ORIGINAL ARTICLE

Survival of COVID-19 among the Iranian population before and after the Delta variant spread

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ABSTRACT

COVID-19 has been considered the most important issue in the last two years. Some characteristics and factors can play a pivotal role in the survival time and mortality of COVID-19 patients. The Delta variant was one of the most important variants of COVID-19. This study aimed to investigate the risk factors of COVID-19 survival before and after the spread of the Delta variant. In this historical cohort study, 6,117 hospitalized patients with positive COVID-19 PCR tests between January and September 2021 participated. Some characteristics such as age, sex, death by COVID-19, and presence/absence of some comorbidities were registered for the patients. Log-rank test and Cox proportional hazards model were done to check the effect of the potential risk factors on the survival of COVID-19 patients by considering the onset of symptoms to death as the time variable. The mean age of patients was 47.29 (SD=18.70). 53% of patients were female, 4.6% were admitted to the ICU, and 3.6% died from COVID-19. Age (HR=9.81, p<.001), cardiovascular disease (HR=2.86, p<.001), chronic kidney disease (HR=6.21, p<.001), diabetes (HR=2.16, p=0.002), hypertension (HR=2.67, p<.001), ICU admission (HR=12.92, p<.001), pO_2<93% (HR=6.75, p<.001), and intubation (HR=21.54, P<.001) were risk factors that were influential on the survival of COVD-19 patients before the spread of the Delta variant. Although the effect of some variables changed after the spread of the Delta variant, some of them, like chronic kidney disease and hypertension were no longer significant. Although the effect of some comorbidities was significant only in the crude models, they were not influential in the adjusted model. Conversely, in the presence of other risk factors, especially age, most of the comorbidities were not significant in the adjusted model. Older age, ICU admission, intubation, and pO_2<93% are the most important variables which played a pivotal role in the survival of individuals infected by COVID-19.

Key words:
COVID-19; comorbidities; survival; Delta variant; Cox regression

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INTRODUCTION

It has been over two years since COVID-19 become a global health issue. In late 2019, the SARS-COV-2 was first detected in Wuhan Province, China, and quickly spread to other countries, especially Iran.[1,2] Till February 2022, there were more than 390 million people with COVID-19 infection and more than 5.5 million of them had died worldwide. The number of infections and deaths were about 20 million and 325,000 in the Eastern Mediterranean region, respectively. In Iran, there were 133,000 deaths by COVID-19 among 6.6 million infections.[3,4]

Patients with COVID-19 infection vary in severity. While many patients have asymptomatic or mild symptoms, some have more severe symptoms and need to be hospitalized.[5] Among hospitalized patients, some have very severe symptoms and were admitted to the ICU.[6]

Several variants of SARS-COV-2 were detected during the COVID-19 pandemic, each with its characteristics.[7] Usually, each new variant had a higher transmission rate than the previous one. Some variants increased the number of hospitalization and deaths.[8]

The World Health Organization (WHO) has introduced 5 variants of COVID-19 as the Variants of Concern (VOC), namely Alpha, Beta, Gamma, Delta, and Omicron.[9] Until August 2021, the approximate number of countries that reported cases with Alpha, Beta, Gamma, and Delta variants were 185, 136, 81, and 142, respectively.[10] The Delta was one of the most important variants which caused the hospitalization and death of patients due to COVID-19.[7] The Delta variant was identified in Iran in early July, which brought about an intense wave of COVID-19 until the end of September.[11]

Several factors affect the survival and mortality of COVID-19 patients.[12, 13] Evidence shows that higher age and various underlying diseases are the most important risk factors affecting COVID-19 mortality and survival.[14] It is important to mention that the prevalence of some diseases is high in Iran and may be different from other countries such as diabetes, chronic kidney disease (CKD), and cardiovascular disease (CVD).[15-17] Also, admission to the ICU and intubation are considered in some studies as risk factors and as an expression of the severity of the disease in the individuals.

In this regard, it is necessary to conduct some studies on the survival of COVID-19 patients to identify its risk factors to plan and control the disease. The risk factors of COVID-19 mortality and their impacts may be different in each region and country. In addition, the Delta variant may be a potentially influential variant that could affect the survival of COVID-19 patients. To the best of our knowledge, no studies were conducted in Iran which focused on the Delta variant. Also, few studies have been focused on the importance of Delta variant on COVID-19 infection period. This study aims to evaluate the survival of hospitalized COVID-19 patients and its influential risk factors in Sirjan City (Iran) in 2021 before and after the spread of the Delta variant.

