

COVID-19

Analysis of death risk factors among COVID-19 patients in Yazd, Iran: A case-cohort study

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Keywords

COVID-19 • Iran • Epidemiologic Studies • Risk factors • Mortality • SARS-CoV-2

Summary

Background. The COVID-19 epidemic control has become a global challenge and many contributing variables are still unknown to policymakers. This case-cohort study was conducted to investigate the risk factors of mortality in COVID-19 patients.

Methods. This case-cohort study was conducted on 956 samples in Ardakan and Meybod counties, Yazd Province, between February 20 and May 20, 2020. The data collection tool was a researcher-made questionnaire. Data analysis was done using descriptive statistics and paired t-test, chi-square, and logistic regression analysis.

Results. Of a total cohort population of 993 in Ardakan and Meybod counties, 435 were assigned to the control group and 521 were assigned to the case group. The results of outcome analysis showed that 14.4% of the patients in the case group and 11.5% of

the patients in the control group died. According to the results of logistic regression analysis in COVID-19 patients, each one-year increase in age increased the risk of mortality by 6% ($HR = 1.06$, $p < 0.001$), each one-day increase in the hospital stay increased the risk of death by 8% ($HR = 1.08$, $p < 0.001$). Moreover, the presence of cardiovascular disease, chronic neurological disease, and chronic pulmonary disease increased the risk of death. The patients who underwent mechanical ventilation had 85% less chance of survival ($HR = 0.15$, $p < 0.001$).

Conclusions. The results showed a higher mortality rate in the elderly patients as well as those with underlying diseases. Attention should be paid to at-risk and elderly patients in terms of ensuring a healthy diet, improving their self-care practices, and providing long-term medical and healthcare facilities.

Introduction

Despite advances in laboratory sciences and medicine, epidemics are still a great challenge threatening the lives of millions. A series of unexplained cases of pneumonia were reported from Wuhan, China in the December 2019. On January 12, 2020, the WHO temporarily named this new virus as Coronavirus Disease 2019 (COVID-19). The WHO officially announced COVID-19 as the name of this new disease on 11 February 2020 [1] and identified it as a public health emergency on 30 January 2020 [2].

This virus has a high infectivity rate and incubation period (2-14 days), which increase its prevalence and hinder prevention and control [3].

This virus easily transmits from one person to another through respiratory droplets and direct contact with virus-containing body secretions via the eyes, mouth, and nose [4].

The mortality rate is high in COVID-19 patients requiring mechanical ventilation due to severe pulmonary injuries [5]. No specific antiviral drug has proven effective for severe COVID-19 and treatment is mainly

supportive, including maintain the vital signs, oxygen saturation level, and blood pressure and decreasing the complications like secondary infections and organ failure [6].

Early studies showed that patients with underlying diseases were at higher risk of complications and death from COVID-19. About 50% of the inpatients suspected of COVID-19 have other chronic diseases and 41% of inpatients with confirmed COVID-19 also suffer from cardiovascular or cerebrovascular disease. The researchers have also found a marked difference in mortality rate according to age group [7].

Despite global efforts to understand COVID-19, many issues are still unknown. The majority of the new studies are based on univariate comparisons. Moreover, most of the studies investigating the risk factors of mortality were conducted in confirmed cases in China and little information is available on the risk factors of death in other parts of the world. Furthermore, few studies have addressed the risk factors of this disease during the epidemic. Due to the fact that the risk factors of mortality in patients with covid-19 differ according to climatic and locational conditions and these risk factors cannot

be accurately generalized to all regions, therefore, this study was conducted in the center of Iran. Also, in this study, mortality risk factors have been investigated as a cohort study, which increases the reliability of the results by comparing the results in the cohort population.

Considering the above research gaps, this case-cohort study was conducted to evaluate the risk factors of mortality in COVID-19 patients.

Materials and Methods

STUDY DESIGN

This study was a case-cohort study. Such studies are used to investigate rare disease [8]. In these studies, the controls are selected from the at-risk population in the beginning of the follow-up time and these groups are selected using random sampling.

Population and research sample

The study was conducted in Ardakan and Meybod counties, Yazd Province. Considering cultural, geographic, climatic, and demographic conditions between these two counties and the relatively high prevalence of COVID-19 infection in these counties, population homogeneity, simultaneous onset of disease, and the similar origin of the population, the residents of these two counties were selected as the cohort population. The reference population was at suspected cases admitted to infectious and ICU wards of Ardakan and Meybod hospitals. The research sample was consistent with the reference population. The patients were selected by census. In this study, exposure was defined as a positive PCR test and survival or death was considered as the outcome of interest. All at-risk subjects that had direct contact with confirmed COVID-19 patients and had a positive PCR test for SARS-CoV-2 were selected as cases. The control group was selected randomly from at-risk subjects who have negative tested for SARS-CoV-2.

