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Evaluation of Relationship Between Risk Factors of Cardiovascular Disease and Morbidity and Mortality of COVID-19 Patients

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Abstract

Background: The coronavirus disease 2019 (COVID-19) global pandemic is a life-threatening condition with high morbidity and mortality rate in Iran. Based on several studies, COVID-19 clinical outcomes are associated with co-morbidities, such as Cardiovascular Diseases (CVD). It appears that there is a relationship between the COVID-19 prognosis and the existence of CVD-related risk factors, for instance hypertension, obesity, diabetes, *etc.*

Methods: A descriptive-analytical cross-sectional study was designed to investigate the relationship between CVD risk factors and COVID-19 with a total of 100 participants in Imam Khomeini hospital, Tehran, Iran. A checklist of anthropometric and prognostic information was filled for each patient and finally the data were analyzed.

Results: There was a statistically significant dependence between hospitalization in ICU, reservoir bag-mask, intubation, life-threatening complications, and the final outcome ($p<0.01$). However, there was no significant correlation between CVD risk factors and prognostic parameters like length of Intensive Care Unit (ICU) hospitalization, the requirement to reserve bag-mask oxygenation, *etc.*

Conclusion: In this investigation, no significant association was observed between CVD-related risk factors and COVID-19 prognosis among Iranian adult COVID-19 cases.

Keywords: Cardiovascular diseases, Coronavirus disease 2019, Morbidity

Introduction

Coronavirus disease 2019 (COVID-19) is a viral disease that is caused by Severe Acute Respiratory Syndrome-Coronavirus disease 2019 (SARS-COV2), and it has become a global pandemic. The first case of this disease occurred on 8 December 2019 in the Hubei province of China (1-3). Since then, within a short span of just over three months, the infection has spread to 177 countries/areas/territories across the world. Among the top-ranking countries, Iran was placed among countries with a high prevalence that caused high morbidity and mortality (4,5).

Primary reports suggest that the most common symptoms are fever and dry cough, which are common in many other viral syndromes. Other symptoms include myalgia, headache, weakness, and respiratory involvement. Complications of this virus are as follows: pneumonia, septicemia, Acute Respiratory Distress Syndrome (ARDS), Acute Kidney Injury (AKI), myocarditis, and Trumbo-emboli (6). The severity of the symptoms is linked to a series of co-morbidities in which Cardiovascular Disease (CVD) is the most important one that is a common co-morbidity in patients with COVID-19 predecessors SARS and Middle East Respiratory Syndrome (MERS). CVD was present in ~30% of these patients. The increased presence of cardiovascular co-morbidities holds true for COVID-19 as well, most notably among those with more severe diseases. It seems that the associated risk factors can affect the severity of symptoms (7,8). Older age, diabetes mellitus, hypertension, dyslipidemia, smoking, obesity, and history of myocardial infarction are the risk factors for CVD (9-11). Previous studies have shown that SARS can cause these complications and symptoms. During the SARS epidemic, as well as the MERS, it was observed that CVD is related to adverse outcome and poorer prognosis. In some studies, it was observed that obesity, diabetes and hypertension could increase the risk of people infected by COVID-19 (7,8,12,13). Since the early epicenter for this outbreak was China, the majority of information on patients with COVID-19 came from there. Although a systematic effort was made to include reports and viewpoints from other heavily affected countries, data related to CV risk factors or presentations are limited. Notably, whereas reports outside of China are limited, data from Italy suggest similar mortality rates and an elevated risk for death in patients with co-morbidities. As emerging international data become available, analysis from multinational cohorts can help inform risk stratification for the severe disease, especially for patients with prior CVD.

Although widely reported in the media that CVD risk factors increase the probability of severe COVID-19, some early reports found no association between CVD risk factors and disease severity. Therefore, this study was aimed to investigate the possible existence of a clinical interplay between CVD risk factors and COVID-19, investigating whether CVD patients infected by SARS-CoV-2 may be at particularly enhanced risk of worst clinical outcomes, and if so, the strength of such associations.