METHODS

This historical cohort was performed using a data set collected in Imam Reza and Gharazi hospitals, two medical centers for tackling COVID-19 infections in Sirjan city (Iran), from the beginning of 2021 to 20 September 2021. The information of the people that went to the hospital with early symptoms (14,096 COVID-19 cases until 20 September) was recorded by their nurses in a check list. Then, the data set was registered by the head of statistics and information unit of each hospital in the Medical Care Monitoring Center (MCMC) system.

Among these individuals, only hospitalized patients with positive COVID-

19 tests (6,117 cases) were included in the study. There was no missing data set. The individuals with negative COVID-19 tests or those who were not admitted to the hospital were excluded from the study.

There was some information for every patient such as age, sex, death by COVID-19, CVD, diabetes, hypertension, CKD, neurological disease, asthma, etc. Also, some dates were extracted from the data, including the time from the beginning of symptoms to hospitalization, duration of hospitalization, and time from the onset of symptoms to death. Since the Delta variant may have influenced the death and survival rates of patients, we conducted a survival analysis in both periods before and after the emergence of the Delta variant, in addition to the general survival analysis of the patients. The first cases of COVID-19 patients with the Delta variant had been detected in Iran in 22 June 2021. So, the time period from the beginning of the study to this date had been considered as before delta and period from 22 June 2021 to the end of the study was referred to as after delta.

The name and addresses of individuals were kept secret. The study received the approval code from the Ethics Research Committee as IR.SIRUMS.REC.1400.015.

Statistical analysis

The continuous variables were described by mean and standard deviation (±SD), and the number and percentage (%) were used for the categorical variables. The Shapiro-Wilk test was used to test the normality assumption in which all the covariates were abnormal. So, the Mann-Whitney-U test and Chi-square tests were used to compare the patients who died versus those who survived.

The time from the beginning of symptoms to death was considered as the outcome variable for survival analysis with censoring on 20 September 2021 for patients who were alive at the end of the study. The Kaplan-Meier method and the log-rank test were used to compare the survival rates. Crude and adjusted Cox proportional hazard models were fitted on the significant variables in the log-rank test before and after the Delta variant emergence.

All analyses were done by using STATA software (16.1, StataCorp LLC, College Station, TX).

RESULTS

There were 6,117 patients during the study period aged between zero and 100 years, with a mean age of 47.29 (SD=18.70). Among the patients, 3,242 (53%) were female. Also, 281 (4.6%) patients were admitted to ICU, and 222 (3.6%) cases died from COVID-19. A median duration of 9 days from the onset of symptoms to the end of disease (dead or alive) (IQR 6-11) and a median period of 4 days from hospital admission to the end of disease (IQR 3-5) were identified. Table 1 shows more information about hospitalized COVID-19 patients. Some early symptoms of patients are depicted in figure 1 before and after the emergence of the Delta variant.