Data collection tool

The data collection tool was a researcher-made questionnaire based the data available in the COVID-19 data dashboard of Shahid Sadoughi University of Medical Sciences. The questionnaire included demographic, diagnostic, and clinical data of the patients such as age, sex, occupation, history of underlying diseases (cardiovascular disease, diabetes, renal disease, chronic neurological disease, and chronic pulmonary disease), length of hospital stay, history of mechanical ventilation, and final situation.

The follow-up time in case and control groups was three months starting from detecting the first case of COVID-19 in these counties (20 February 2020 to 20 May 2020). The COVID-19 data dashboard of Shahid Sadoughi University of Medical Sciences was used to collect the data of the subjects in case and control groups.

Statistical analysis

Frequency, percentage, mean, standard deviation, and median are used to describe the data. Independent t-test and chi square were applied to compare the variables between the two groups. Multiple logistic regression

analysis and binary logistic regression analysis with survival or death as outcome were used to evaluate the effect of each variable. All data were analyzed through SPSS.21 software.

Results

Of a cohort population of 993 in Ardakan and Meybod, 530 with positive PCR results were assigned to the case group as COVID-19 patients and 463 with negative PCR results were assigned to the control group. After applying the inclusion and exclusion criteria, 521 and 435 subjects were included in the case and control group, respectively (Fig. 1).

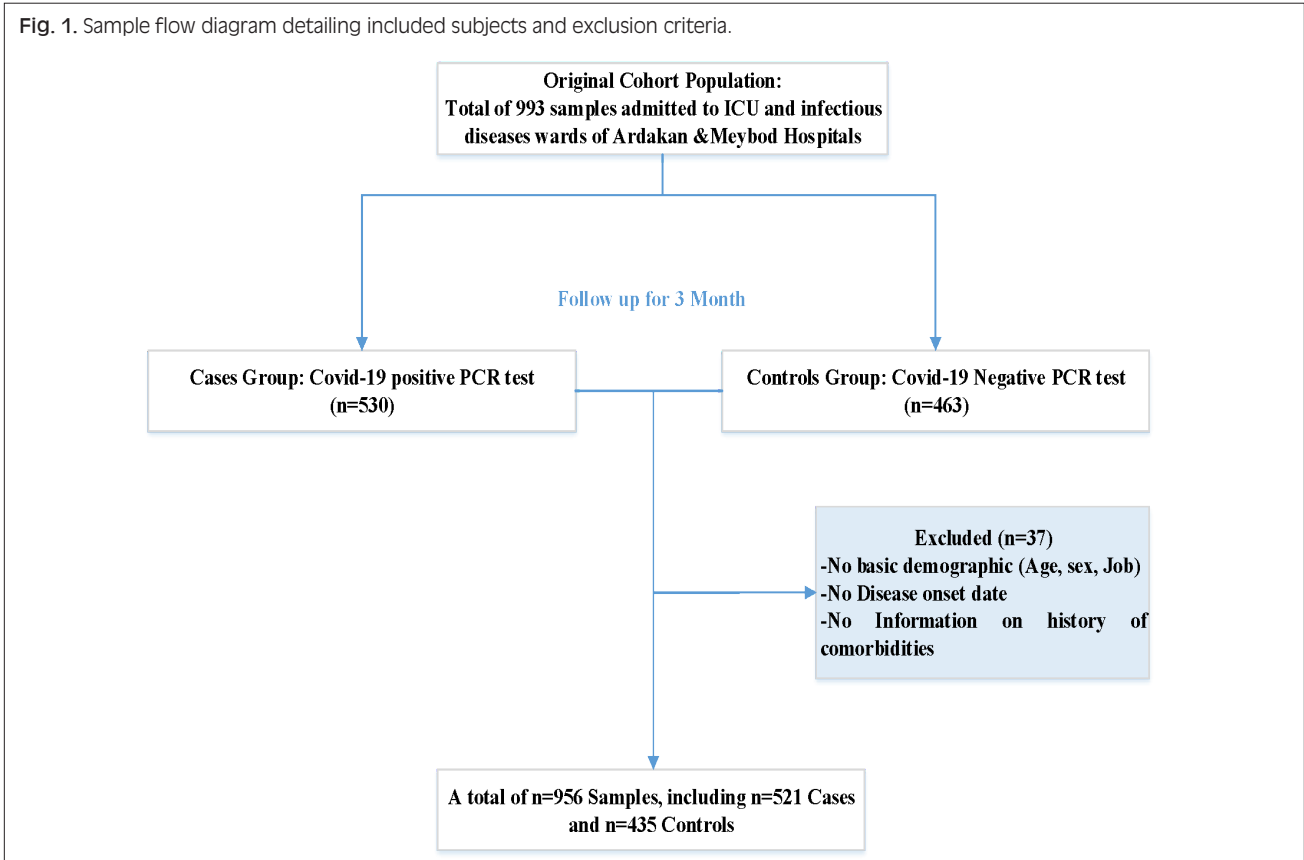
The results of chi square showed no significant difference in the distribution of age, sex, and occupation between the two groups ($p > 0.05$). No significant difference was also observed in the distribution of underlying diseases between case and control groups ($p > 0.05$) and both groups were similar in terms of having at least one underlying condition. Overall, 25.7% ($n = 246$) of the subjects had cardiovascular disease, 18.8% ($n = 180$) had diabetes, 9.2% ($n=88$) had chronic pulmonary disease, 4.1% ($n = 39$) had chronic neurological disease, 3.1% ($n = 30$) had renal disease. The results of outcome analysis showed that 14.4% of the cases ($n = 75$) and 11.5% of the controls ($n = 50$) died, indicating a significant difference ($p = 0.04$). Moreover, 12.9% of the cases ($n = 67$) and 12% of the controls ($n = 52$) were admitted to the ICU. The length of hospital stay was also significantly longer in the case group compared to the control group ($p = 0.001$) (Tab. I). The results show that the length of stay is longer in patients with a positive corona test and also in patients who have died (Fig. 2).

