Research Paper

Determining the Related Factors to the Survival Time of Inpatients With COVID-19 in Northern Iran: A Retrospective Study

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ABSTRACT

Background: Coronavirus disease 2019 is a new viral disease and in a short period, it has affected the world in various economic, social, and health aspects. This disease had a high mortality rate at the time of its occurrence. This article aims to determine the related factors to the survival time of inpatients with COVID-19 in northern Iran.

Methods: In this retrospective study, the data of 3480 patients with laboratory confirmation of the virus caused by COVID-19 infection in 17 hospitals covered by Golestan University of Medical Sciences from February 20 to July 20, 2020 were used. For all patients included in the study, until the end of the study, the follow-up has been done through the hospital information system unit. Statistical analysis was performed using R statistical software version 3.6.2 with a survival package.

Results: Out of 3480 definitive patients with COVID-19, the average age of the patients was 52.93±19.20 years and 51.1% of them were women. A total of 77.6% of patients recovered and 22.4% died at the end of the study (781 patients, 22.4%). The median survival time among deceased patients was less than one day (interquartile range [IQR]: 0–5) days. Patients with an age group above 49 years had a 2.1 times higher chance of death than other patients. Patients who had no history of hospitalization in the intensive care unit (ICU) had a 1.77 times higher chance of death than other patients. Patients who did not use ventilators had a 1.21 times higher chance of death than other patients.

Conclusion: Finally, according to the results of this study, in the early days of hospitalization, it is necessary to investigate the spread of COVID-19 in people younger than 49 years, hospitalized in intensive care unit (ICU), and hospitalized in other cities.

Keywords: COVID-19, Cox proportional hazard models, Survival, Iran

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1. Introduction

Human coronavirus is one of the main pathogens of respiratory infection. The two highly pathogenic viruses, severe acute respiratory syndrome coronavirus 2 (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), cause a severe respiratory syndrome in humans, and four other human coronaviruses (HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-HKU1) induce mild upper respiratory disease. Since Dec 8, 2019, several cases of pneumonia of unknown etiology have been reported in Wuhan, Hubei Province, China [1]. On Jan 7, a novel coronavirus was identified by the Chinese Center for Disease Control and Prevention (CDC) from a patient's throat swab sample [2]. As the number of deaths increased, on January 30, 2020, the WHO declared a "global emergency" and on February 11, it announced that the new coronavirus would be called "COVID-19". Cases with mild clinical symptoms, and a lack of adequate infrastructure to isolate infected individuals, especially in low- and middle-income countries, are barriers to disease control [3].

On February 19, Iran confirmed two deaths due to COVID-19 in Qom City, Iran, 150 km south of the capital, Tehran City, Iran [4]. Despite the detection of this disease within a few weeks, the necessary measures to control the disease epidemic have not been enough. On May 2, 2020, in 215 countries, 3 449 718 cases existed, of which 242 789 people died and 1 102 408 improved, and in Iran, 96 448 new cases existed, of which 6 156 people died and 77 350 people improved [5]. Golestan Province, Iran was in an unfavorable situation at the beginning of the outbreak of the disease in Iran so that in the period from February 1, 2020, to the end of April 2020, more than two thousand patients with suspected COVID-19 were admitted to the Province's medical centers [6].

People with only mild symptoms recover within 3 to 7 days, while those with conditions, such as pneumonia or severe diseases take weeks to recover. Sharing of crucial data, as unearthed by epidemiologists around the world, is highly critical and can help definitively determine the characteristics of this new infectious disease, and containing its additional spread accordingly is urgent [7]. In the Murillo-Zamora and Hernandez-Suarez study, factors associated with an increased risk of dying were male gender, age, pneumonia at hospital admission, immunosuppression, and personal history of chronic non-communicable diseases [8]. In the study conducted by Kargarian et al. at the end of 1-year follow-up, the cumulative incidence (risk) of COVID-19 was estimated 7% [9]. The results of Faraji et al.'s study showed that the survival of patients on the tenth day was about 75%; while on the 20th day, the survival decreased to 50% and after 30 days, about 25% of the patients survived [10]. Assessing the survival rate of COVID-19 patients and its related factors in different regions can help manage the disease in the treatment process and prepare for the epidemic. This article was conducted to determine factors related to the survival time of patients with COVID-19 in northern Iran.

2. Methods

This study was retrospective and the study population included all definite cases of hospitalization in 17 hospitals covered by Golestan University of Medical Sciences from February 20 to July 20, 2020. The required information was obtained from the hospital information system unit in the statistics and information management of Golestan University of Medical Sciences.