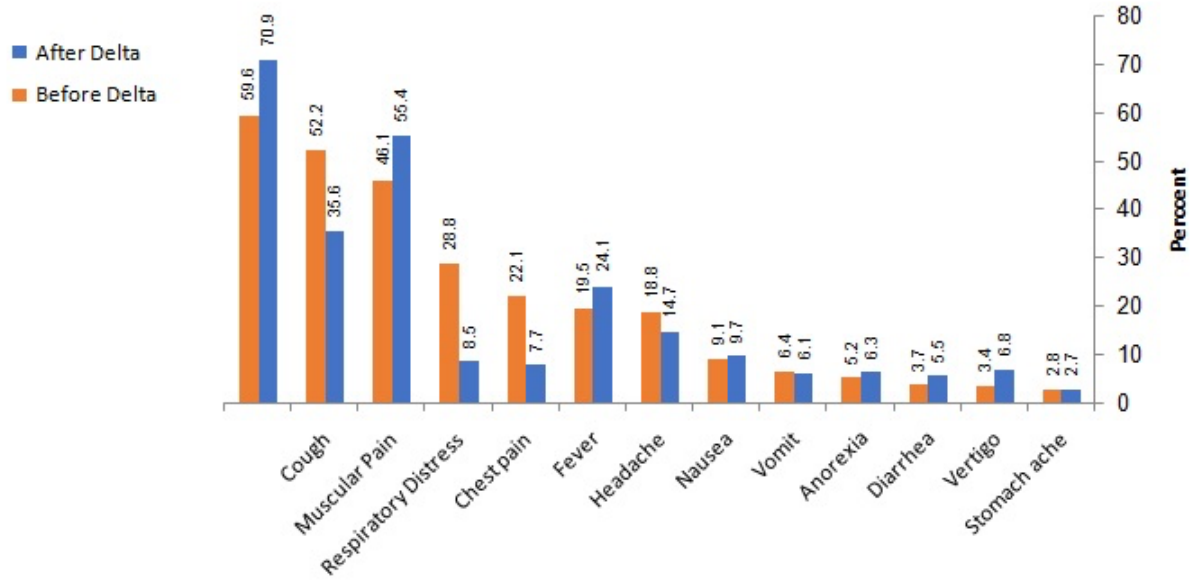

Figure 1 Symptoms of COVID-19 before and after the Delta variant spread

The patients who died were older than those who survived, with a mean percentage of 67.05±19.80 (p < .001). Death occurred in 10.92% of CVD patients (p < .001), 9.95% in diabetic patients (p <.001), 22.73% in individuals with CKD (p <.001), 12.07% in patients with pulmonary disease except for asthma (p = 0.001), 16.13% in patients with neurological disorders (p <.001), 9.73% in individuals with hypertension (p <.001), 33.10% in those admitted in ICU (p < .001), 5.59% in patients with pO_2<93 (p < .001), and 28.77% in patients with intubation (p < .001) (table 1).

Table 1 General characteristics by the outcome

Variable	Total n=6117 Mean±SD or N (%)	Died n=222 Mean±SD or N(%)	Survived n=5895 Mean±SD or N (%)	P-value
Age (year) (0 to 100)	47.29±18.70	67.05±19.80	46.54±18.24	<.001
Sex				
Male	2875 (47)	109 (3.79)	2766 (96.21)	0.523
Female	3242 (53)	113 (3.49)	3129 (96.51)	
Cardiovascular disease				
Yes	174 (2.8)	19 (10.92)	155 (89.08)	<.001
No	5943 (97.2)	203 (3.42)	5740 (96.58)	
Diabetes				
Yes	392 (6.4)	39 (9.95)	353 (90.05)	<.001
No	5725 (93.6)	183 (3.20)	5542 (96.80)	
Immunodeficiency				
Yes	7 (0.11)	1 (14.29)	6 (85.71)	0.131
No	6110 (99.89)	221 (3.62)	5889 (96.38)	
Chronic kidney disease				
Yes	22 (0.36)	5 (22.73)	17 (77.27)	<.001
No	6095 (99.64)	217 (3.56)	5878 (96.44)	

Variable	Total n=6117 Mean±SD or N (%)	Died n=222 Mean±SD or N(%)	Survived n=5895 Mean±SD or N (%)	P-value
Asthma				
Yes	26 (0.43)	1 (3.85)	25 (96.15)	0.953
No	6091 (99.57)	221 (3.63)	5870 (96.37)	
Neurological disorders				
Yes	31 (0.51)	5 (16.13)	26 (83.87)	<.001
No	6086 (99.49)	217 (3.57)	5869 (96.43)	
Hypertension				
Yes	524 (8.57)	51 (9.73)	473 (90.27)	<.001
No	5593 (91.43)	171 (3.06)	5422 (96.94)	
ICU				
Yes	281 (4.59)	93 (33.10)	188 (3.20)	<.001
No	5836 (95.41)	129 (58.1)	5707 (96.8)	
pO_2 (%)				
>93	2753 (45.01)	34 (1.24)	2719 (98.76)	<.001
<93	3364 (54.99)	188 (5.59)	3176 (94.41)	
Intubation				
Yes	219 (3.58)	63 (28.77)	156 (71.23)	<.001
No	5898 (96.42)	159 (2.70)	5739 (97.30)	
Onset of symptoms-admission	4.74±2.98	3.95±2.64	4.77±2.99	0.001
Onset of admission-death	4.34±2.63	6.41±5.23	4.26±2.45	<.001

The Kaplan-Meier survival plots of potential risk factors are shown in figure 2 for the variables which were statistically significant in log-rank test. The survival functions of age groups ($p < 0.001$), CVD ($p = 0.002$), diabetes ($p < .001$), CKD ($p < .001$), hypertension ($p < .001$), ICU ($p < .001$), pO_2 group ($p < .001$), and intubation ($p < .001$) were different (table 2). Also, the hazard rate of each variable is presented in table 2.

