Assessing Sex Differential in COVID-19 Mortality Rate by Age and Polymerase Chain Reaction Test Results; An Iranian Multi-Center Study

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Abstract

Background: Males are more likely to die from COVID-19 than females. In addition, the mortality rate among positive and suspected COVID-19 patients were reported in many literatures. The aim of this study is to evaluate the sex differential effect in the COVID-19 mortality by different age groups and polymerase chain reaction (PCR) test results.

Methods: in a multicenter cross-sectional study from 55 hospitals in Tehran, Iran, patients were categorized as the positive, negative and suspected cases. Age group, sex and hospital wards were also assessed in analysis.

Results: A total of 25481 cases (14791 males) were included in the study with the mortality rate of 12.0%. The mortality rate in positive, negative and suspected cases were 20.55%, 9.97% and 7.31%, respectively. Although the mortality in negative test group was considerable, sex was not associated with the death rate in this group. Using Cox regression model, sex had a significant effect on the hazard of death due to COVID-19 in adults and senior patients having positive and suspected PCR test results. However, sex was not found as significant factor for mortality in patients with negative PCR test occurring to different age groups.

Conclusion: Regardless of other risk factors, we found that sex differential effect in COVID-19 mortality varies significantly in different age groups; therefore, appropriate strategies should be designed to protect adult and senior men from this deadly infectious disease. Furthermore, owing to the considerable death rate of COVID-19 patients with negative test results, new policies should be launched increase the accuracy of diagnosis tests.

1. Background

Currently, coronavirus disease 2019 (COVID-19) have seriously affected people's life worldwide (1). This deadly novel human infectious disease is known as the fifth pandemic after 1918 flue pandemic (2) which was first reported in Wuhan, China since late December 2019 and subsequently has spread all over the world (3). Up to now over 2.0 million people infected by COVID-19 experienced death all over the world [21/01/2021] (4).

The highest number of Covid-19 cases observed in the USA and India, respectively (5). COVID-19 outbreak in Iran started since February 19, 2019 in the city of Qom and, until January 07,2021, a total of 1,261,903 positive cases and 55,830 deaths were reported in the country (4). On the basis of the latest online global statistics, Iran ranks second in the middle east area in terms of number of death due to COVID-19 and 15th according to the number of positive cases of COVID-19 in the world (5).

Among all critical risk factors, demographic factors including sex and age are recognized as the major risk factors of COVID-19 (6). Although there are various unanswered questions regarding these risk factors, age and sex could affect the prevalence of COVID-19 resulting in different clinical outcome across the world (7, 8). According to recent studies men are more susceptible to COVID-19 compared to women. The results of different studies indicated that the mortality rate among older men with COVID-19 was higher than women (9, 10). Furthermore, according to a study assessing the mortality ratio among two genders in several European countries, male to female sex ratio was different in various age groups (11). Consequently, evaluation of sex-specific data in different age groups is of importance to identify poor and early health between different sexes infected by COVID-19 (12). In order to assess the impact of sex among COVID-19 patients, essential health policies should be taken to account to implement targeted treatment plans including early recognition and aggressive testing and also to avoid treatment bias among males and females (12).

In order to screen and clinical management of patients with COVID-19, using an accurate and rapid diagnostic tests such as reverse transcriptase polymerase chain reaction (RT-PCR) was recommended by World Health Organization (13). Although RT-PCR is a molecular test currently used as the gold standard for diagnosis of COVID-19, many studies reported that it might fail to identify positive cases leading to produce false negative results (14–16). Hence, it is critical to evaluate the prevalence and incidence among patients with different test results in order to better management and control the disease among these categorizes.

This study aimed to assess the effect of sex in different age groups on mortality rate in a large Iranian sample of Covid-19 patients with different PCR test results including suspected, negative and positive. In addition, we compared the death rate of COVID-19 patients with positive, negative, and suspected test results to check if PCR test results could be taken as moderator variable for the effect of sex on the death event in different age groups.