The inclusion criteria included all hospitalized cases, i.e. a person with laboratory confirmation of the virus caused by COVID-19 infection, regardless of the presence of symptoms, clinical signs, and close association, and all suspected COVID-19 patients with vital signs (respiratory rate >24, heart rate >125 beats/min, oxygen saturation [Spo2] <90% on ambient air) and laboratory findings (D-dimer >1000 ng/mL, creatine phosphokinase [CPK] > twice the upper limit of normal, C-reactive protein [CRP] >100, lactate dehydrogenase [LDH] >245 U/L, elevated troponin, progressive lymphopenia, high ferritin [ferritin >300 ug/l]) [11] and patients who lived in Golestan Province. Also, patients with large information deficits were excluded from the study. Data collection was a census.

This paper describes continuous variables (age, survival time) using median, means, and standard deviations, and categorical variables (gender, residence, hospitalization in the intensive care unit [ICU], and use of a ventilator) expressed as number and percentage (%). According to a similar study [2], the average age of 49 years is considered the cut-off point of the age group. Cox's regression proportional hazard (PH) was used to model and we used the goodness of fit based on the Schoenfeld residuals to test the PH assumption. We used the Kaplan-Meier curve and log-rank test to compare survival times between groups.

The time interval between identifying individuals with COVID-19 and the time of death or the end of the study (July 20, 2020) was considered as the time of survival or censorship (response variable). For all patients included in the study, until the end of the study, the follow-up has been done through the hospital information system unit. Statistical analysis was performed using R statistical software version 3.6.2 with a survival package. For all the statistical analyses, P<0.05 was considered significant.

3. Results

The average age of the patients was 52.93 ± 19.20 years and 51.1% of them were women. Out of 3 480 definitive patients with COVID-19, 77.6% of patients recovered and 22.4% died at the end of the study (781 patients, 22.4%). In this study, the median survival time among deceased patients was less than one day (interquartile range [IQR]: 0–5) days while the duration of hospitalization was from 0 to 97 days. The mean age of patients was 52.93 years so that 58.4% of patients were older than 49 years. The age range of patients was less than one year to 99 years. A total of 51.1% of patients were female;

Table 1. Frequency (%) and log-rank test in patients with COVID-19 in Golestan Province, Iran

Variables		Mean±SD/No. (%)			P*
		Censored	Event	Total	
Age (y)		50.09±18.79	62.74±17.26	52.93±19.20	
Age group	≤ 49	1305(48.4)	141(18.1)	1446(41.6)	<0.001
	> 49	1394(51.6)	640(81.9)	2034(58.4)	
Gender	Male	1287(47.7)	415(53.1)	1702(48.9)	0.200
	Female	1412(52.3)	366(46.9)	1778(51.1)	
Residence	Capital	567(21.0)	149(19.1)	716(20.6)	<0.001
	Other	2132(79.0)	632(80.9)	2764(79.4)	
Hospitalization in the ICU	No	2603(96.4)	650(83.2)	3253(93.5)	<0.001
	Yes	96(3.6)	131(16.8)	227(6.5)	
Use a ventilator	No	2345(86.9)	642(82.2)	2987(85.8)	0.200
	Yes	354(13.1)	139(17.8)	493(14.2)	

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* Probability values are reported from the log-rank test.

Abbreviations: ICU: intensive care unit

Table 2. Results of the test of the proportional hazard (PH) assumption in the patients with COVID-19 in Golestan Province, Iran

Variables	Chi-square	df	P
Age group (RC: ≤ 49)	0.01	1	0.907
Gender (RC: male)	0.01	1	0.994
Residence (capital)	8.33	1	0.004
Hospitalization in the ICU (yes)	0.54	1	0.463
Use a ventilator (yes)	0.02	1	0.959
Global test	9.09	1	0.106

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Abbreviations: ICU: intensive care unit; RC: reference category

Table 3. Results of Cox proportional hazard (PH) model in the patients with COVID-19 in Golestan Province, Iran

Variables	β	SE	Wald	HR	95 % CI		P
					Lower	Upper	
Age group (RC: ≤ 49)	0.74	0.09	7.8	2.10	1.74	2.52	<0.001
Gender (RC: male)	-0.07	0.07	-0.96	0.93	0.81	1.08	0.340
Residence (capital)	0.47	0.09	4.93	1.59	1.32	1.92	<0.001
Hospitalization in the ICU (yes)	0.57	0.10	5.80	1.77	1.46	2.14	<0.001
Use a ventilator (yes)	0.19	0.10	1.98	1.21	1.00	1.47	0.048

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Abbreviations: ICU, intensive care unit; RC, reference category; CI, confidence interval; HR, hazard ratio; SE, standard error.

20.6% of patients were hospitalized in the capital of the province; 6.5% of patients were admitted to ICU and 14.2% of patients also used ventilators. Table 1 presents the frequency distribution of demographic and clinical characteristics in definitive patients with COVID-19.

