cardiovascular system and COVID-19, albeit underlying mechanisms are not recognized exactly (5). The higher prevalence of cardiovascular risk factors has been frequently reported in patients with more severe manifestations of COVID-19 (5-7), but whether the pre-existing CVD is independently associated with poor outcomes is not truly defined yet. The more comprehensive perception we gain of the role of underlying CVD in the progression of COVID-19, the more effective therapeutic strategies can be applied, resulting in achieving better outcomes. The present article sought to discuss the clinical characteristics and laboratory markers of CVD patients suffering from COVID-19 and unveil the parameters influencing the severity of illness and outcome so as to expand the current knowledge in this special category of patients.

Materials and Methods

Study Population

The medical records of 468 consecutive adult patients (aged > 18), suspected of COVID-19 infection, admitted to the Farshchian Heart Center, Hamadan, Iran between 2020 and 2021 were assessed retrogradely. Overall, 212 patients with laboratory-confirmed COVID-19 and a medical history of CVD were enrolled in the study. Patients suffering from systemic diseases, immune deficiency, severe liver or kidney dysfunction, as well as those with incomplete medical data records, were excluded, leaving the 184 eligible patients in the final analysis. It should be noted the patients with a history of *coronary artery bypass grafting* and percutaneous coronary intervention remained in the study. Patients with CVD had formerly been diagnosed with hypertension (HTN), coronary heart disease (CHD), or heart failure (HF). The diagnosis and management of HTN and HF were based on the relevant guidelines (8,9). Patients with CHD had a history of previous infarction or at least 1 epicardial main vessel stenosis of > 50% on either coronary angiography or coronary computed tomography (CT) (10). COVID-19 cases were laboratory-confirmed by a positive result to the real-time reverse-transcriptase polymerase-chain-reaction assay of nasal and pharyngeal swab specimens. The medical data consisted of demographic and clinical characteristics, drug history, calculated body mass index (BMI), and resting fingertip oxygen saturation (O_{2sat}). In addition, laboratory test results included complete blood count, specific markers of myocardial injury (creatine kinase-myocardial band [CK-MB] and troponin I), aspartate aminotransferase (AST), and lactate dehydrogenase, prothrombin time (PT). The other laboratory test results were activated partial thromboplastin time, blood sugar, blood lipid profiles, and liver and kidney function tests.

Clinical Classification

Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia released by the Iran Health Ministry was applied for the classification of patients (11). Accordingly, mild cases had mild symptoms without abnormalities on imaging. Moderate ones had respiratory infection symptoms, along with pneumonia manifestations on imaging. Severe cases had respiratory rate ≥ 30 breaths/min, resting fingertip $O_{2sat} \leq 93\%$, or oxygen partial pressure (PaO_2)/fraction of inspired O_2 (FiO_2) ≤ 300 mm Hg. Critical cases had respiratory failure requiring mechanical ventilation, multiple organ dysfunction or symptoms of shock, or a need for intensive care. In this study, patients were divided into the non-severe (mild and moderate ones) and severe (severe and critical cases) groups.

Patient Outcomes

There were two outcomes of interest. The first one was the cure, namely, when the patient showed the disappearance of clinical symptoms or significant improvements in lung CT images. The second outcome was considered death, including all deaths causes in the hospital.

Data Collection

All the patients' data comprising clinical, laboratory, and outcomes were collected from electronic medical records by an experienced member of the team.

Statistical Analysis

Normally distributed data were reported in the form of the arithmetic mean and standard deviation, while the median with range (minimum and maximum or percentile range) was utilized for not normally distributed data. Categorical variables were summarized by raw frequencies and percentages. The potential association between categorical and numerical variables with illness severity and outcome was assessed by applying the chi-square test and independent *t* test. Moreover, a multiple binary logistic regression model was further practiced for a more complete investigation of factors linked to disease severity and final prognosis. The statistical significance of the factors was expressed as odds ratios (ORs) with 95% confidence intervals (CIs). All statistical analyses were performed using SPSS 18.0 software (IBM, Chicago, IL, USA), and a $P < 0.05$ was considered to address statistical significance.