2. Material And Methods

2.1| Participants

This is multicenter cross-sectional study from 55 hospitals in the city of Tehran metropolitan between 20 February 2019 and 8 June 2020. Patients who included to the study were categorized as the positive, negative and suspected cases. Accordingly, tested patients were classified positive if at least one of their PCR tests were positive, and negative otherwise. Patients with negative test results who had clinical signs of ground-glass opacity pattern, consolidation, reticular pattern, or mixed pattern on their chest computed tomographic (CT) scan were considered as the suspected cases.

2.2| Data Collection

All detailed information of patients was obtained using Health Information System (HIS).
HIS was used in the hospitals to improve the quality, effectiveness, and efficiency of health services. Accordingly, the collecting, processing, storing and transferring health information were improved (17). In this study, we used the demographic data (sex and age), laboratory findings (PCR), CT scans, outcome (deceased or survivor), date of admission and discharge or death. Age was categorized to four groups of children (0–14 years), youth (15–24 years), adults (25–64 years), and seniors (> 65 years) (18). Survival time was defined as the time interval between hospital admission and discharge or death. Patients who did not experience a death event or were discharged or excluded from the study were considered censored.
The study was approved by Research Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.RETECH.REC.1399.087).

2.3| Statistical Analysis

Descriptive statistics were expressed by mean (SD) or median (first quartile – third quartile) and frequency (percentage) for numeric and categorical variables. The independent t-test and Mann-Whitney U test were used to compare difference in numeric variables between two independent groups (deceased and survivors). The Chi-square independence test was used to determine whether there is an association between categorical variable and outcome. Logistic regression was applied to evaluate the impact of sex on the death due to COVID-19 by age group. The Cox regression model was used to investigate the effect of variables upon the time the death takes to happen due to COVID-19. Statistical assumptions were considered and checked before performing any methods. Statistical analyzes were done using R 3.6.2 and p-values less than 0.05 were considered as statistically significant.

3. Results

A total of 25481 cases (14791 males) were included in the study which 21791 cases with the mean age of 52.8 were survived and 3057 cases experienced death due to COVID-19 (deceased cases) with the mean age 67.5 years old. Also, the status of 633 cases were unknown. Based on the patients’ test results, study data divided into the three groups of confirmed (positive) (n = 8800), negative (n = 3489) and suspected patients (n = 13192). A significant association between age and hospital length with patients’ status (deceased vs. survivors) were observed among negative, confirmed and suspected cases. Although hospital ward (ICU & CCU; others) was identified as a significant risk factor for death outcome in suspected and confirmed cases of COVID-19, its association with patient status was not significant in cases with negative PCR test results. Among confirmed COVID-19 patients, 1781 cases (20.6%) died, whereas only 928 suspected cases (7.3%) experienced the outcome of interest. However, 348 deaths (10.0%) were reported among individuals having negative test results of COVID-19 (Table 1). In addition, a large number of deaths were occurred in patients with negative PCR test results compared to suspected cases among both sexes. However, the death rate of COVID-19 patients with negative test results was approximately the same among male and females (Fig. 1).

Table 1
Descriptive Statistics by sex and mortality status classified by COVID-19 Status