According to the results of logistic regression analysis in COVID-19 patients, each one-year increase in age increased the risk of mortality by 6% ($HR = 1.06$, $p < 0.001$) and each one-day increase in the hospital stay increased the risk of death by 8% ($HR = 1.08$, $p < 0.001$). Moreover, the presence of cardiovascular disease, chronic neurological disease, and chronic pulmonary disease increased the risk of death. The patients who underwent mechanical ventilation had 85% less chance of survival ($HR = 0.15$, $p < 0.001$) (Tab. II).

Discussion

The results of outcome analysis showed that 14.4% of the patients in the case group and 11.5% of the patients in the control group died, indicating a significant difference. A study in Wuhan, China reported that 28% of the COVID-19 patients died [9]. The mortality rate of COVID-19 was 10.5% and 6% in studies conducted by Shi [10] and Liu [11], respectively. The mortality rate was rather higher in the present study compared to the above studies. The difference in the mortality rate between different studies may be related to heterogeneity in the reported data, inclusion criteria for COVID-19

Fig. 1. Sample flow diagram detailing included subjects and exclusion criteria.



patients, and the conditions of health systems in different countries.

The results showed that the chance of death increased with age. Liu et al. also found a higher mortality percentage in the elderly patients [11]. The results of a study conducted in the U.S. showed that 80% of deaths occurred in patients aged above 65 years [12], which was similar to a study conducted in China that found that 80% of the mortalities occurred in people above