Results

Baseline Characteristics

The demographic and clinical characteristics of the 184 patients are provided in Table 1. The patients had a mean age of 67.12 ± 13.38 years ranging from 30 to 98 years with a mal-to-female ratio of 100: 84. There were 86 (46.7%) and 98 (53.3 %) patients in the non-severe and severe groups, respectively. The mean ages of the cases in non-severe and severe COVID-19 subgroups were 64.8 ± 13.01 (33.00-94.00) and 69.18 ± 13.44 (30.00-98.00) years, respectively ($P = 0.03$). The mean BMI of patients in the severe group

Table 1. Clinical Characteristics of Patients at Admission, Treatment, and Clinical Outcomes

	All	Non-severe	Severe	*P* Value
Age (y), mean (range)	67.12 (30-98)	64.80 (33.00-94.00)	69.18 (30.00-98.00)	0.03
Gender, No. (%)				
Female	84	35 (40.7)	49 (50)	0.21
Male	100	51 (59.3)	49 (50)	
BMI (kg/m^2), mean	24.99±2.97	23.09±2.5	26.66±2.28	<0.001
Onset to admission (day), median (range)	9.00 (5.00-13.00)	9.00 (5.50-12.00)	10.00 (7.00-13.00)	0.35
Signs and symptoms, No. (%)				
Fever	36 (19.56)	17 (47.2)	19 (52.8)	0.91
Cough	85 (46.19)	36 (42.35)	49 (57.64)	0.19
Dyspnea	139 (75.54)	59 (42.4)	80 (57.6)	0.05
Fatigue	48 (26.08)	18 (37.5)	30 (62.5)	0.14
Diarrhea	9 (4.89)	3 (33.3)	6 (66.7)	0.41
Chest pain	78 (42.39)	36 (46.2)	42 (53.8)	0.94
Chill	40 (21.73)	20 (50.0)	20 (50.0)	0.61
Coexisting disorders, No. (%)				
Diabetes	55 (29.89)	20 (24.7)	35 (36.1)	0. 10
CAD	109 (58.7)	53 (61.6)	56 (57.1)	0. 54
HTN	110 (59.78)	50 (58.1)	60 (61.2)	0.67
HF	81 (44)	30 (34.9)	51 (52.0)	0.02
AF	10 (5.4)	5 (5.8)	5 (5.1)	0.83
Oxygen therapy at admission, No. (%)				
Non-invasive	137 (74.5)	72 (83.7)	65 (66.3)	0.007
Invasive	47 (25.5)	14 (16.3)	33 (33.7)	
Complications, No. (%)				
Respiratory failure	20 (44.4)	6 (60)	14 (41.2)	0.39
Heart failure	16 (35.5)	4 (40)	12 (35.3)	
Myocardial infarction	7 (15.55)	0 (0)	7 (20.6)	
Others	2 (4.4)	0 (0)	2 (2.9)	
Death, No. (%)	45 (24.5)	10 (22.22)	35 (77.77)	

Note. BMI: Body mass index; CAD: Coronary artery disease; HF: Heart failure; AF: Atrial fibrillation; HTN, Hypertension.

was significantly higher than that of patients in the non-severe group (26.66 vs. 23.09 kg/m^2, $P<0.001$). The median time between the onset of symptoms and hospital admission was 9.00 days (5.00-13.00) for all patients, and the pre-hospital delays for patients in the severe and non-severe groups were 10.00 (7.00-13.00) and 9.00 (5.50-12.00) days, respectively ($P=0.35$). Upon arrival at the hospital, 137 (74.5%) patients received oxygen with non-invasive methods, of which 14 patients (10.22%) required invasive therapy during the hospitalization period. Dyspnea (n=139, 75.54.%) and cough (n=85, 46.19%) were the most common symptoms at the onset of illness for all patients, followed by chest pain (n=78, 42.39%) and fatigue (n=48, 26.08%). HTN (59.78 %) and *ischemic heart disease* (IHD, 58.7%) were the common coexisting CVDs in COVID-19 patients. Although the frequency of *congestive HF* (CHF) was significantly higher in the severe group compared to the non-severe group (52% vs. 34.9%, $P=0.02$), no significant difference was found between the groups regarding HTN (61.2% vs. 58.1% $P=0.67$) and CHD (61.6% vs. 57.1 % $P=0.54$). Similarly, the prevalence of coexisting diabetes and atrial fibrillation (AF) did not differ significantly in both groups (24.7% vs. 36.1% $P=0.1$ and 5.1% vs. 5.8% $P=0.83$), respectively. Finally, 45 (24.5%) patients passed away, and the mortality rate of patients with severe disease (35.7%) was significantly higher ($P<0.001$) than that of non-severe patients (11.6%). The most common cause of death was respiratory failure (44.4%). The other causes of death included HF (35.55%), acute myocardial infarction (15.55%), and the like (4.40%). There was no significant difference in the proportion of patients taking angiotensin-converting enzyme (ACE) inhibitor/(ARB) between the non-severe and severe groups ($P=0.49$), as well as the deceased and cured patients ($P=0.23$). The laboratory parameters of the patient study are summarized in Table 2. Although the mean white blood cell counts on admission was within normal limits in both groups (8.49×103 vs. 9.80×103), the