			Male			**Female**			**Total**		
			Survivor	**Deceased**	**P-value**	**Survivor**	**Deceased**	**P-value**	**Survivor**	**Deceased**	**P-value**
Total											
	No. of Cases		12492	1901	< 0.001	9299	1156	< 0.001	21791	3057	< 0.001
	Age	Mean (SD)	51.8 (18.6)	66.7 (16.3)	< 0.001	54.2 (18.6)	68.8 (15.7)	< 0.001	52.8 (16.1)	67.5 (18.7)	< 0.001
		Median (Range)	52.0 (38.0–65.0)	69.0 (57.0–79.0)	< 0.001	55.0 (40.0–68.0)	71.0 (60.3–80.0)	< 0.001	53.0 (38.0–67.0)	70.0 (58.0–80.0)	< 0.001
		Children	194 (1.6)	14 (0.7)	< 0.001	115 (1.2)	8 (0.7)	< 0.001	309 (1.4)	22 (0.7)	< 0.001
		Youth	563 (4.5)	20 (1.1)		329 (3.5)	12 (1.0)		892 (4.1)	32 (1.0)	
		Adult	8418 (67.4)	712 (37.5)		5945 (63.9)	364 (31.5)		14363 (65.9)	1076 (35.2)	
		Seniors	3317 (26.6)	1155 (60.8)		2910 (31.3)	772 (66.8)		6227 (28.6)	1927 (63.0)	
	Wards				< 0.001			< 0.001			< 0.001
		ICU & CCU	597 (4.8)	614 (32.3)		438 (4.7)	354 (30.6)		1035 (4.7)	968 (31.7)	
		Others	11895 (95.2)	1287 (67.7)		8861 (95.3)	802 (69.4)		20756 (95.3)	2089 (68.3)	
	Hospital Length	Median (Range)	3.0 (1.0–7.0)	6.0 (3.0–11.0)	< 0.001	3.0 (1.0–7.0)	6.0 (3.0–11.0)	< 0.001	3.0 (1.0–7.0)	6.0 (3.0–11.0)	< 0.001
Positive											
	No. of Cases		3996	1127	< 0.001	2888	654	< 0.001	6884	1781	< 0.001
	Age	Mean (SD)	53.6 (16.9)	67.2 (15.3)	< 0.001	55.6 (16.3)	68.0 (15.3)	< 0.001	54.5 (16.7)	67.5 (15.3)	< 0.001
		Median (Range)	53.0 (41.0–66.0)	69.0 (58.0–79.0)	< 0.001	56.0 (44.0–67.0)	70.0 (60.0–80.0)	< 0.001	55.0 (42.0–66.0)	70.0 (58.0–79.0)	< 0.001
		Children	36 (0.9)	2 (0.2)	< 0.001	13 (0.5)	4 (0.6)	< 0.001	49 (0.7)	6 (0.3)	< 0.001
		Youth	89 (2.2)	12 (1.1)		57 (2.0)	6 (0.9)		146 (2.1)	18 (1.0)	
		Adult	2795 (69.9)	415 (36.8)		1931 (66.9)	216 (33.0)		4726 (68.7)	631 (35.4)	
		Seniors	1076 (26.9)	698 (61.9)		887 (30.7)	428 (65.4)		1963 (28.5)	1126 (63.2)	
	Wards				< 0.001			< 0.001			< 0.001
		ICU &	118	381		109	212		227	593	

	CCU	(3.0)	(33.8)		(3.8)	(32.4)		(3.3)	(33.3)	
	Others	3878 (97.0)	746 (66.2)		2779 (96.2)	442 (67.6)		6657 (96.7)	1188 (66.7)	
Hospital Length	Median (Range)	6.0 (3.0–9.0)	7.0 (4.0–11.0)	< 0.001	6.0 (3.0–9.0)	7.0 (3.8–12.0)	< 0.001	6.0 (3.0–9.0)	7.0 (4.0–11.0)	< 0.001

