Risk Factors Associated with Mortality in COVID-19 Patient's: Survival Analysis

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Abstract

Background: The effect of related factors on recovery or death rates may vary from country to country. Therefore, we aimed to investigate the relationship between demographic, clinical, laboratory factors on the survival rates of confirmed cases of COVID-19 in Shahroud, Iran.

Methods: This is an analytical study of the estimation of the survival of patients with COVID-19. Patients who had positive PCR test were considered as COVID-19 cases, and the 2-month survival of these patients was estimated. Among the diseases, heart disease and diabetes were considered as separate variables, and the patients' histories of other diseases were included in the model as comorbidities.

Results: Of 396 confirmed patients hospitalized, 109 patients (27.5%) had a history of heart disease, 100 (25.3%) were diabetic, and 80 (20.2%) had a history of other comorbidities. The number of deaths due to the disease was 59 (14.9%). The median age of those who died was 76 years. The multivariate Cox regression analysis shows that heart disease increases hazard ratio more than two times (HR=2.37, 95% CI: 1.33-4.23). The neutrophil-to-lymphocyte ratio (NLR) factor, (HR=1.15, 95% 1.08-1.22), and older age (HR=1.06, 95% CI: 1.03-1.08) increases the risk of death significantly.

Conclusion: The heart disease history, NLR factor and older age are associated with death of COVID-19 and may be helpful for the early warning and prediction of disease progression.

Keywords: COVID-19; Iran; Mortality; Risk factors; Survival

Introduction

Since late 2019, the world has been plagued by an acute respiratory infection syndrome caused by the coronavirus, which originated in Wuhan, China. The disease had spread to 215 countries as of June 5, 2020, causing an estimated 6,850,000 infections and 398,000 deaths. These numbers are continuing to increase (1-4). Up to June 5, 2020, the number of COVID-19 patients in Iran was approximately 167,000, and approximately 8,000 of

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them had passed away. The mortality rate of this disease is 5.9% worldwide and 4.99% in Iran (4, 5). The prevention of infection from the virus and death is very important. The WHO considers the incidence and mortality rates of this disease to be serious indicators of its severity (6).

The most common clinical signs of COVID-19 at its onset include fever, dry cough, fatigue, shortness of breath, myalgia, decreased lymphocytopenia, and abnormal computerized tomography (CT) scan images (7, 8). In addition to causing respiratory tract infections in acute cases, this disease causes respiratory distress, heart dysfunction, liver damage, and kidney failure and can eventually lead to death (9, 10). Various factors are involved in increasing the mortality rates in people with COVID-19 and have caused differences in morbidity and mortality rates in different parts of the world. There are four such factors: demographic, clinical, and laboratory findings and therapeutic interventions (11). Of the demographic factors, a patient's age is directly related to the severity and outcome of the disease. In the United States, 31% of patients, 45% of patients who required hospitalization, 53% of patients admitted to intensive care units (ICUs), and 80% of patients who died from COVID-19 were over 85 years of age (3, 12). Smoking is another demographic factor affecting the outcomes; in studies, the incidence of the disease in smokers was 9% and the mortality rate in smokers was higher than in nonsmokers (11, 13). Among the clinical risk factors, comorbidities including diabetes, hypertension, coronary heart disease, and chronic obstructive pulmonary disease increased the incidence and mortality rates associated with COVID-19. Based on studies, about 48% of people with COVID-19 had a comorbidity, and this was the case in 23% to 67% of patients who died from COVID-19 (11, 14, 15). Laboratory indices, such as levels of albumin, creatinine, troponin, prothrombin, C-reactive protein, and fibrinogen, also affected the morbidity and mortality rates (16, 17). Other laboratory findings that had an effect were impaired liver function indices, including the total bilirubin, direct bilirubin, and alanine aminotransferase; impaired myocardial function indices, including creatine kinase, myoglobin, lactate dehydrogenase, and aspartate aminotransferase; and impaired renal function indices, including creatine, urea nitrogen, and uric acid (9, 18-21). Therapeutic interventions had a significant impact on patient survival and recovery rates, including the use of antibiotics, antiviral drugs, corticosteroids, and oxygen therapy (11).

