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Research Article

Prevalence and Risk Factors Associated with Organ Complications in Patients with COVID-19 Admitted to the Intensive Care Unit: A Cohort Study

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ABSTRACT

Background: Exploring risk factors for the development of COVID-19 in vital organs of the body is necessary to improve patient survival and reduce disability and morbidity due to disease progression. By identifying these underlying risk factors and controlling them, it is possible to prevent extra-pulmonary involvement and even alleviate pulmonary involvement in patients, resulting in a significant reduction in mortality and morbidity rates. This study aimed to identify the underlying risk factors associated with pulmonary and extrapulmonary organ complications of COVID-19.
Methods: This study was a cross-sectional descriptive-analytical study. Patients with a definitive diagnosis of COVID-19 who were admitted to the intensive care unit of Imam Khomeini Hospital in Tehran due to respiratory distress and poor clinical condition were included in the study population and were clinically followed up on. Patients' information was collected by reviewing patients' records and the hospital information system.
Results: A total of 123 patients were included in the study (63.4% were male, mean age = 58.87 ± 12.37). Using ROC curve analysis, the calculated risk score is considered statistically significant for diagnostic accuracy (AUC = 0.862 [0.797–0.927], P value < value<0.001). A risk score cutoff greater than 1.5 (sensitivity 89.9%, specificity 38.9%) favors an increased likelihood of in-hospital mortality. According to multiple linear regression (F (9,93).369, P value=0.001), chronic obstructive pulmonary disease, asthma, diabetes, SOFA score on days 2 & 3, and ventilation support were predictors of ICU length of stay.
Conclusion: A history of chronic heart failure with renal impairment, liver cirrhosis with liver complication, and any underlying disease are associated with pulmonary complications in COVID-19 patients.

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Introduction

Coronaviruses are a large family of viruses that include pathogens such as SARS, MERS, and COVID-19. Researchers have identified seven types of human-transmitted coronaviruses. The last of these is SARS-CoV-2, which spread to humans in Wuhan, China, in December 2019 and has since spread worldwide, leading to an epidemic [1-2]. Transmission of the disease occurs through inhaling tiny respiratory droplets from infected individuals. Although most people with the virus initially experience mild symptoms like the common cold—such as dry cough, dizziness, sore throat, fever, shortness of breath, muscle aches, and loss of smell—more severe symptoms can develop a few days after infection or, in some cases, slightly later [3-5]. Some patients have also reported experiencing gastrointestinal symptoms like diarrhea, skin complications, and red eyes [6-8]. Some patients with COVID-19 also exhibit dysfunction of the central nervous system, heart, kidneys, and liver.

In this study, old age, high blood pressure, cardiovascular disease, diabetes, and immunocompromise are the most common risk factors for COVID-19 infection. Depending on the patient's age, physical health condition, underlying diseases, or immune system defects, the mortality rate in these patients varies greatly, with an estimated average of 7.5% [9-10]. Furthermore, reports indicate that the intubation rate varies from 5 to 88% [11].

The main cause of organ complications in the pathophysiology of organ involvement, particularly the respiratory system and other vital organs, is the occurrence of microthrombosis in the blood vessels of these organs. Researchers have identified the presence of vascular microthrombosis in 91.3% of patients with coronary artery disease as a predictor of adverse outcomes, particularly in the involvement and complication of vital organs [12]. Therefore, we can expect complications in vital organs, especially in the advanced stages of the disease. In certain instances, it's reasonable to anticipate multiple organ complications. However, there have been few reports of these organ complications following COVID-19, especially associated risk factors, from countries with significant disease incidences, including Iran, and further evaluation is needed. Therefore, the aim of this study was to determine the prevalence and risk factors associated with organ complications in patients with COVID-19 admitted to the intensive care unit.

Methods

Study design

This study was a prospective cohort study conducted in the Imam Khomeini Hospital Complex. Patients with a definitive diagnosis of COVID-19 (based on a positive molecular test by PCR) who were admitted to the hospital's intensive care unit from March 2020 to August 2021 due to respiratory distress comprised the study population.