Table 2. Laboratory Findings of Patients at Admission

	All	Non–severe	Severe	*P* Value
White blood cell count (4-10 × 10^3/mL), mean (Range)	9.19 ± 4.58 (2-37)	8.49 (4.54-12.44)	9.80 (4.80-14.80)	0.14
Neutrophil/lymphocyte ratio		4.02 (2.35-7.80)	10.02 (7.89-19.85)	<0.001
Blood urea nitrogen (5-25 mmol/L)	28.6 ± 18.01 (9-106)	25.21 ± 15.68	31.53 ± 20.14	0.02
Creatinine (0.8-1.3 µmol/L)	1.27 ± 0.65 (0.4-4.1)	1.12 ± 0.52	1.39 ± 0.72	0.005
Troponin I (0-19 pg/mL)	14.74 ± 5.67	11 ± 3.50	19 ± 7.40	<0.001
Lactate dehydrogenase (140-280 U/L)	634.4 ± 305.66 (239-1432)	574.11 ± 264.86	701.92 ± 338.39	0.13
Total cholesterol (0-200 mmol/L)	127.1 ± 34.05 (46-272)	128.03 ± 34.55	126.29 ± 33.79	0.73
Triglycerides (0-150 mmol/L)	112.85 ± 45.88 (50-324)	117.81 ± 55.38	108.49 ± 3524.	0.17
Low-density lipoprotein cholesterol (30-200 mmol/L)	74.63 ± 27.86 (29-201)	75.12 ± 26.84	74.19 ± 28.86	0.82
High-density lipoprotein cholesterol (>60)	30.47 ± 8.44 (6-64)	31.13 ± 8.42	29.89 ± 8.45	0.32
Prothrombin time (12.5-13.5 s)	16.09 ± 4.66 (12-36)	16.15 ± 4.77	16.05 ± 4.59	0.89
Activated partial thromboplastin time (24-40 s)	33.31 ± 6.45 (22.2-57.5)	33.73 ± 6.89	32.92 ± 6.04	0.32
AST (U/L), median (0-45)	43.5 (30-2602)	45	43	0.46
CK-MB (U/L, 0-25)	13.41 ± 7.40	6.75 ± 2.5	21.30 ± 10.5	<0.001
Blood sugar (75-115)	151.97 ± 99.59 (57-679)	136.10 ± 78.75	165.89 ± 113.39	0.04

Note. ATS: Aspartate aminotransferase; CK-MB: Creatine kinase-myocardial band.