In most studies worldwide, the mentioned demographic, clinical, laboratory, and therapeutic factors affected the survival rates and could reduce or increase them (11). However, due to the differences in the behavior of the virus in different parts of the world, the effect of these factors on recovery or death rates may be different. Therefore, we aimed to investigate the relationship between demographic, clinical, and laboratory factors on the survival rates of confirmed cases of COVID-19 (confirmed by PCR testing) in Shahroud, Iran, to determine whether survival rates can be improved by modifying variables that influence outcomes.

Methods

This is a descriptive, analytical study of the estimation of the survival of patients with COVID-19 who were referred to the medical and health centers in Shahrood City, Iran within 60 d after the epidemic started. Demographic and clinical information of these patients was used to analyze their survival.

After obtaining informed consent from the patients and obtaining a permit from the Ethics Committee of Shahroud University of Medical Sciences (ethical code IR.SHMU.REC.1398.160), the required information was obtained from the Corona Information Registration System.

This System includes the following sections, i.e., 1) demographic information of patients, including age and gender; 2) comorbidities; and 3) the outcomes of the disease and the associated dates. In the cases in which the clinical outcomes were unclear, the outcomes were determined by contacting the patients or members of their families.

In this study, patients who had positive PCR test were considered as COVID-19 cases, and the 2-month survival of these patients was estimated.

The survival times of the patients who died were considered to be the times from their admission to the hospital to the dates they died. The survival times of the patients who survived were considered to be the times from their hospitalizations until the end of the study.

To examine the factors that affected the survival times of patients with COVID-19, the quantitative variables included the patients' ages, their Body Mass Indices (BMIs), and their neutrophil-to-lymphocyte ratios (NLRs). Among the diseases, heart disease and diabetes were considered as separate variables, and the patients' histories of respiratory diseases, asthma, kidney diseases, and liver diseases were included in the model as comorbidities. To evaluate survival, both the times until patients died and the times until patients recovered were measured in days.

Statistical analysis of the data was performed using SPSS Inc. Released 2009. PASW Statistics for Windows, Version 16. Chicago: SPSS Inc and descriptive statistics (frequency and percentage), the chi-squared test, and Cox regression also were used.

Results

Of 396 confirmed patients by PCR testing who were hospitalized, the mean age was 59.16 year, 210 (53%) were male, and the mean body mass index (BMI) was 27.58; 109 patients (27.5%) had a history of heart disease, 100 (25.3%) were diabetic, and 80 (20.2%) had a history of comorbidities. The median length of hospitalization was 7 days. The number of deaths due to the disease was 59 (14.9%). Factors affecting death were age, the presence of heart disease or comorbidities, and the neutrophil-to-lymphocyte ratio. The median age of those who died was 76 years and of those who recovered was 57.20 year. The mean neutrophil-to-lymphocyte ratio in patients who died was 6.08 and in those who recovered was 3.43. Almost 56% of deceased patients V.S 23% Survivors patients have heart disease. Also the percentage of comorbidities is 30% in patients who have died and 18% in recovered patients. Factors that did not make a significant difference in the death rates were gender, the BMI, and the presence of diabetes. (Table 1).

Table 1: Baseline patients' characteristics and Cox regression analysis for the variables affecting survival rates

Variables		Baseline Characteristics		Cox Regression Model			
		N (%) or Mean(SD)		Unadjusted Model		Adjusted Model	
		Deceased	Survivors	HR(95% CI)	P-value	HR(95% CI)	P-value
Age		76(19)	57.20(22.95)	1.06(1.04-1.08)	<0.001	1.06(1.03-1.08)	<0.001
BMI		26.12(5.53)	26.61(5.76)	0.95(0.90-1.00)	0.067	0.98(0.93-1.04)	0.580
Neutrophil/lymphocyte		6.08 ±4.34	3.43±2.66	1.18(1.12-1.25)	<0.001	1.15(1.08-1.22)	<0.001
Hospitalization (median,IQR)*		7(6)	7(5)	-	-	-	-
Sex	Female	23(39)	163(49.1)	Ref	0.183	Ref	0.400
	Male	36(61)	174(50.9)	1.38 (0.82-2.34)		1.27(0.72-2.22)	
Heart Disease	No	26(44.1)	261(77.4)	Ref	<0.001	Ref	0.004
	Yes	33(55.9)	76(22.6)	3.75(2.24 – 6.28)		2.37(1.33-4.23)	
Background Diseases**	No	41(69.5)	275(81.6)	Ref	0.033	Ref	0.912
	Yes	18(30.5)	62(18.4)	1.86(1.07-3.25)		0.97(0.53-1.77)	
Diabetes	No	40(67.8)	256(76)	Ref	0.183	Ref	0.321
	Yes	19(32.2)	81(24)	1.42(0.82-2.45)		1.34(0.75-2.42)	