Table 1
Continue

			Male			Female			Total		
			Survivor	Deceased	P-value	Survivor	Deceased	P-value	Survivor	Deceased	P-value
Suspected											
	No. of Cases		6791	572	< 0.001	4975	356	< 0.001	11766	928	< 0.001
	Age	Mean (SD)	49.0 (18.8)	65.5 (18.6)	< 0.001	51.1 (19.1)	69.4 (17.0)	< 0.001	49.9 (19.0)	67.0 (18.1)	< 0.001
		Median (Range)	48.0 (35.0–63.0)	68.5 (56.0–80.0)	< 0.001	51.0 (36.0–65.0)	72.0 (61.0–81.0)	< 0.001	49.0 (35.0–64.0)	70.0 (57.0–80.0)	< 0.001
		Children	148 (2.2)	12 (2.1)	< 0.001	89 (1.8)	4 (1.1)	< 0.001	237 (2.0)	16 (1.7)	< 0.001
		Youth	395 (5.8)	7 (1.2)		229 (4.6)	4 (1.1)		624 (5.3)	11 (1.2)	
		Adult	4733 (69.7)	218 (38.1)		3348 (67.3)	110 (30.9)		8081 (68.7)	328 (35.3)	
		Seniors	1515 (22.3)	335 (58.6)		1309 (26.3)	238 (66.9)		2824 (24.0)	573 (61.7)	
	Wards				< 0.001			< 0.001			< 0.001
		ICU & CCU	473 (7.0)	230 (40.2)		315 (6.3)	140 (39.3)		788 (6.7)	370 (39.9)	
		Others	6318 (93.0)	342 (59.8)		4660 (93.7)	216 (60.7)		10978 (93.3)	558 (60.1)	
	Hospital Length	Median (Range)	2.0 (1.0–4.0)	4.0 (2.0–8.0)	< 0.001	1.0 (1.0–4.0)	4.0 (2.0–8.0)	< 0.001	1.0 (1.0–4.0)	4.0 (2.0–8.0)	< 0.001
Negative											
	No. of Cases		1705	202	< 0.001	1436	146	< 0.001	3141	348	< 0.001
	Age	Mean (SD)	58.8 (19.1)	67.7 (14.2)	< 0.001	61.7 (19.0)	70.5 (14.6)	< 0.001	60.1 (19.1)	68.9 (14.4)	< 0.001
		Median (Range)	61.0 (46.0–73.0)	69.0 (58.8–80.0)	< 0.001	64.0 (48.0–77.0)	73.0 (63.0–82.0)	< 0.001	62.0 (47.0–75.0)	71.0 (60.3–81.0)	< 0.001
		Children	10 (0.6)	0 (0.0)	< 0.001	13 (0.9)	0 (0.0)	< 0.001	23 (0.7)	0 (0.0)	< 0.001
		Youth	79 (4.6)	1 (0.5)		43 (3.0)	2 (1.4)		122 (3.9)	3 (0.9)	
		Adult	890 (52.2)	79 (39.1)		666 (46.4)	38 (26.0)		1556 (49.5)	117 (33.6)	
		Seniors	726 (42.6)	122 (60.4)		714 (49.7)	106 (72.6)		1440 (45.8)	228 (65.5)	
	Wards				0.061			0.654			0.096
		ICU & CCU	6 (0.4)	3 (1.5)		14 (1.0)	2 (1.4)		20 (0.6)	5 (1.4)	

		Male			Female			Total		
	Others	1699 (99.6)	199 (98.5)		1422 (99.0)	144 (98.6)		3121 (99.4)	343 (98.6)	
Hospital Length	Median (Range)	5.0 (2.0–9.0)	9.0 (4.0–15.0)	< 0.001	5.0 (2.0–8.0)	7.5 (3.0–14.0)	< 0.001	5.0 (2.0–9.0)	8.0 (4.0-14.8)	< 0.001

Death frequency distribution was indicated for total cases, and patients with suspected, positive and negative test results (Fig. 2). Results showed a gradual decrease after experiencing a constant trend in death frequency of patients having negative PCR test results. Moreover, death frequency followed an approximately normal distribution over time in patients with positive and suspected PCR test results (Fig. 2). Kaplan Meier curve was employed to evaluate the hazard of death from COVID-19 between different PCR test results groups. As is shown, survival probability of cases with negative test results was remained almost zero two months after admission (**Supplementary 1**)

Logistic regression model was applied to assess the effect of sex on the outcome of interest by age groups. As can be seen, the overall sex effect on mortality was not significant in the groups of children and youth patients. However, male patients were more likely to experienced death in adults (OR = 1.38, 95% CI: 1.21–1.57) and seniors (OR = 1.31, 95% CI: 1.18–1.46) patients. Also, we observed similar results regarding the strong association between male sex and the outcome of interest among patients with positive and suspected PCR test results in adults (OR = 1.33, 95% CI: 1.11–1.58; OR = 1.40, 95% CI: 1.11–1.77) and senior (OR = 1.34, 95% CI: 1.16–1.56; OR = 1.22, 95 % CI = 1.01–1.46) groups. Besides, adult male patients with negative PCR test results (OR = 1.56, 95% CI: 1.04–2.32) were more prone to died due to COVID-19. We also observed that the effect of sex between senior patients in ICU/CCU wards was significant on the outcome of interest (OR = 1.49, 95% CI: 1.15–1.94) (Table 2).