Data collection procedure

We collected patient background characteristics from their electronic medical records, including demographics, body mass index (BMI), underlying comorbidities (diabetes, hypertension, cancer, heart failure, etc.), and ventilation support (invasive and non-invasive ventilation).

Also, we closely monitored and followed the patients throughout their hospitalization in the intensive care unit, assessing the progress of the disease and evaluating the complications of various organ systems, including the respiratory system, cardiac, liver, kidneys, and central nervous system. This ongoing follow-up continued until either an organ complication occurred or the patient was discharged from the hospital.

Exposure and outcome measures

Exposures in this study were risk factors of organ complications. The primary outcome of this study was organ complications using the following:

1. Acute kidney damage or renal impairment according to AKIN criteria in the form of an increase in blood creatinine more than 1.5 times normal or a creatinine level greater than or equal to 0.3 mg/dL (stage 1).
2. Acute Respiratory Distress Syndrome, or ARDS (according to the Berlin classification): In this definition, the amount of oxygenation is classified into three levels, which include the following:
   - Mild: $200 < PaO_2 / FiO_2 \leq 300$ with PEEP or CPAP ≥ 5 cm H_2O
   - Moderate: $100 < PaO_2 / FiO_2 \leq 200$ with PEEP or CPAP ≥ 5 cm H_2O
   - Severe: $PaO_2 / FiO_2 < 100$ with PEEP ≥ 5 cm H_2O
3. Cardiac complications: in the form of Left Ventricle Ejection Fraction (LVEF) less than or equal to 40% and the need for vasopressor or inotropic agents;
4. Neurological complications: in the form of paralysis, paresis or Cerebrovascular accident (CVA);
5. Liver complications, increase in liver enzymes by more than 3 times normal and coagulation disorders;

6. Multiple-organ complication: presence of more than 1 organ complication.

In-hospital mortality and the need for ventilation support were secondary outcomes.

Statistical analysis

The results were expressed as the mean and standard deviation (mean ± SD) for quantitative variables and as a percentage for stratified qualitative variables. Multiple logistic regression was used to predict in-hospital mortality and multiple-organ complications. The significance level was considered less than 0.05 (P value < 0.05). For statistical analysis of the data, SPSS software version 26 was used.

Results

A total of 123 patients were included in the study. Of these, 63.4% were male. The mean age of the population was 58.87±12.37 and the mean body mass index (BMI) of the patients was 27.58 ± 5.23. The overall mortality rate is 56.1%. 85 patients (49.6%) required ventilation support during hospitalization. 78.0% of patients had at least one comorbidity and the frequency of comorbidities is as follows (Table 1). At baseline, 11.7% of patients showed cardiac dysrhythmias.

According to the results, the most common underlying diseases (comorbidity) included diabetes (36.6%), hypertension (33.3%), and ischemic heart disease (17.1%), respectively.

Pulmonary complications (respiratory distress syndrome), neurological complications, cardiac complications, renal complications, and liver complications were the most common complications during hospitalization, respectively. Multiple-organ complication was reported to be 22.8 percent.

Table 1– Clinical results of patients

Co-morbidity	
Diabetes	45 (36.6)
Hypertension	41 (33.3)
Ischemic Heart Disease	21 (17.1)
Cancer	19 (15.4)
Hypothyroidism	17 (13.8)
Dysrhythmia at ICU admission (any)	14 (11.7)
Obesity	13 (10.6)
Chronic Kidney Disease	9 (7.3)
Asthma	7 (5.7)
Heart Failure	5 (4.1)
COPD	3 (2.4)
Cirrhosis	3 (2.4)
Organ Complications	
Respiratory complications /ARDS	111 (90.2)
Multiple-organ complications	28 (22.8)
Neurological complications / CVA	12 (9.8)
Acute kidney Injury (AKI)	10 (8.1)
Heart complications	10 (8.1)
Liver complications	7 (5.7)
Final outcome	
Ventilation support	61 (49.6)
In-hospital death	69 (56.1)
Patients' demographic and lab data	
Age (years)	58.87±12.37
BMI (kg/m2)	27.59±5.24
APACHE score II	11.16±5.57
SOFA score at the day of admission (day 1)	4.59±2.75
SOFA score day 2	4.79±3.11
SOFA score day 3	5.22±3.30
Length of ICU stay (days)	7.93±5.29
Ventilation support duration (days)	125.0±108.55
SPO2 (%)	86.97±11.24
PaO2	81.96±28.25
paCO2	37.25±9.48
PH	7.41±0.09
WBC ($\times 10^3$)	9232.52±8598.97