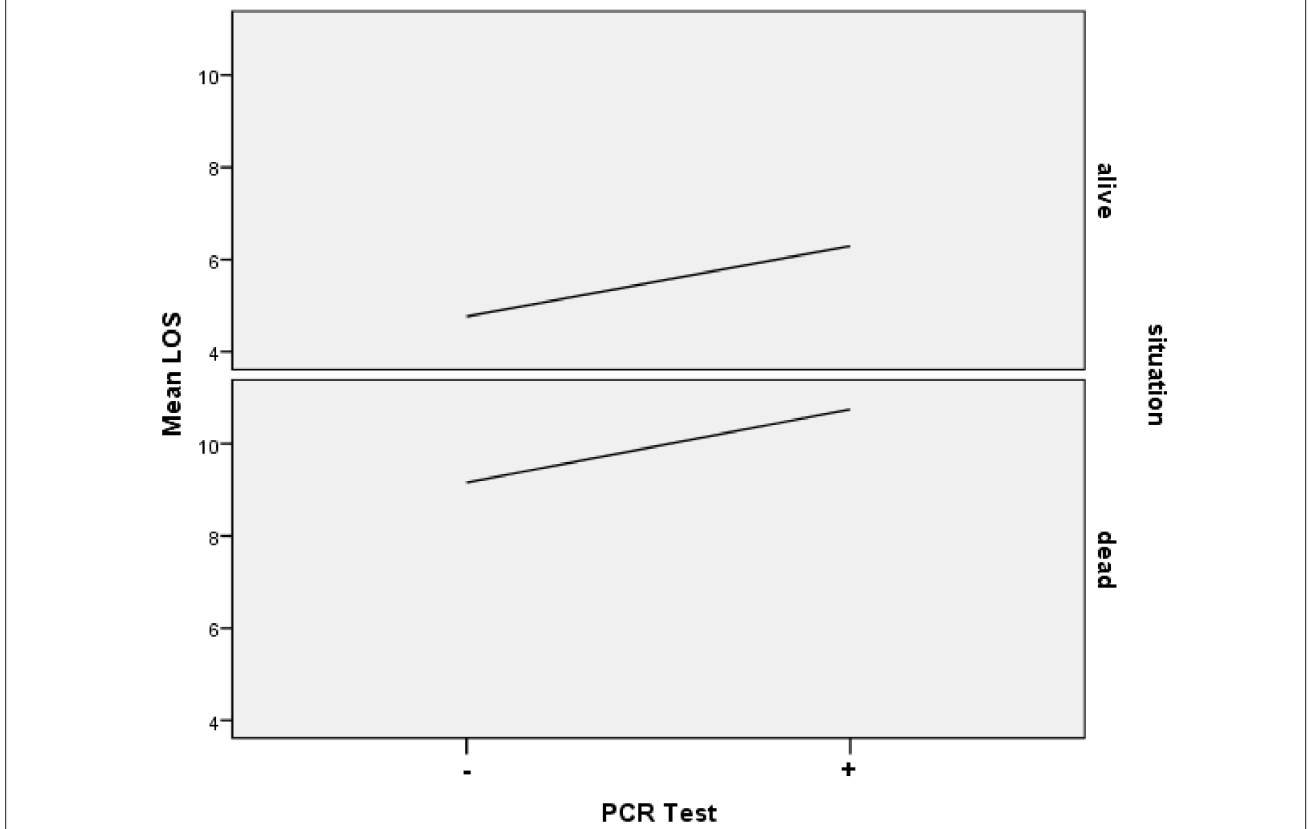
80 years [13]. COVID-19 is usually more severe in elderly patients and they often suffer from underlying diseases; therefore, they require better care and the risk of mortality is higher in this population.

According to the results of this study, the presence of cardiovascular disease, chronic neurological disease, and chronic pulmonary disease increased the chance of death in COVID-19 patients. According to the results of several studies, patients with cardiovascular diseases

Tab. I. Baseline characteristics of study population.

Variables	Levels	All patients (n = 956)	Control (n = 435)	Case (n = 521)	p*
Age (years)	Mean ± SD	57.79 ± 18.02	57.08 ± 19.64	58.29 ± 16.43	0.29
Sex	Male	476 (49.8)	214 (49.2)	262 (50.3)	0.39
	Female	480 (50.2)	221 (50.8)	259 (49.7)	
Occupation	Hospital Jobs	21 (2.2)	13(3)	8 (1.6)	0.094
	Other Jobs	511 (53.4)	229 (52.6)	282 (54.1)	
	Unknown	424 (44.4)	193 (44.4)	231 (44.3)	
Chronic medical illness	Coronary heart disease	246 (25.7)	119 (27.4)	127 (24.4)	0.29
	Diabetes mellitus	180 (18.8)	77 (17.7)	103 (19.8)	0.45
	Chronic kidney disease	30 (3.1)	15(3.4)	15 (2.9)	0.71
	Chronic neurological disease	39 (4.1)	21(4.8)	18 (3.5)	0.32
	Chronic pulmonary disease	88 (9.2)	41(9.4)	47 (9)	0.91
LOS	Mean ± SD	6.20 ± 5.78	5.29 ± 4.88	6.94 ± 6.33	0.001
	Median, range	5 (1-53)	4 (1-41)	5 (1-53)	
Inpatient in ICU		119 (12.4)	52 (12)	67 (12.9)	0.37
Final Situation	Alive	831 (86.9)	385 (88.5)	446 (85.6)	0.04
	Dead	125 (13.1)	50 (11.5)	75 (14.4)	

Fig. 2. The length of stay depends on the patient's final situation and PCR test.



have the highest sensitivity to COVID-19 followed by patients with diabetes, chronic respiratory disease, hypertension, and cancer [3, 5, 14]. In a study by Zhang et al., the mortality rate was 41% higher in patients with a history of respiratory disease and 13% higher in

patients with a history of cardiovascular disease [15]. Shi et al. also found that the mortality rate was 9% and 11% higher in patients with a history of cardiovascular and pulmonary disease, respectively [10]. A one-day increase in the length of hospital stay

Tab. II. The effective epidemiological factors on Mortality of COVID-19 Patients.