Table 2 Log-rank test and hazard ratio for the death outcome

Variable	Log-rank test P-value	HR	95% CI fo HR
Age group			
<=60			
>60	<.001	5.28	(3.96- 7.04)
Sex			
Male			
Female	0.440	0.9	(0.69- 1.17)
Cardiovascular disease	0.002	2.07	(1.29- 3.32)
Diabetes	<.001	1.84	(1.30- 2.62)
CKD	<.001	4.55	(1.87- 11.08)
Asthma	0.632	0.62	(0.09- 4.45)

Variable	Log-rank test P-value	HR	95% CI fo HR
Neurological disorders	0.082	2.15	(0.88- 5.25)
Hypertension	<.001	1.99	(1.45- 2.73)
ICU	<.001	9.26	(7.03- 12.21)
pO_2 (%) < 93	<.001	4.75	(3.29- 6.84)
Intubation	<.001	9.53	(7.07- 12.84)

The log-rank test demonstrated that the survival function was different before and after the spread of the Delta variant ($p < 0.001$). Therefore, the crude and adjusted Cox proportional hazards regressions were fitted in two time periods separately (table 3). Only variables that had a significant difference in survival functions based on the log-rank test (table 2) were chosen for the Cox regression models. The variables with significant hazard rates in crude models were entered in the adjusted models.