Table 2
Sex differential effect on COVID-19 mortality between different age and wards using logistic regression

Variables	Levels	Age Group	Sex	OR (95% CI)	Sig.
Wards	ICU.CCU				
		Children (0–14)	*Male vs. Female*	0.62 (0.10–3.66)	.593
		Youth (15–24)	*Male vs. Female*	0.92 (0.22–3.92)	.911
		Adults (25–64)	*Male vs. Female*	1.30 (0.99–1.70)	.062
		Seniors (> 65)	*Male vs. Female*	1.49 (1.15–1.94)	.003
	Others				
		Children (0–14)	*Male vs. Female*	1.20 (0.40–3.62)	.740
		Youth (15–24)	*Male vs. Female*	0.95 (0.39–2.32)	.916
		Adults (25–64)	*Male vs. Female*	1.37 (1.17–1.61)	< 0.001
		Seniors (> 65)	*Male vs. Female*	1.27 (1.13–1.43)	< 0.001
COVID-19 Status	Negative				
		Children (0–14)	*Male vs. Female*	----	----
		Youth (15–24)	*Male vs. Female*	0.27 (0.02–3.09)	0.294
		Adults (25–64)	*Male vs. Female*	1.56 (1.04–2.32)	0.030
		Seniors (> 65)	*Male vs. Female*	1.13 (0.86–1.50)	0.386
	Positive				
		Children (0–14)	*Male vs. Female*	0.18 (0.03–1.11)	0.064
		Youth (15–24)	*Male vs. Female*	1.28 (0.46–3.61)	0.639
		Adults (25–64)	*Male vs. Female*	1.33 (1.11–1.58)	0.001
		Seniors (> 65)	*Male vs. Female*	1.34 (1.16–1.56)	0.000
	Suspected				
		Children (0–14)	*Male vs. Female*	1.80 (0.56–5.76)	0.320
		Youth (15–24)	*Male vs. Female*	1.01 (0.29–3.50)	0.982
		Adults (25–64)	*Male vs. Female*	1.40 (1.11–1.77)	0.005
		Seniors (> 65)	*Male vs. Female*	1.22 (1.01–1.46)	0.035
Total					
		Children (0–14)	*Male vs. Female*	1.04 (0.42–2.55)	0.936
		Youth (15–24)	*Male vs. Female*	0.97 (0.47–2.02)	0.943
		Adults (25–64)	*Male vs. Female*	1.38 (1.21–1.57)	< 0.001
		Seniors (> 65)	*Male vs. Female*	1.31 (1.18–1.46)	< 0.001

Cox regression model showed that sex had a significant effect on the hazard of death due to COVID-19 in adults (HR = 1.28, 95% CI: 1.13–1.46) and seniors (HR = 1.27, 95% CI: 1.15–1.39). Similar results were found regarding the effect of sex on the death outcome in adults and seniors patients having positive (HR = 1.34, 95% CI: 1.14–1.58; HR = 1.23, 95% CI:1.09–1.39) and suspected PCR test results (HR = 1.26, 95% CI:1.00-1.59; HR = 1.22, 95% CI: 1.03–1.44). However, sex was not found as significant factor for the death outcome in patients with negative PCR test results (Table 3).