In this study, to compare the survival rate in the subgroups of the studied variables, first, the log-rank test was used to identify the variables affecting the survival time of patients. The results of the log-rank test in definitive patients with COVID-19 showed a significant relationship between patients' survival function and age group, location, and hospitalization in the ICU (Table 1).

Figure 1.a shows the patient survival curve. Figure 1.b shows the patient survival curve by age. Due to the significance of the age variable in the log-rank test and according to the chart, before 40 days, patients with an age of younger than 49 years had lower survival and after that, they had similar survival. Figure 1.c shows the survival curve of patients in terms of hospitalization in the ICU. Before 40 days, patients hospitalized in ICU had higher survival, but after this time, they had similar survival to patients not hospitalized in ICU. Figure 1.d shows the patient survival curve by location. Before 40 days, patients hospitalized in the center of the province had higher survival, but after this time, they had similar survival to other patients. Before fitting the Cox model to survival data, the goodness-of-fit test was used to test the PH hypothesis.

The results of this test showed that the PH hypothesis is valid for the variables of age, sex, hospitalization in the ICU, and the use of a ventilator ($P<0.05$) and is not valid for the variable of residence ($P<0.05$) (Table 2).

Finally, all variables were included in the multivariate Cox regression model and the variables of age, location, ventilator use, and ICU hospitalization were significant. Finally, according to the results of the PH hypothesis test, the variables of age, ventilator use, and ICU hospitalization have been identified as related factors to the survival of patients with COVID-19 (Table 3). Patients with an age group of older than 49 years had a 2.1 times higher chance of death than other patients. Patients who had no history of hospitalization in the ICU had a 1.77 times higher chance of death than other patients. Patients who did not use ventilators had a 1.21 times higher chance of death than other patients.

4. Discussion

The results of studies showed a huge economic burden of COVID-19 on society and the health system [12]. The high prevalence of this disease has imposed huge economic damage on society and the country's health system. Considering the very high costs of treating hospitalized patients, it is necessary to identify patients and control disease severity in hospitals. This study was conducted to investigate the factors affecting the survival time of patients with COVID-19.

Out of 3 480 hospitalized patients, the number of deaths during the study period was 22.4%. In a study conducted in Kurdistan Province, Iran [13], deaths were reported at 8.7%, which was lower than in our study. A study on nearly 1 100 patients from China suggested a case-fatality ratio of 1.4% [14]. From a dataset of 44 672 confirmed cases in China, a report from the Chinese Center for Disease Control and Prevention (CDC) estimated an overall case-fatality ratio of 2.3% [15]. Another study conducted in Latin America reported a death rate of 3.72% [16]. Therefore, the results of this study and other studies in other countries showed that the proportion of deaths due to COVID-19 is higher than the cases reported in China at the beginning of the outbreak of the disease.