Variable	Levels	Univariate			Multivariate		
		HR	95% CI	p	HR	95% CI	p*
Age	Year	1.066	1.046-1.086	<.001	1.061	1.036-1.087	<.001
LOS	Day	1.085	1.050-1.121	<.001			
Sex	Male	1	-	0.669			
	Female	1.113	.682-1.816				
Job	Hospital Jobs	1	-	0.999			
	Other Jobs	0	0.000-				
Coronary heart disease	Yes	2.942	1.768-4.898	<.001	2.211	1.118-4.371	0.023
	No	1	-		1	-	
Diabetes mellitus	Yes	1.462	0.825-2.591	0.193			
	No	1	-				
Chronic kidney disease	Yes	2.228	0.690-7.189	0.180			
	No	1	-				
Chronic neurological disease	Yes	5.206	1.984-13.659	0.001	3.955	1.179-13.259	0.026
	No	1	-		1	-	
Chronic pulmonary disease	Yes	2.541	1.271-5.079	0.008			
	No	1	-				
Mechanical Ventilation	Yes	1	-	<.001	0.090	0.032-0.252	<.001
	No	0.15	0.061-0.354				

HR: Hazard ratio; LOS: Length of Stay; CI: Confidence interval; * Logistic regression. SD: Standard deviation; LOS: Length of Stay; * Chi square.

increased the risk of death by 8%. The mean length of hospital stay was longer in the case group compared to the control group such that the mean length of stay was 7 days in the case group. The results of a study conducted in Vietnam showed a higher mean length of hospital stay in COVID-19 patients (16). Studies performed in the U.S. [16, 17] and European countries reported a mean length of stay of 6-7 days for COVID-19 [18, 19]. Differences in the results may be related to differences in strategies employed by different countries for disease prevention and treatment, timing of the incidence and peak, and treatment facilities offered by hospitals. According to the results, the risk of death was 85% higher in patients receiving mechanical ventilation. A meta-analysis by Taylor et al. also showed a mortality rate of 72% in patients under mechanical ventilation [20]. Similar studies have also found a longer hospital stay in patients requiring mechanical ventilation [21-24]. Patients that need mechanical ventilation are admitted to the ICU. They usually suffer from acute respiratory problems and therefore require more care than other patients do. The mean length of hospital stay and mortality rate is higher in these patients [25-26].

Conclusions

This study showed a higher mortality rate in cases compared to controls. Moreover, the disease was more lethal in elderly patients and those with underlying diseases. Since these patients have a weaker physical condition and immune system, they are more vulnerable to infectious diseases and acute respiratory syndrome. As for social factors, the elderly face social isolation in many societies, which impairs their self-care and immunity. Therefore, to reduce the mortality rate of COVID-19, especially in at-risk subjects, attention should be paid to early patients and those with underlying diseases. Moreover, it is necessary to develop long-term care facilities to control and contain disease progress. Since COVID-19 is a global threat, more in-depth analyses and studies are required.

Strengths and limitations

In this study, the effects of different risk factors and variables were compared between cases and a sample of the cohort population as controls, which provide more accurate information compared to other epidemiologic studies. However, the effects of many variables were not evaluated since their data were not available. It is recommended that these variables, especially clinical and laboratory variables, be compared in future studies.

Declarations

Ethics approval and consent to participate:
The article's proposal was approved by the ethics

committee of Shahid Sadoughi University of Medical Sciences with the ID of IR.SSU.REC.1399.194. Due to the retrospective nature of the study, no study specific consent form was used. However, patients admitted to our hospital are asked to sign a general consent upon admission, which covers the collection of patient data and publication of these results. Therefore, the individual's informed consent was waived by the above ethics committee. We received administrative permission from (Secretary of University/Regional Research Ethics Committee Shahid Sadoughi University of Medical Sciences) to access and use the data. Data used in the study were anonymized. The ethics committee approved this procedure with the above ethical code. The present study was conducted in terms of the principles of the revised Declaration of Helsinki, which waived requirement for informed consent.

Consent for publication

Not applicable.

Conflict of interest statement:

All authors report no conflicts of interest relevant to this article.

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Availability of data

The data-sets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Authors' contributions

MMi and AD have designed the study and supervised the thesis. MR and MJF collected the data and analyzed it. They also prepared the first draft of the manuscript. MD, MMA and SM. HP has edited and finalized the manuscript; methodology: MB; performed a search of literature: MMi, AD, MM; editing MM. All authors read the manuscript and approved it.

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