*chi-squared test p=0.603
**Include Acute respiratory disease, , Asthma, Kidney, Liver

Figure 1 shows the percentage of deaths on different dates. The highest number of deaths was on

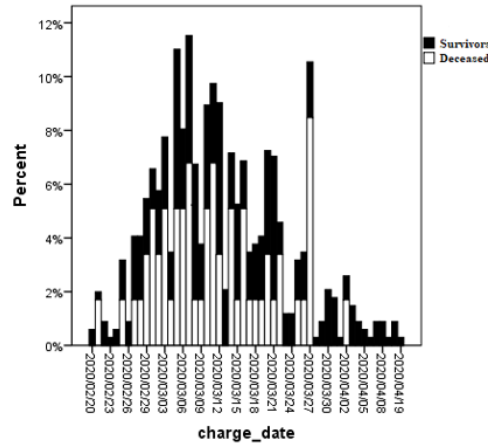Mar 27, 2020. According to the figure, there have been no deaths on some dates.

Fig. 1: Percentage of deaths status on daily hospitalizations during the study period

Figure 2 and section 2 in Table 1 show the results of the log rank test and Cox regression analysis for the variables affecting survival rates. To evaluate the effect of the unadjusted variables, the univariate Cox regression analysis was fitted, and to evaluate the simultaneous effect of the variables, the multivariate Cox regression analysis was fitted. In the univariate Cox regression analysis, the age, presence of heart disease, presence of comorbidities, and neutrophil-to-lymphocyte ratio were significant. Each increased year of age increased the risk of death by 6%. The presence of heart disease increased the risk of death by 3.75 times, the presence of comorbidities by 86%, and the presence of a unit increase in the neutrophil-to-lymphocyte ratio by 18%.
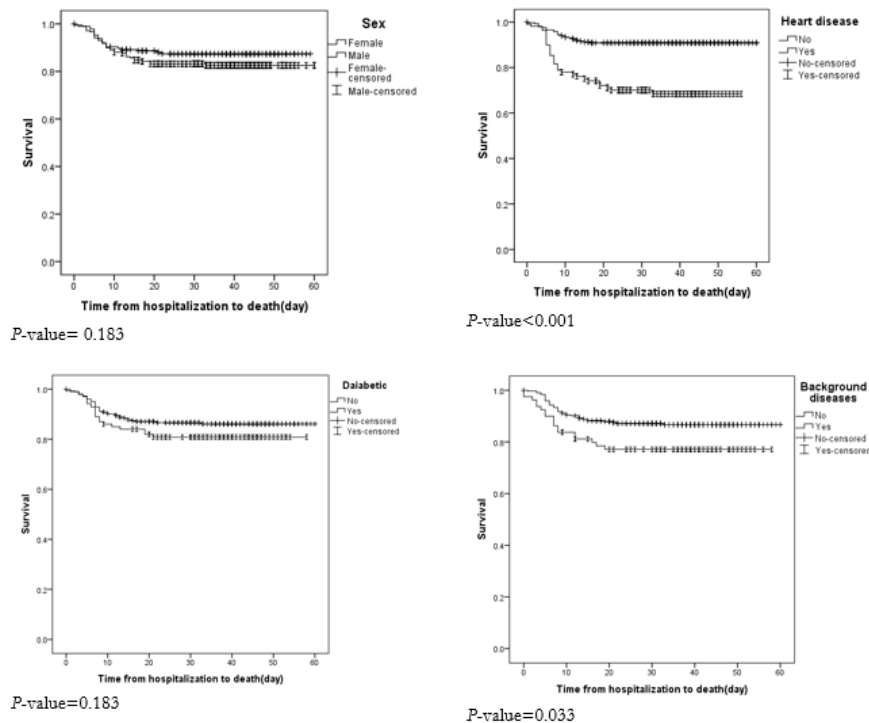

Fig. 2: Results of log rank test to evaluate the effect of variables on survival of patients with COVID-19

After adjusting for the effect of the variables, all variables that were significant in terms of survival in the univariate Cox regression analysis were significant again except for the presence of comorbidities; each increased year of age, the increase in the risk of death was 6%; for the presence of heart disease, 137%; and for a unit increase in the neutrophil-to-lymphocyte ratio, 15%.