Hb (g/dl)	12.34±2.18
Platelets ($\times 10^3$)	249.97±142.37
CRP (mg/dl)	120.05±64.80
LDH (U/l)	683.90±295.35
ESR (mm/hr)	78.05±31.93
D-dimer	2006.32±2283.29
Blood glucose (mg/dl)	154.46±72.18
AST	71.84±107.67
ALT	67.59±133.40
ALP	218.03±166.14
Direct bilirubin	0.67±1.02
Total bilirubin	1.45±1.69

In univariate analysis (Table 2), there was a statistically significant association between cirrhosis and liver complications ($\chi 2$=50.97, P<0.001), so that all cirrhosis patients developed liver complications. Furthermore, cirrhosis history was significantly associated with multiple-organ complication ($\chi 2$ = 10.43, P value = 0.011); however, all cirrhosis patients eventually developed multiple-organ complication. HF was associated with the development of AKI ($\chi 2$=18.77, P value=0.004), out of 5 patients with heart failure (HF), 3 of them developed AKI (OR=23.78 [3.40-166.41], P value=0.033). Diabetes was statistically significantly associated with cardiac complications ($\chi 2$=5.23, P value=0.036); patients with diabetes were more likely to develop heart complications (OR=4.60 [1.12-18.81], P value=0.033). All patients with liver complications required ventilation support. All patients who developed AKI and liver and heart complications expired in the hospital (Table 2).

Multivariate logistic regression was performed to predict multiple-organ complications, in-hospital mortality, and ventilation support (Table 3).

Patients aged 60 and up, as well as those with a SOFA score higher than 6 on the third day of ICU admission, were more likely to develop multiple-organ complications.

Table 2– Organ complications and need for ventilation support and in-hospital mortality

	Ventilation support		**Mortality**	
	OR [95%CI]	**P value**	**OR [95%CI]**	**P value**
Acute kidney Injury (AKI)	10.55 [1.29-86.11]	0.028	N/A	0.002
Liver complications	N/A	0.006	N/A	0.18
Cardiac complications	10.55[1.29-86.11]	0.008	N/A	0.002
Respiratory complications /ARDS	0.98 [0.29-3.23]	0.97	0.94	0.87
Neurological complications / CVA	13.42 [1.67-107.52]	0.014	2.81	0.06
Multiple-organ complications	13.65 [3.85-48.49]	<0.001	7.66 [1.99-29.50]	<0.001

Table 3– Multiple variable regression results

	OR [95%CI]	**P value**	**Nagelkerke R^2**
Multiple-organ complication			
Age group	3.63 [1.09 – 12.10]	0.036	0.376
SOFA score at day 3 of admission	1.41 [1.18 – 1.67]	<0.001	
Mortality			
Ventilation support	0.005[0.001-0.051]	<0.001	
Cancer	0.010 [0.001-0.121]	<0.001	0.790
SOFA score at day 2 of admission	2.99 [0.99-9.00]	0.051	
SOFA score at day 3 of admission	0.206 [0.064-0.667]	0.008	
Ventilation support			
Diabetes	0.176[0.030-1.022]	0.053	
Cancer	0.022 [0.002-0.276]	0.003	0.709
APACHE score II	1.360 [1.166-1.592]	<0.001	
SOFA score at day 3 of admission	2.170 [1.438-3.274]	<0.001	

Need for ventilation support, a history of cancer, and a SOFA score greater than 6 on the third day of ICU admission were all significant predictors of hospital discharge, lowering the odds of discharge.