Materials and Methods

Study design

This descriptive-analytical study was conducted from April to June 2020 in Tehran Imam Khomeini hospital with the ethical code of IR.TUMS.VCR.REC.1399.355..In this study, 549 patients hospitalized with the initial diagnosis of COVID-19 were examined.

Subjects

Patients were included in the study if the symptoms, lungs CT scan (Computed Tomography Scan), and/or their Polymerase Chain Reaction (PCR) test were in favor of COVID-19. Written informed consent was taken from all the patients. Patients with any underlying non-cardiovascular disease, with both previous cardiovascular and non-cardiovascular disease and patients without the underlying disease. Also, patients who did not consent to enter the study or were discharged during hospitalization with personal consent were excluded from the study. Finally, 100 COVID-19 patients with a previous history of any cardiovascular disease including any coronary and systemic vascular disorders, myopathies, valvular heart disorders, and conduction disorders of the heart entered the study.

Data collection

The checklist, consisting of demographic and anthropometric information of patients such as age, gender and Body Mass Index (BMI) were completed. Morbidity of patient such as the length of

hospitalization of the patient in the hospital [divided in the ward or Intensive Care Unit (ICU)], the appropriate response to treatment based on SPO_2, and requirement to oxygenation with reserve bag-mask, requirement for intubation, life-threatening complication and death or discharge were registered, and data were entered into the checklist.

Statistical analysis

Finally, the obtained data were entered into SPSS 25 software, and the relationship between prognosis of COVID-19 patients in patients with a previous cardiovascular disease and risk factors of cardiovascular disease was evaluated and analyzed. At all statistical stages, a significance level of 0.05 was the criterion for statistical judgments.

Results

A total of 100 COVID-19 patients with a previous cardiovascular disease agreed to participate in the study. Thirty-four patients were adult females. A quarter of the patients were transferred to the intensive care unit. Sixty-four patients had needed the oxygen reservoir bag-mask. In 10% of the patients, intubation was performed. Thirty-eight patients experienced life-threatening complications during their hospitalization (Table 1). Eighty-five patients were elderly, and 20 patients were smokers. 55% of patients were hypertensive, 39% diabetes, and 38% dyslipidemia. Seventeen patients had a family history of heart disease, 12 patients had a history of Percutaneous Coronary Intervention (PCI) and six patients, a history of Coronary Artery Bypass Graft (CABG). The total mean age was 63.43 years. On average, each patient was hospitalized for 6.12 days. In patients transferred to the ICU, the mean length of hospital stay was 4.88 days (Table 1), the frequency of each qualitative variable was examined and their mean (standard deviation) was also calculated for quantitative variables shown in table 1.

The average age for deceased patients was 8.19 years older than discharged patients ($p<0.05$). The mean duration of hospitalization was higher in patients who died. There was no difference between the length of hospital stay in the ICU in the two groups (Table 2). In table 2, the variables of age, the total length of hospital stay, and length of hospital stay in the ICU were calculated as total frequency (standard deviation) based on the final prognosis (death or discharge). Also, their statistical relationship was examined using the chi-square test.

Tables 3 and 4 examine the relationship between the study variables and the outcome and considering that the final prognosis and the studied variables are binary variables, then the Chi-Square test was used. There was no statistically significant dependence between gender and the final outcome (standardized contingency coefficient=0.012, $p=0.902$). This indicates that the relationship is weak. There was a statistically significant dependence between hospitalization in ICU, reservoir bag-mask, intubation, life-threatening complications, and the final outcome ($p<0.01$). The contingency coefficient for comparison of these variables shows medium-to-high relationship for them. From life-threatening complications, ARDS, sepsis, AKI, and Deep Vein Thrombosis (DVT) had a statistically significant dependence on the final outcome ($p<0.01$).