Discussion

In this study, we investigated the relationship between demographic, clinical, laboratory factors on the survival rates of confirmed cases of COVID-19 in Shahroud, Iran. Although this study did not observe a significant sex-related difference in mortality such as in a meta-analysis study (22), studies conducted in Italy and China found that the mortality rate due to COVID-19 was higher in men than women (1, 2). The Centers for Disease Control and Prevention in China reported 2.8% and 1.7% mortality rates in men and women, respectively (23). Meanwhile, in Europe, 57% of COVID-19 cases and 72% of COVID-19 deaths occur in men. In addition, the higher mortality rate in men may be attributed to lifestyle factors, including more smoking and alcohol consumption. Conversely, the lower mortality rate of COVID-19 in women may be related to the fact that the mortality rate in women is lower than in men across all age groups. According to the world life table, the male-to-female ratio of deaths is higher than 1, and this ratio gradually increases in adulthood, reaching 1.6 before the age of 60 (24). In our study, the male-to-female ratio of COVID-19 mortality was 1.56, which is consistent with the reported global sex-mortality ratio. This may be because most deaths from COVID-19 occur in people over the age of 55 (25). Such discrepancy between the sex ratio findings of different studies may be related to differences in the number of tests performed, the quality of the healthcare system, therapeutic options, and the duration of the epidemic in different geographical areas; accordingly, this issue needs further consideration in future studies.

In our study, the median length of hospitalization for COVID-19 cases was seven days. This is consistent with the results of studies conducted in the United States and European countries, which reported an average hospitalization length of 7-8 days (3, 26, 27). However, the results of our study differ from others carried out in China and Vietnam, which reported an average hospitalization length of 19-21 days (28). This difference in duration may be due to differing quality of the healthcare systems and the COVID-19 prevention and control strategies implemented in different countries.

Based on our findings, having a history of heart disease was a strong risk factor for death from COVID-19, with those patients having a risk of death about two times higher than patients without such history. Similar to our findings, cardiovascular disease has previously been reported as a risk factor for death from COVID-19. For instance, the risk of death from COVID-19 was reported to be almost nine times higher in people with heart disease (29). In general, most current studies have reported a strong association between cardiovascular disease and death from COVID-19 (12, 30).

According to our findings, the age of death from COVID-19 is significantly higher than those who had recovered from it. With an increase of one unit in age, the risk of death from this disease increases by about 6%. Because aging is associated with many physiological and anatomical changes in the human body, aging can increase the risk of death from COVID-19 in a number of ways. For example, aging alters the structure of the lungs and the external organs that support the lungs, such as the chest wall and spine. These structural changes lead to a less than optimal respiratory mechanism and disruption of gas exchange (5). The immune system also weakens with age (4), which means the immune system can become less resistant to coronavirus infection, leading to more severe illness and death. In general, considering that age is the most important cause of death, it seems reasonable to observe an increase in the mortality rate due to COVID-19 with more advanced age.

Another factor associated with COVID-19 mortality in our study was an increase in the neutrophil-to-lymphocyte ratio (NLR). In agreement with the results of our study, several other studies have found the NLR to be an important factor in the mortality of patients with COVID-19 (31-33). Increased mortality from COVID-19 with increases in the NLR may be due to the increase in the number of neutrophils, which are a component of the body's non-specific immune system. Increasing the number of neutrophils releases reactive oxygen species that damage both normal and foreign cells and reduces the number of lymphocytes needed to fight infectious diseases. Thus, a high NLR means greater inflammation and consequently more damage (31). Generally, based on the findings of this study, age factors, heart disease, and increased NLR levels increase the risk of death in patients with COVID-19.

One of the limitations of our study was the model's lack of consideration of smoking behavior, which may also affect COVID-19 survival rates. In addition, weight and height variables were obtained by asking the patients and were not measured, so it is possible that the body mass index values in the study were in error. The best survival calculation is based on the time interval between the onset of symptoms and death, as well as taking into account all inpatients and outpatients that this issue was not considered in this study.

Conclusion

Heart disease was the most important factor in increasing the risk of death. The NLR factor and older age are associated with death of COVID-19 and thus could be used as early identification indicators of disease progression during hospitalization.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interest.

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