Cancer patients were less likely to need ventilation support; however, patients with higher APACHE score II (>14) and SOFA score day 3 (>7) had a higher probability of needing ventilation support. To address the risk of in-hospital mortality, a risk score was developed. To design

this risk score, the results of logistic regression of mortality were used. The smallest beta coefficient of the variable was determined in the regression (SOFA score day 2); then the beta coefficient of each variable was divided by the smallest beta coefficient; thus, the score of each variable was determined. As a result, the need for ventilation support was assigned 5 points, the history of cancer was assigned 4 points, and the SOFA score on the third day was 6 points higher than 2 points

Using ROC curve analysis, the calculated risk score is considered statistically significant for diagnostic accuracy (AUC = 0.862 [0.797–0.927], p<0.001). A risk score cutoff greater than 1.5 (sensitivity 89.9%, specificity 38.9%) favors an increased likelihood of in-hospital mortality (Figure 1).

According to multiple linear regression (F (9,93) =3.369, P value=0.001; (Table 4)), cirrhosis, COPD, asthma, diabetes, SOFA score day 3, ventilation support, and SOFA score day 2 were the predictors of length of ICU stay.

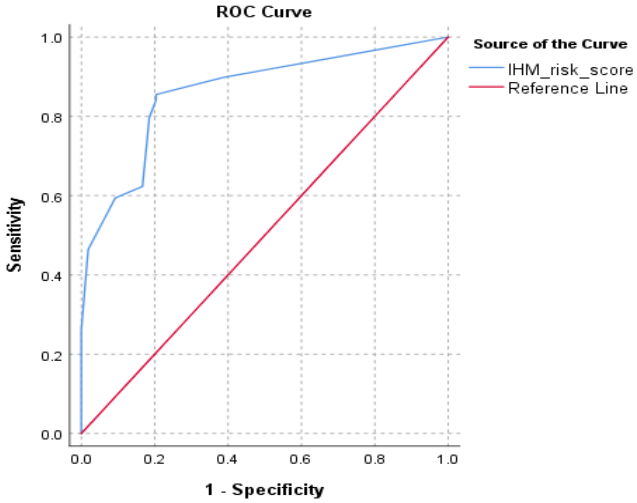

Figure 1– ROC curve analysis of risk score, calculated risk score (blue line) can significantly predict in-hospital mortality (IHM; AUC=0.862, P value<0.001)

Table 4– Multivariate logistic regression to predict in-hospital mortality

	β	t	P value
Ventilation support	3.367	2.486	.015
DM	-2.178	-2.030	.045
Cancer	-2.769	-1.969	.052
Asthma	-8.169	-3.238	.002
COPD	-6.157	-2.083	.040
Cirrhosis	-7.912	-2.485	.015
SOFA score day 2	1.046	2.252	.027
SOFA score day 3	-1.134	-2.435	.017
Heart failure	-3.092	-1.157	.250

Discussion

Extrapulmonary complications, which involve vital organs of the body, were evident from the beginning of COVID-19. In this regard, the more severe the disease, the higher the risk of extrapulmonary organ complications such as the cardiovascular, central nervous system, hepatic, and renal systems. Even in many cases, no pathophysiological cause was found to extend the complications to extrapulmonary organs. But what was crucial and necessary to maintain patient survival and reduce disability and morbidity due to disease progression was to find risk factors for the development of COVID-19 in vital organs of the body. In fact, by identifying and controlling these underlying risk factors, it was possible to prevent extrapulmonary complications and even alleviate pulmonary complications in patients, resulting in a significant reduction in mortality and morbidity rates. In addition to cellular and molecular processes, the presence of some major underlying risk factors seems to be completely related to the occurrence

of extrapulmonary complications caused by COVID-19, and the identification of these clinical risk factors is essential. What we did in the present study was to identify the underlying risk factors associated with the involvement of each of the pulmonary and extrapulmonary organs associated with COVID-19 disease.

The first step in the present study was to determine the rate of pulmonary and extrapulmonary complications in patients with COVID-19. In this regard, the results showed that most cases of complications caused by COVID-19 were related to pulmonary complications in 92%, cardiac complications in 7%, renal complications in 7%, liver complications in 32% of cases, and central nervous system complications in 9% of cases.

As the first step in identifying risk factors for organ complications, age over 60 was identified as a risk factor for pulmonary or cardiac complications, and BMI > 30 was a risk factor for neurological complications following COVID-19. Regarding the rate of complications in various organs caused by COVID-19, reports have shown highly variable results. In fact, the reported range for extrapulmonary complications has varied greatly from study to study.