Table 1. Summary of socio-demographic variables, anthropometric characteristics, and risk factors of patients participating in the study (n=100)

Variables		Frequency	Mean (SD)
Gender	Female	34	-
	Male	66	-
Hospitalization in ICU	No	75	-
	Yes	25	-
Reservoir bag- mask	No	36	-
	Yes	64	-

Intubation	No	90	-
	Yes	10	-
Life-threatening	No	52	-
	Yes	48	-
Type of life-threatening complicationwww	Pneumonia	1	-
	ARDS (Acute respiratory distress syndrome)	15	-
	Sepsis	7	-
	Acute kidney injury	10	-
	Deep veinthrombosis	4	-
	Seizure	2	-
	QT prolongation	3	-
	Myocardial infarction	1	-
	Heart failure	4	-
	Pyelonephritis	1	-
Elderly patient	No	15	-
	Yes	85	-
Smoker	No	80	-
	Yes	20	-
Hypertension	No	45	-
	Yes	55	-
Diabetes	No	61	-
	Yes	39	-
Dyslipidemia	No	62	-
	Yes	38	-
High BMI	No	60	-
	Yes	40	-
Family history	No	83	-
	Yes	17	-
PCI history	No	88	-
	Yes	12	-
CABG history	No	94	-
	Yes	6	-
Age		-	63.43(13.78)
Length of hospital stay		-	6.12(4.23)
Length of hospital stay in ICU		-	4.88(3.07)

Table 2. Comparison of the mean and standard deviation of age, LOS, and LOS in ICU

Variables	Final outcome		Mean difference	p-value*
	Discharge	Death		
Age (year)	62.04(13.61)**	70.24(12.93)	8.199	0.025
LOS1	5.71(3.95)	8.12(5.06)	2.407	0.032
LOS in ICU2	4.33(1.50)	5.19(3.69)	0.854	0.516
	Notes: * t-test, ** Mean (SD)			

1. Length of hospital stay.
2. Length of hospital stay in ICU.

Table 3. Association between socio-demographic variables and anthropometric characteristics with the final outcome

Variables		Final outcome		Contingency coefficient	Chi-Square test p-value
		Discharge	Death		
Gender	Female	28	6	0.012	0.902
	Male	55	11		
Hospitalization in ICU	No	74	1	0,586	<0.001
	Yes	9	16		
Reservoir bag-mask	No	36	0	0.321	0.001
	Yes	47	17		
Intubation	No	81	9	0.488	<0.001
	Yes	2	8		
Life-threatening complications	No	62	0	0.500	<0.001
	Yes	21	17		
Pneumonia	No	83	16	0.217	0.170
	Yes	0	1		
ARDS	No	76	9	0.376	<0.001
	Yes	7	8		
Sepsis	No	80	13	0.281	0.003
	Yes	3	4		
Acute kidney injury	No	78	12	0.281	0.003
	Yes	5	5		
Deep vein thrombosis	No	83	13	0.411	0.001
	Yes	0	4		
Seizure	No	82	16	0.125	0.209
	Yes	1	1		
Prolongation of QT interval	No	81	16	0.071	0.432
	Yes	2	1		
Myocardial infarction	No	83	16	0.217	0.170
	Yes	0	1		
Heart failure	No	80	16	0.043	0.531
	Yes	3	1		
Pyelonephritis	No	83	16	0.217	0.170
	Yes	0	1		

ARDS: Acute Respiratory Distress Syndrome.

Table 4. Association of risk factors of cardiovascular disease with the final outcome

Variables		Final outcome		Contingency coefficient	p-value
		Discharge	Death		
Elderly patient	No	15	0	0.187	0.068
	Yes	68	17		
Smoker	No	65	15	0.093	0.512
	Yes	18	2		
Hypertension	No	40	5	0.140	0.188
	Yes	43	12		
Diabetes	No	53	8	0.128	0.275
	Yes	30	9		
Dyslipidemia	No	50	12	0.080	0.585
	Yes	33	5		
High BMI	No	52	8	0.119	0.281
	Yes	31	9		
Family history	No	68	15	0.063	0.730
	Yes	15	2		
PCI history	No	73	15	0.003	>0.999
	Yes	10	2		
CABG history	No	78	16	0.002	>0.999
	Yes	5	1		

BMI: Body Mass Index; CABG: Coronary Artery Bypass Graft; Percutaneous Coronary Intervention.