neutrophil/lymphocyte ratio was found to be significantly higher in the severe group than that in the non-severe one (10.02 vs. 4.02, $P<0.001$). In terms of myocardial injury markers, CK-MB and troponin I were higher in the severe group compared to non-severe group one (21.30 vs. 6.75, $P<0.001$; and 19.00 vs. 11.00, $P<0.001$, respectively). In the patients of the severe group, blood urea nitrogen, creatinine, and blood sugar were significantly higher compared to the patients of the non-severe group (31.53 vs. 25.21, $P=0.02$; 1.39 vs. 1.12, $P=0.005$; and 165.89 vs. 136.10, $P=0.04$), respectively. However, no statistical difference was found between the two groups in terms of AST (45 vs. 43, $P=0.46$), total cholesterol (126.29 vs. 128.03, $P=0.73$), triglycerides (108.00 vs. 117.81, $P=0.17$), low-density lipoprotein cholesterol (73.76 vs. 75.12, $P=0.75$), high-density lipoprotein cholesterol (29.89 vs. 31.13, $P=0.32$), and PT (16.05 vs. 16.15, $P=0.89$). Possible parameters related to the outcome of COVID-19 patients with underlying CVD were investigated as well. There was no significant difference in the proportion of patients with HTN, IHD, and AF between deceased and cured patients ($P=0.75$, $P=0.82$, and $P=0.74$, respectively); however, the proportion of patients with CHF was significantly higher ($P=0.005$) in deceased ones. Additionally, the severe group owned a significantly higher proportion of deceased patients than the non-severe group (35 cases [77.8%] vs. 10 cases [22.2%], $P<0.001$). In patients who finally died, the level of O_{2sat} at admission time was significantly lower compared to the cured patients (77.48 vs. 87.38, $P<0.001$). Regarding the medication history of ACEI/(ARB) in patients with CVD, no significant difference was found for outcomes between patients with severe and non-severe manifestations ($P=0.23$). It was also revealed that obese patients were far more likely to pass away ($P=0.004$). In addition, the logistical regression was applied to have a more comprehensive investigation of the potential factors related to the outcome (Table 3). Variables presented in Table 3, probably being clinically relevant or showing a univariate relationship with the prognosis, were put into the multivariate logistic regression model. In the category of CVD patients infected with the corona virus, those over 75 years of age (Odds ratio [OR]: 2.82, 95% CI: 1.19-6.68) or dyspnea at the admission time (OR: 0.29, 95% CI: 0.11-0.76) or lower O_{2sat} (OR: 0.94, 95% CI: 0.91-0.96) were at the stake of an increased chance of death.

Discussion

Farshchian Hospital is a tertiary center for CVD; therefore, it is completely rational that a considerable number of admitted patients with COVID-19 have a medical history of cardiovascular comorbidities, including CVD. COVID has been found to be a multisystemic condition in which the cardiovascular system is engrossed seriously (12,13). Not only has COVID-19 frequent cardiac expressions but a poorer prognosis is reported for COVID-19 patients suffering from CVD compared to those with COVID-19 alone (1,2,13). In the present study, while investigating COVID-19 patients with underlying CVD, we witnessed that the patients with HF were more prone to severe presentations and worse outcomes. It may be related to the known trigger role of viruses in cardiac decompensation (14), impaired cardiopulmonary reserve, and poorer baseline characteristics in CHF patients (12,13). Additionally, discontinuing the medications prescribed for HF during the treatment course of COVID can notably deteriorate cardiac performance (12,13). The most prevalent cause of death was respiratory failure. Although viral pneumonia seems to be the main leading cause of respiratory failure, the influence of impaired cardiac function is not deniable in this subcategory of patients. The importance of the renin-angiotensin system in the pathophysiology of HTN is truly defined. *Angiotensin-*

Table 3. Multiple Binary Logistic Regression Analysis of Factors Associated With Illness Severity and Final Outcome of CVD Patients Suffering From COVID-19

Variables	Illness-Severity (Severe vs. Non-severe)			Final Outcome (Cure vs. Death)		
	OR	95% CI		OR	95% CI	
Gender (Male vs. Female)	1.55	0.44	5.45	0.68	0.30	1.56
BMI (kg/m^2)	2.10	1.62	2.73	1.09	0.99	1.19
History of CHF (Yes vs. No)	2.59	0.70	9.61	2.91	1.19	7.13
History of HTN (Yes vs. No)	1.43	0.40	5.16	0.89	0.36	2.21
History of IHD (Yes vs. No)	2.25	0.64	7.91	2.03	0.83	4.99
History of dyspnea (Positive vs. Negative)	4.80	1.12	20.68	0.29	0.11	0.76
History of diabetics (Yes vs. No)	0.52	0.11	2.52	0.72	0.26	2.00
Age (≥75 vs. <75)	3.32	0.88	12.51	2.82	1.19	6.68
Creatinine (≥1.1 vs. <1.1)	1.21	0.35	4.12	1.16	0.48	2.80
WBC	1.09	0.94	1.27	1.08	0.98	1.18
BS	1.00	1.00	1.01	1.00	1.00	1.00
O_{2sat}	0.77	0.70	0.84	0.94	0.91	0.96

Note. CVD: Cardiovascular disease; COVID-19: Coronavirus disease 19; OR: Odd ratio; CI: Confidence interval; BMI: Body mass index; CHF: *Congestive heart failure*; IHD: *Ischemic heart disease*; WBC: White blood cell; BS: Blood sugar; O_{2sat}: Oxygen saturation; HTN: Hypertension.