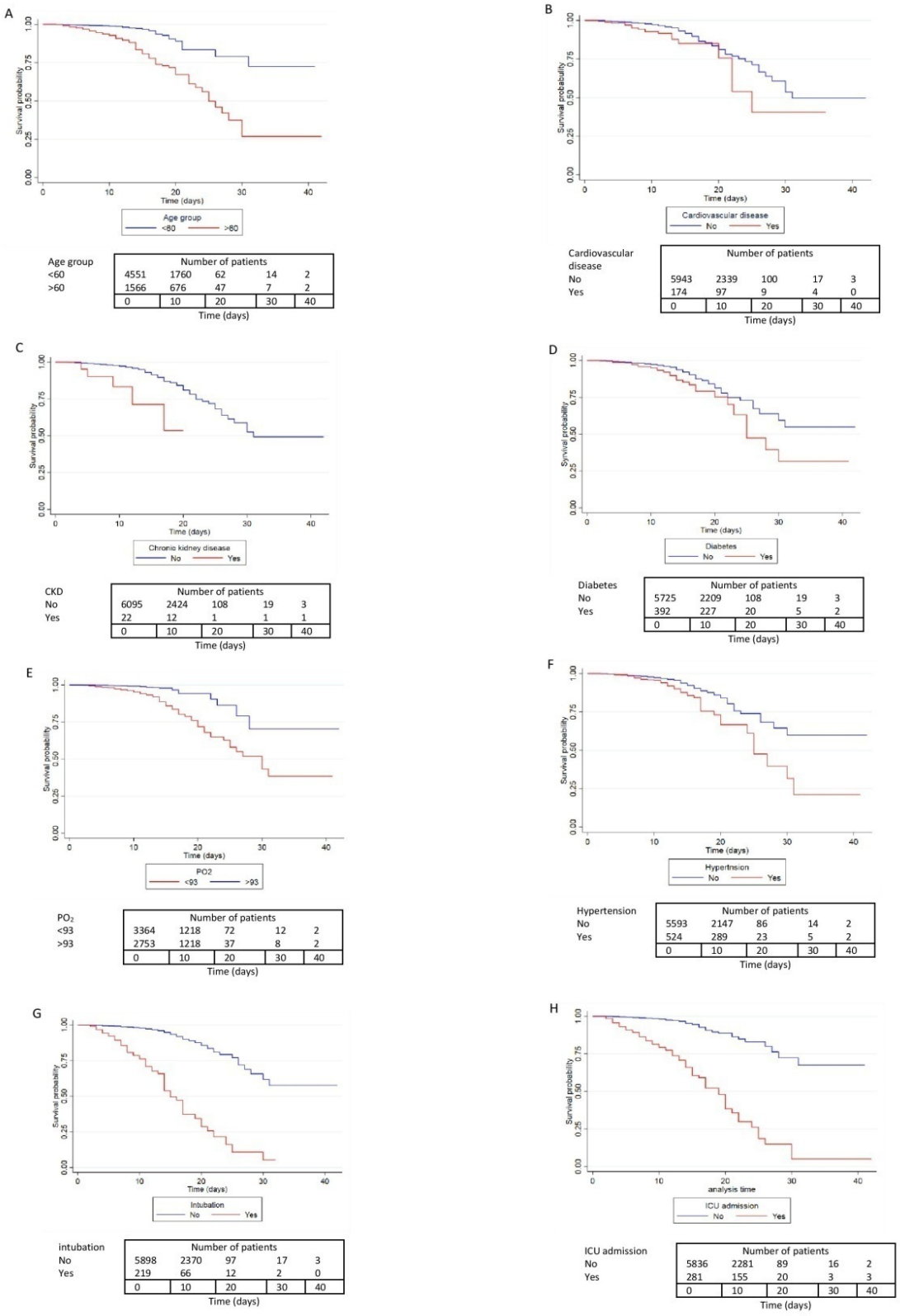

Figure 2 Kaplan-Meier survival plots of risk factors

In the crud models, the hazard rate for the elderly age group, ICU, intubation, pO_2, hypertension, and diabetes was significant in both periods. The hazard rate of CKD and CVD were significant only before the Delta variant (table 3).

Table 3 Hazard ratio for the death outcome in crude and adjusted Cox regression models before and after the Delta variant spread

Variable	Before Delta				After Delta			
	crud		Adjusted		crud		Adjusted	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age				**<.001**				**<.001**
<=60								
>60	9.81 (5.29- 18.17)	<.001	5.17 (2.61- 10.24)		4.79 (3.41- 6.73)	<.001	3.57 (2.52- 5.06)	
CKD	6.21 (2.24- 17.17)	<.001	1.03 (0.35- 3.02)	0.957	5.09 (0.71-36.54)	0.105	-	-
ICU	12.92 (8.16- 20.46)	<.001	2.33 (1.21- 4.47)	**0.011**	9.15 (6.36- 13.16)	<.001	5.37 (3.63- 7.95)	**<.001**
pO2 (%) <93	6.75 (3.25- 14.03)	<.001	2.52 (1.16- 5.46)	0.158	4.29 (2.8- 6.57)	<.001	2.69 (1.73- 4.18)	**<.001**
Intubation	21.54 (13.67-33.95)	<.001	8.61 (4.58- 16.18)	**<.001**	6.14 (3.77- 10.00)	<.001	3.27 (1.95- 5.50)	**<.001**
Hypertension	2.67 (1.69- 4.22)	<.001	0.66 (0.37- 1.18)	0.163	2.09 (1.30- 3.36)	0.002	1.79 (0.99-3.22)	0.054
CVD	2.86 (1.60- 5.12)	<.001	2.00 (1.09- 3.66)	**0.025**	1.94 (0.79- 4.75)	0.145	-	-
Diabetes	2.16 (1.32- 3.53)	0.002	0.79 (0.44- 1.42)	0.437	2.25 (1.33- 3.81)	0.002	1.72 (0.90- 3.29)	0.100

In the adjusted models, the elderly age group, intubation, and ICU admission had significant hazard rates in both periods. The hazard rate of CVD and pO_2 were significant before and after Delta emergence, respectively (table 3).

DISCUSSION

The results of this study showed the survival of the hospitalized COVID-19 patients and its potential risk factors using the log-rank and Cox regression methods in Sirjan city (Iran) before and after the spread of the Delta variant separately. The patients experiencing early symptoms such as pO_2<93%, muscular pain, fever, loss of appetite, and diarrhea after the Delta outbreak were more than before. In comparison, the deceased group had a higher mean age than the and survived group. Also, there were significant relationships between some risk factors and comorbidities such as pO_2<93%, admission to ICU, intubation, CVD, CKD, diabetes, neurological disorders, and hypertension with the outcome of COVID-19. The mean period from the onset of symptoms to hospital admission and from hospitalization to the outcome was different in the two groups.