Discussion

In our study, there was no statistically significant dependence between gender and final outcome (was noted in conclusion part). Although the mortality was more in elderly patients and patients with hypertension, there was no statistically significant dependence between other risk factors and the final outcome.

Some theories exist regarding the elevated risk of adverse events for patients with CVD who develop COVID-19. In particular, a better understanding of the relationships involving the Angiotensin-Converting Enzyme-2 (ACE-2) protein, anti-hypertensive agent use, and COVID-19 prognosis will have important implications for patients with both COVID-19 and CVD.

Early reports from China found that CVD and its risk factors, such as hypertension and diabetes mellitus, were common pre-existing conditions in patients with COVID-19. In an early report from Wuhan involving 41 patients who were hospitalized with COVID-19 by 2 January 2020, the prevalence of any co-morbidity was 32% and the most common underlying diseases were diabetes (20%), hypertension (15%), and other CVDs (15%) (14). The high prevalence of these co-morbidities was confirmed in subsequent studies (15-22).

In a single-center cohort study of 138 patients hospitalized with COVID-19 in Wuhan, 46% of the patients had any co-morbidity (72% of patients in the ICU), 31% of patients had hypertension (58% of patients in the ICU), 15% of the patients had other CVDs (25% of patients in the ICU) and 10% of the patients had diabetes (22% of patients in the ICU) (15). Also, regarding the association of obesity, in the case series study of COVID-19 patients in Shenzhen, Cai Q, *et al*, found that obesity, especially in men, significantly increased the risk of developing severe COVID-19. During the pandemic first two months, of 383 patients aged ≥18 years hospitalized with COVID-19 in Shenzhen, the prevalence of overweight (BMI 24-28 kg/m^2) and obese (BMI ≥28 kg/m^2) patients was respectively 32% and 10.7%. In comparison with patients with normal weight, patients who were obese were at increased odds of progressing to severe disease (7).

It is reasonable that the obesity might raise the risk of severe COVID-19, as previous studies have revealed that excessive weight gain might increase the risk of developing community-acquired pneumonia (23,24)

and may hinder lung function. Obese patients assign a unreasonably high ratio of total body oxygen consumption to the respiratory work, leading to a decline in functional residual capacity and expiratory volume (25,26). A following ventilation-perfusion abnormality can decrease ventilatory reserve and predispose the obese to respiratory failure after even mild pulmonary challenges (27,28). Furthermore, individuals with obesity are at increased risk of developing pulmonary emboli and aspiration pneumonia (29) and may develop a sustained rise in the arterial carbon dioxide tension owing to chronic daytime-hypoventilation. Patients with obesity were more expected to need an intensive care unit for acute lung injury and to have continued mechanical ventilation and hospital stay when compared with normal-weight patients. Besides the detrimental effects on lung function, obesity is a confirmed cause of diabetes and cardiovascular disease, leading to higher overall mortality (28,30).

In another study conducted on the relationship between high blood pressure and COVID-19, Lippi G *et al* observed that hypertension carries a nearly 2.5-fold higher risk of developing severe disease or dying from SARS-CoV-2 infection. Although this association seems weaker than that reported earlier for other co-morbidities, such as chronic obstructive pulmonary disease (COPD; over 5-fold higher risk) or chronic kidney disease (CKD; over 3-fold higher risk), it still carries important clinical implications (12).