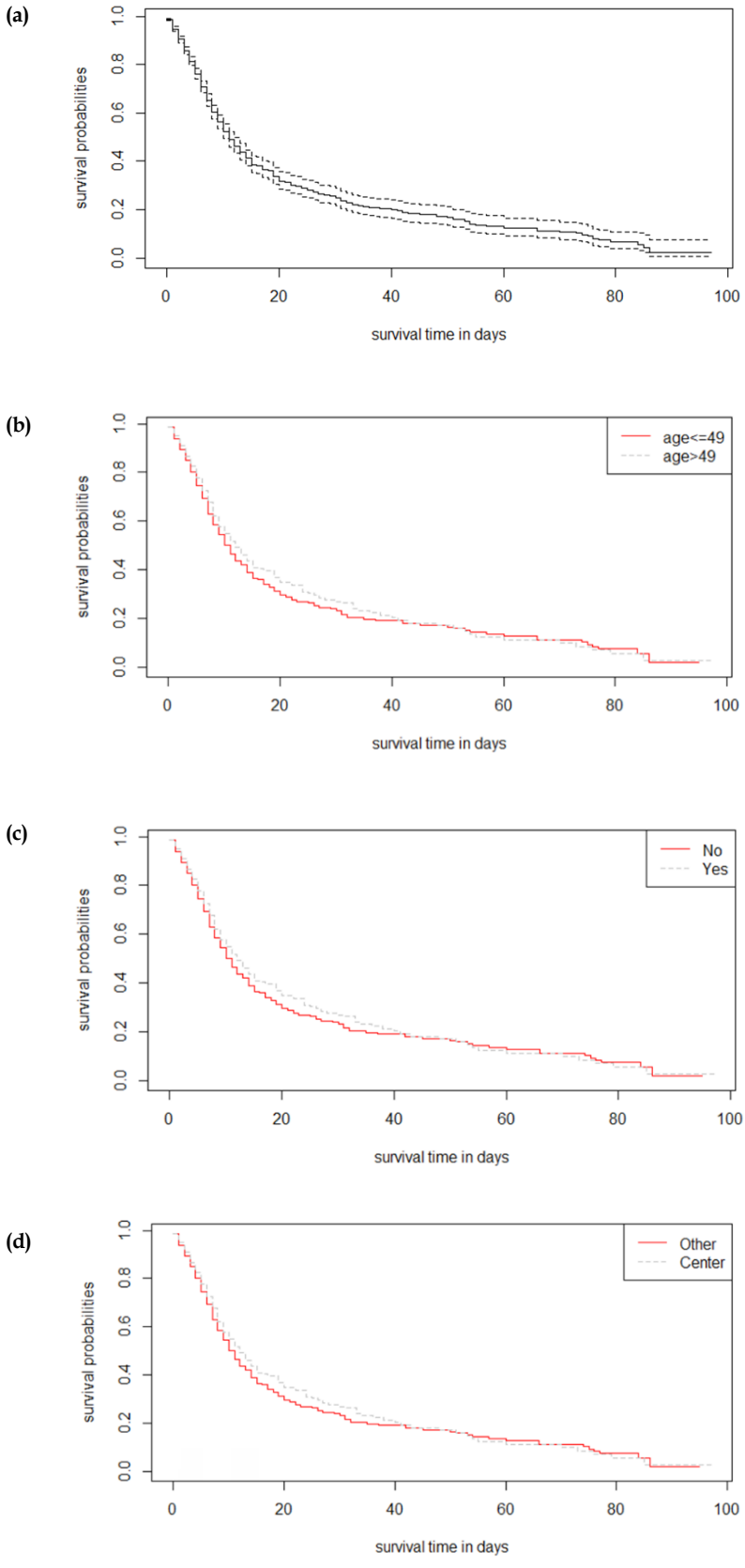

Figure 1. The Kaplan-Meier curve in the COVID-19 patients of Golestan Province, Iran, (a) total, (b) age group, (c) hospitalization in the intensive care unit (ICU), (d) residence

The results showed that the average age of the deceased was approximately 63 years. In previous studies, older age has been reported as a crucial prognostic factor of mortality in SARS and MERS [17, 18]. Several studies have confirmed that increasing age in patients with COVID-19 is associated with death [13, 19-21]. Esharti et al.'s study showed that being older than 50 years increases the risk of death in these patients [22].

The hazard ratio of death in the patient's age group less than or equal to 49 years was 2.10 compared to the older than 49 years. In the study conducted by Nemati et al., the recovery rate of patients younger than 46 years was higher than those older than 47 years [23]. Elderly people have less immunity to infectious challenges; therefore they are more susceptible to infected diseases. On the other hand, based on the previous research, aging has been expressed as a crucial independent risk factor for mortality in SARS and MERS. Initial studies in macaques treated with SARS-CoV discovered that the production of inflammatory factors and deficiency in control of viral replication is higher in more adult macaques than in younger adults [19, 24].

According to the results, 53.1% of those who died were male which was consistent with the results of the studies by Chen et al. and Carlos del Rio et al. [25, 26]. In the study conducted by Zand Karimi et al. (2020) in the Kurdistan Province, the number of dead men was more than women during the study period [13].

The results of the Cox PH regression model showed no statistically significant difference between men and women in terms of survival time. This result has been confirmed in other studies [13, 27]. Although significant differences were observed in the mortality rates between men and women in the early outbreak of the COVID-19 disease [1, 2].

The median survival time among deceased patients was less than one day (IQR: 0–5) days while the duration of hospitalization was from 0 to 97 days. The results of a study conducted by Cummings et al. in a prospective cohort study showed that the median survival time of hospitalized patients was 9 days [28]. According to Zhou et al., the median duration of virus shedding and recovery of patients with coronary artery disease was 20 days, ranging from 8 to 37 days [19]. In another study, the median time of hospitalization was 19 days [26].

The strength of this study was access to a suitable sample size (3 480 people) of different age and gender categories so that the results of this study can be generalized to the whole community. One of the main limitations of this study was the reliance on a limited number of factors due to the incomplete recording of clinical and laboratory information in the prepared data file. The most critical weakness of hospital data is the inaccuracy of the recorded information, and this is one of the limitations of our study; hence the results may not be generalizable.

5. Conclusion

Finally, according to the results of this study, in the early days of hospitalization, it is necessary to investigate the spread of COVID-19 in people younger than 49 years, hospitalized in ICU, and hospitalized in other cities.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Research Committee of Golestan University of Medical Sciences (Ethic Code: IR. GOUMS.REC. 1399.271). Then the authors pledged that no personal and confidential information will be used individually.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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