The survival plot of gender, asthma patients, and neurological disorders did not show any difference between subgroups. According to the results, among people over the age of 60, those with CVD, diabetes, CKD, or hypertension had different survival functions and the risk of death was higher in these patients. Also, the hazard rate of death was different in patients admitted to the ICU, individuals

who required intubation, and cases with pO_2<93%. The effect of age on the survival of COVID-19 patients has resulted in some studies similar to ours.[18-25]

There are different results concerning the effect of gender in various studies. Unlike the present study, some papers such as Galbadage et al.[19], Galvão et al.[20], Nijman et al.[22], Escudero et al.[23], and Nikpouraghdam et al.[26] have shown that the risk of mortality from COVID-19 in men was higher than in women. It seems that there are more gaps in the results of various studies regarding the effect of comorbidities on the survival of individuals infected with COVID-19. Although some studies have shown the effect of comorbidities on the survival or death of patients, the types of comorbidities investigated were different. As shown in our study, some comorbidities such as CVD, CKD, diabetes, and hypertension had a higher risk of mortality based on the log-rank test. Nijman et al.[22] in 2021 have shown that pulmonary disease, CVD, and hypertension were significant. Escudero et al.[23] in 2020 showed that apart from pulmonary disease, CKD can also affect the mortality of patients. In 2020, Sousa GJB et al.[24] found that besides pulmonary disease and CKD, other conditions such as diabetes, obesity, neurological disorders, and CVD can also play a significant role. CVD and pulmonary disease were significant factors in the study by Thai et al.[25] in 2020. Also, CKD was the only comorbidity affecting the mortality of patients with COVID-19 in Cheng et al.[27] in 2020. It appears that the types of comorbidities which can affect the mortality of COVID-19 patients are different in each region and population. Further studies are suggested in this regard.

The survival functions of patients were different before and after the spread of the Delta variant. Thus, the risk of death after the Delta variant became almost two times more than before. Accordingly, we fitted the crude and adjusted the Cox regression models in these two time periods, separately.

Based on crude models, the hazard rate of death in the elderly age group was almost 10 before the Delta spread, while this measure plunged to 4.79 after the emergence of Delta variant. It may be concluded that after the outbreak of this variant, the mortality of COVID-19 in younger age groups had got close to that of elderly patients. Except for CKD and CVD, which were not significant in the crude model after the Delta variant emergence, all the other variables were effective on the risk of death in both crude models. This result could have occurred under the influence of age. Because CKD and CVD occur more in older people and after the Delta variant spread, the mortality rate of the two age groups became close.

In the adjusted models, only CVD was significant after the spread of Delta variant and other comorbidities had no significant hazard ratio. It seems that the risk of death was influenced more by admission to the ICU, pO_2<93%, intubation, and elderly patients. It appears that the risk factors such as CKD, Hypertension, and diabetes which are not significant in the adjusted model, were more influenced by age as the prevalence of these diseases is more in older age. In the study conducted by Nijman et al.[22], there were no significant comorbidities in the adjusted Cox regression model, although pulmonary disease, hypertension, and CVD were effective in the crude models. Results from the study done by Sausa GJB et al.[24] indicated that only pulmonary disease, CVD, and neurological disorders were significant in the adjusted Cox regression model and obesity, CKD, and diabetes had no effect on the mortality risk of COVID-19.

Individuals admitted to the ICU with intubation and pO_2<93% can be considered severe patients. Our results are consistent with the studies concerning the effect of these risk factors on the mortality of patients.[23-24, 28]

Although this study was performed in a large population and considered the delta variant, it had some limitations. All the possible comorbidities had been not considered in the study and the time period of each comorbidity was unknown, which could affect COVID-19 mortality. Also, the duration of intubation and length of stay at the ICU were not clear and not recorded in the research. The number of comorbidities of each patient had been not considered in the present study, which can be another limitation.

CONCLUSION

We assert that the HR of the age group after Delta variant emergence was decreased in both crude and adjusted models. It seems that factors like older age, ICU admission, intubation, and pO_2<93% are the most important variables which play a pivotal role in the survival of COVID-19 patients.

RECOMMENDATIONS

There is no doubt about the importance and effect of comorbidities on COVID-19 mortality, but further studies are suggested to investigate the effect of comorbidities on the mortality of COVID-19 patients in different age groups. In the other words, comorbidities may have different effects on the mortality of COVID-19 patients in each age group.

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