As previously discussed, SARS-CoV-2 enters the cells by binding ACE2. Some interesting studies have previously shown that administration of some anti-hypertensive drugs such as ACE inhibitors (ACEis) (31) and Angiotensin Receptor Blockers (ARBs) (32) may be associated with enhanced ACE2 expression at the cell surface, thus ultimately supplying SARS-CoV-2 with a larger number of "anchors" for infecting cells. While this is still the matter of contentious debate, it cannot be excluded that some hypertensive patients undergoing Renin-Angiotensin-Aldosterone System (RAAS) inhibition, especially those taking ACEis, might be more susceptible to SARS-CoV-2 infection, which would finally translate into a higher risk of developing local (*i.e.*, ARDS) or systemic (*i.e.*, SIRS/MOF) adverse COVID-19 consequences (33). On the other hand, others have claimed that hypertensive patients may experience a decreased ACE2 expression, which attenuates residual ACE2 when it is bound by SARS-CoV-2, leading to elevated angiotensin II levels driving the development of ARDS (34). Furthermore, evidence convincingly attests that both pulmonary and systemic hypertension is a risk factor for unfavorable progression in patients with pneumonia (35), ARDS (36,37), and Multiple Organ Failure (MOF) (38). It is therefore probable that the co-occurrence of hypertension and SARS-CoV-2 infection would interplay to synergistically increase the risk of unfavorable prognosis compared to normotensive COVID-19 patients.

Scarce data exist regarding glucose metabolism and the development of acute complications of diabetes (*e.g.,* ketoacidosis) in patients with COVID-19. Infection of SARS-CoV-2 in those with diabetes possibly triggers higher stress conditions, with the greater release of hyperglycemic hormones, *e.g.*, glucocorticoids and catecholamines, leading to increased blood glucose levels and abnormal glucose variability (39). On the other hand, a retrospective study from Wuhan reported that around 10% of the patients with type 2 diabetes mellitus and COVID-19 suffered at least one episode of hypoglycemia (<3.9 *mmol/L*) (39).

Hypoglycemia has been shown to mobilize pro-inflammatory monocytes and increase platelet reactivity, contributing to higher cardiovascular mortality in patients with diabetes (40). Yet, it remains largely unknown how exactly the inflammatory and immune response occurs in these patients, as well as whether hyper- or hypoglycemia may alter the SARS-CoV-2 virulence, or the virus itself interferes with insulin secretion or glycemic control. Furthermore, the impact of usual diabetes drug treatment on COVID-19 outcomes, as well as therapeutic approaches for COVID-19 on glucose regulation remains unspecified.

Hyperglycemia and insulin resistance promotes the amplified synthesis of glycosylation end products and pro-inflammatory cytokines, oxidative stress, as well as exciting the production of adhesion molecules that mediate tissue inflammation (41,42). This inflammatory process may compose the underlying mechanism that leads to a higher propensity to

infections, with worse outcomes thereof in patients with diabetes (41).

The strength of our study was that this study includes all confirmed patients with COVID-19 in a city inside the epidemic centers of Iran (Tehran). However, our hospital is one of the most important COVID-19 treatment hospitals in Tehran, and thus, would represent patients in the region.

Limitations

Our study is subject to several limitations. First, our study is hypothesis-generating and does not represent a definitive prospective study. The causal inference between risk factors of CVD and progression to severe COVID-19 should be examined in further studies. Second, since this is a case series investigation of all adult patients with COVID-19 admitted to a referral hospital rather than a prospective population-based cohort study, we cannot calculate the relative risk of developing COVID-19 and cannot estimate whether CVD patients are more likely to develop the infection. Third, owing to the insignificant number of patients with diabetes, hypertension, and other pre-existing diseases in our case series, the relations of these diseases with disease progression could not be assessed. Fourth, the current study did not have enough statistical power to exclude a small or moderate effect of CVD risk factors on disease progression. Finally, a limited number of patients with CVD risk factors have been diagnosed in the study. Thus far, we have only involved adult patients in this study. The effects of CVD risk factors on coronavirus infection or disease progression in children are yet to be reported. In spite of everything, one of the most important restrictions of studies related to COVID-19 is that the results of this disease are changing every day in the world, and no hypothesis about it can be stated with certainty.

Conclusion

In conclusion, this cross-sectional study does not reveal a significant association between CVD risk factors and prognosis of COVID-19 among the Iranian adult population. More studies, particularly of prospective nature, are needed to approve our results.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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