converting enzyme 2 (ACE2) binding the spike proteins of the severe acute respiratory syndrome coronavirus 2 acts as a functional receptor for coronavirus-induced infection both in the lung and heart (15). Based on the findings of previous research indicating that patients with HTN are more susceptible to infection with COVID-19 compared to non-hypertensive patients (16-18), the main reason can be the greater amount of ACE2 secretion in hypertensive cases (19,20). No definite relation has been precisely determined yet between ACEI/ARB and COVID-19 progressions, but in our study, in the group of patients taking ACEI/ARB, no significant difference was found regarding the severity of illness and outcome, indicating that ACEI/ARB did not affect coronavirus progression. According to other studies, patients with a higher BMI had more severe illnesses and worse outcomes (21,22). The exact clarification of underlying mechanisms needs more effort, but it is found that obese patients are vulnerable to infectious disease due to the weakness of the innate and adaptive immune responses (23,24). The laboratory findings of a higher neutrophil/lymphocyte ratio in the severe group relative to the non-severe group put an emphasis on the consumption of a large number of CD4 + and CD8 + T lymphocytes (1,3,22,25), thus it can be applied as a predictive marker of illness severity. At present, contradicting data regarding the effects COVID-19 might have on the myocardial tissue (26), but a significantly high level of the specific markers of myocardial injury, troponin I, and CK-MB, in the severe group of the study, is in favor of myocyte damage rather than the pure inflammatory infiltration of mononuclear cells in the intercellular stroma (27). Although, in some studies, the mortality rate of patients with coronary artery disease (CAD) was higher than those without it (28,29), this significance was not found in our study population, except in the category of patients with concurrent CAD and HF whose HF may be a consequence of coronary artery involvement. It is also known that myocardial injury caused by COVID-19 by itself is a crucial parameter that significantly worsens the patient's illness and outcome, and better prognosis has been reported in patients with underlying CAD but without myocardial injury compared to patients whose myocardium is injured by COVID-19 viruses (30,31). The second cause of death in the study populations was myocardial infarction. In addition to the given role of produced cytokines during the systemic inflammatory process which can make atherosclerotic plaque vulnerable to instability (32,33) and rupture, coronary artery vasoconstriction secondary to hypoxia should be taken into account as a potential mechanism leading to acute myocardial infarction in COVID-19 patients (34,35). When it came to the biomarkers of renal function, a clear relationship was observed between serum *creatinine* and the severity of the illness, as well as the outcome ($P = 0.005$ and $P < 0.001$). Considering that patients with known renal disease had been excluded from the study, the occurrence of direct interaction between COVID-19 and the kidney seems to be more justifiable. Although the exact mechanism of kidney damage caused by COVID-19 has not yet been proved, different mechanisms such as tubular damage, collapsing glomerular disease, specific immune effect, hypoxemia, and side effects of antiviral treatment have been postulated by previous investigations (36-38). The results of our study regarding the mortality rate are in line with those of other similar studies (13,16,22). According to the logistic regression model results, aging and decreased blood oxygen level, as well as dyspnea at the admission time, are also associated with death and thus can be applied as warning signs, indicating a poorer outcome in COVID-infected patients suffering from CVD.

Limitations of the Study

The first limitation of our study was a relatively small number of included cases which made some difficulties in discovering the precise risk factors associated with the severity of the illness and the outcome. We only focused on the onset of the disease and the outcome, but the patients were not actively chased during hospitalization; therefore, the research suffers from the lack of valuable information which might have affected the interpretation of influential parameters in the disease course and the outcome.

Conclusion

Despite exemplary successes achieved in discovering the unknowns of coronavirus, much remains to be performed to identify the precise interactions between the vinous and different organs. Available evidence indicates that sophistication is even much more in the subcategory of COVID-19 patients with underlying CVD. Obesity and advanced age were associated with more severe disease and poorer outcomes. The presence of dyspnea and hypoxia at the admission time, as well as the neutrophil/lymphocyte ratio, can be used as practical indicators for finding patients who require more intensive medical care.

Authors' Contribution

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Competing Interests

The authors declare that they have no conflict of interests.

Ethical Approval

This protocol retrospective study was designed at the Farshchian Heart Center and approved by the Ethics Committee of Hamadan University of Medical Sciences, Hamadan, Iran (Project No. 9902301166).

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