In the study of Chirag Bavishi et al., reviewing 26 studies including 11,685 patients with COVID-19, the prevalence of heart failure and acute cardiac damage ranged from 5 to 38% [13]. According to two studies by Wong et al. [14] and Zhang et al. [15], hepatic complications were reported in the range of 14.8 to 53.1% of patients, which in about one third of these patients was associated with damage and even irreversible liver failure.

According to a study by Mao et al., about 36.4% of patients with COVID-19 in a cohort assessment had manifestations of the nervous system, which in severe cases were associated with acute cerebrovascular events, impaired level of consciousness, and cognitive impairment [12]. In the study by Pirouz Samidoust et al., reviewing 21 published studies, the prevalence of acute liver failure and injury in patients with COVID-19 was equal to 19.5% [16].

According to a study by Dennis et al., multiorgan complications, including cardiac complications in 26%, pulmonary complications in 11%, renal complications in 4%, liver complications in 28%, pancreatic complications in 40%, and splenic complications in 4%, were determined. Finally, single-organ and multi-organ conflicts were estimated at 70% and 29%, respectively [17]. Based on a systematic review and meta-analysis by Ting et al., an evaluation of 73 studies on organic complications following COVID-19 was performed.

According to this study, the prevalence of multiorgan complications, including pulmonary complications, cerebrovascular accident, liver disorder, renal impairment, tumors, and gastrointestinal complications, was 2%, 3%, 3%, 3%, and 7%, respectively. In this regard, multi-organ conflict was reported in the range of 1% to 8% [18]. In a 2020 study by Sachin A. Adukia et al., the prevalence of cardiac complications in the form of ischemic myocardial injury was between 7% and 28%, and shock and arrhythmia were 7.2%, 8.7%, and 16.7%, respectively. The prevalence of neuromuscular lesions in the form of dizziness was 17%, headaches were 13%, disturbances of consciousness and delirium were 16%, and CVA was 3%. The prevalence of gastrointestinal complications was high and ranged from 3 to 70%. The renal failure (as kidney complications) in severe cases was between 25 and 29%. The prevalence of ocular lesions was 0.9 to 31%. The prevalence of hematologic disorders in severe cases was about 33%.

There is no consensus on the prevalence of pulmonary or extra-pulmonary complications caused by COVID-19. The main reasons for this disagreement can be found in reasons including differences in the severity of underlying COVID-19 disease at the time of admission or evaluation of patients, various definitions of extrapulmonary complications, various tools used to confirm COVID-19, or tracking of pulmonary complications. Extrapulmonary as well as different clinical records of patients were examined. However, what is clear in our study is the significant prevalence of heart disease in COVID-19 disease.

Regarding the relationship between patients' risk factors and the chance of pulmonary and extrapulmonary complications, our study showed that 1) the risk of pulmonary complications in patients with asthma and a history of cancer was not increased, and 2) a history of cancer, hypertension, ischemic heart disease, or diabetes was not associated with COVID-related cardiac complications. 3) A history of liver cirrhosis increased the risk of liver complications. 4) A history of chronic heart failure was identified as a major risk factor in patients with renal impairment. 5) Diabetes and hypertension do not seem to be risk factors for the development of liver complications due to COVID-19 disease. 6) It also seems that central nervous system complications such as strokes with neurological findings (paralysis, paresis) are associated with an increased likelihood of needing ventilation support and a reduced chance of patient survival.

The main strength of the present study was that, for the first time, it evaluated a variety of underlying factors in addition to demographic characteristics as risk factors for multiorgan conflicts. However, the most important weakness of the study was its small sample size, which did not allow for accurate estimates of less common organic disorders such as gastrointestinal, liver, kidney, skin, or ocular disorders. Clearly, the confirmation of the findings of this study should be based on the implementation of larger studies in the future.

Conclusion

As a conclusion, in our selected study population, there is a significant relationship between underlying risk factors and patients' clinical history with pulmonary and extrapulmonary organ complications. A history of chronic heart failure with renal impairment, liver cirrhosis with liver complication, and any underlying disease are associated with pulmonary complications in COVID-19 patients.

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