Table 3
Sex differential effect on COVID-19 survival time between different age and wards using Cox regression

	Ward	Age Group	Sex	HR (95% CI)	Sig.
Wards	ICU.CCU				
		Children (0–14)	*Male vs. Female*	0.67 (0.13–3.34)	0.620
		Youth (15–24)	*Male vs. Female*	0.46 (0.12–1.76)	0.258
		Adults (25–64)	*Male vs. Female*	1.24 (1.00-1.55)	0.051
		Seniors (> 65)	*Male vs. Female*	1.25 (1.06–1.48)	0.009
	Others				
		Children (0–14)	*Male vs. Female*	1.40 (0.47–4.17)	0.541
		Youth (15–24)	*Male vs. Female*	1.04 (0.43–2.51)	0.935
		Adults (25–64)	*Male vs. Female*	1.27 (1.09–1.48)	0.003
		Seniors (> 65)	*Male vs. Female*	1.25 (1.12–1.39)	< 0.001
COVID-19 Status	Negative				
		Children (0–14)	*Male vs. Female*	----	----
		Youth (15–24)	*Male vs. Female*	0.23 (0.02–2.57)	0.234
		Adults (25–64)	*Male vs. Female*	1.22 (0.82–1.80)	0.323
		Seniors (> 65)	*Male vs. Female*	1.21 (0.93–1.57)	0.152
	Positive				
		Children (0–14)	*Male vs. Female*	0.18 (0.02–1.71)	0.135
		Youth (15–24)	*Male vs. Female*	1.15 (0.43–3.08)	0.774
		Adults (25–64)	*Male vs. Female*	1.34 (1.14–1.58)	0.001
		Seniors (> 65)	*Male vs. Female*	1.23 (1.09–1.39)	0.001
	Suspected				
		Children (0–14)	*Male vs. Female*	1.53 (0.49–4.84)	0.466
		Youth (15–24)	*Male vs. Female*	1.11 (0.33–3.80)	0.865
		Adults (25–64)	*Male vs. Female*	1.26 (1.00-1.59)	0.046
		Seniors (> 65)	*Male vs. Female*	1.22 (1.03–1.44)	0.021
Total					
		Children (0–14)	*Male vs. Female*	1.05 (0.43–2.55)	0.917
		Youth (15–24)	*Male vs. Female*	0.96 (0.47–1.97)	0.911
		Adults (25–64)	*Male vs. Female*	1.28 (1.13–1.46)	0.000
		Seniors (> 65)	*Male vs. Female*	1.27 (1.15–1.39)	0.000

In the multiple model controlling the age category and hospital ward, male sex was associated with 26% higher hazard of death (adjusted HR = 1.26, 95% CI: 1.17–1.35). Relative to the children, seniors had significant effect on the hazard death (adjusted HR = 2.57, 95% CI: 1.68–3.91). In addition, the hazard of occurring death among patients in ICU/CCU ward was 2.49 times higher than that of other hospital wards (adjusted HR = 3.49, 95% CI: 3.23–3.77) (Fig. 3).

4. Discussion

Our study showed that the sex differential effect in COVID-19 mortality varied significantly by age in the categories of test result and hospital ward. Besides, the highest death rate was observed for patients with confirmed positive test results, however, the death rate was higher in patients with negative test result compared to suspect ones between both sexes.

In our data, almost 12% of the cases with at least one positive PCR test died due to COVID-19 in the total data. Among positive PCR test cases, the case fatality rate (CFR) was 20%. In the previous multicenter study in Tehran, this figure was 13.5% among patients with positive test results (19). Using the information regarding COVID-19 was extracted on January 13, 2021 from the Worldometer webpage (https://www.worldometers.info/coronavirus/), the CFR was 2.1% for global data, 2.2% for Europe, 2.1% for North America, 1.6% for Asia, 2.6% for South America, and 2.3% for Africa. Among Iranian cases, 56360 (4.3%) died among 1,299,022. There might be different CFRs in local and regional reports. That might be due to reasons such as different stages during the spread of COVID-19, the presence of higher incidence of recognized comorbidity factors including lifestyle and culture, and lack of facilities in healthcare system and intensive care units (20, 21).

We observed that the mortality rate of COVID-19 is high even if the PCR results are negative. Moreover, the fatality rate in cases with suspected tests were even less than those of negative. This finding might be due to multiple reasons. Firstly, the limited and variable sensitivity of the test (reportedly almost 70%) (22) and laboratory equipment might result in false negative cases. The guidelines by the World Health Organization (WHO) recommended chest imaging as the first diagnostic phase to scan patients who need prompt hospitalization in Iran in the absence and some inefficiency of RT-PCR test kits (23, 24). Although there had been a strong association among throat swab and viral loads of the sputum sample, investigating the bio-distribution of COVID-19 in various body tissues recorded positive PCR rates in only 72% of sputum specimens (25, 26). Secondly, it is likely that individuals with a negative result might have had tested when COVID-19 may no longer be detectable by the healthcare (27). Hyam et al. evaluated the impact of risk factors on positive and negative COVID-19. They investigated demographic, social, health, medical, and environmental characteristics. They revealed that within the tested sample, health risk factors and comorbidities are not associated with the outcome of the test. They also showed that male sex, lower educational attainment, and ethnicity are the potential predictors of a positive/negative test outcome (27). Thirdly, negative PCR results might be due to lower viral load in patients' specimens. Xie et al. conducted a study to find the association between chest CT and negative RT-PCR test results and they showed that negative PCR tests are due to laboratory error or insufficient viral material in the specimen (28). Liu et al. also assessed the indispensable role of chest CT in the detection of COVID-19 and reported that this fact might be caused by inadequate amounts of viral microbes extracted for testing or incorrect extraction approaches (29). Finally, some researches also described that a fraction of PCR positive tests, including some severe cases, had originally normal chest X-ray or CT findings (22, 30).

Ignoring the impact of age on the association between sex and COVID-19 outcome, it has been very well discussed that males are more likely to die from COVID-19 than females. The literature justifies this fact due to multiple facts including female sex steroids, sex-specific expression of pro- and anti-inflammatory cytokines, higher density of ACE2 receptors in childbearing age women, higher numbers of CD4 + T cells, CD8 + T cell cytotoxic functioning, more type 1 interferon, and higher B cell production of immunoglobulin (31–35). We addressed the sex difference by age categories. However, reporting the total death rates misleads us about the potential hazards and dangers influenced by age. One country's mortality proportions might not apply to countries with older or younger age structures. It is suggested that data should be published in different age groups to provide much more informative estimate of mortality (36). We reported that the odds of death from COVID-19 is significantly higher in males with negative PCR test and aged 25–64 years than females. However, being older than 25 is strongly associated with higher mortality rate of men compared to women among suspected and positive cases. Moreover, regardless of the COVID-19 status, the likelihood of death is significantly higher among males over 25 years than that of females. It has been argued that the COVID-19 mortality sex-differential is not the same at different age. Bhopal et al. showed that the ratio increases as cases age up to 80 years old and decreases thereafter. They described the fact that sex differences rise from < 60 to 60–69 years but eventually declines with the lowest sex difference at 80 + years of age. Nonetheless, if estrogen protects women against COVID-19, women could be most safe before the menopause because of the larger blood levels of estrogen. (11). Yanez et al. evaluated the COVID-19 mortality risk for older men and women among 16 countries that reported relatively high number of COVID-19. They revealed that men are in higher risk of death from COVID – 19 (37). Ahrenfeldt et al. reported the results of Sex and age differences in COVID-19 mortality in Europe and they found that the rate of death for men is higher than women and the relative rate is the same for cases younger than 60 and older than 80 (21). Moreover, among those hospitalized in ICU-CCU, males over 65 years old are 50% more likely to die than females. It has been shown that a considerable association between ICU admission and age exists so that cases younger than 20 years old, are less prone to experience hospitalization, and ICU admission, and death (38). It has been argued that some chronic diseases such as diabetes and cardiovascular diseases are more common among males than in females, especially in older ages (39).

We used the Kaplan-Meyer survival curve to visualize the survival probability of cases with suspected, positive and negative PCR test results. As expected, we observed lower probability of survival for patients with positive PCR result. The results of survival analysis showed that higher risk of death is associated with male sex, senior age, and being hospitalized in ICU-CCU wards. The survival of cases with negative PCR results was not associated with age and sex. However, among those with suspected or positive tests, the hazard ratio was significant for cases older than 25 years old. Williamson et al. modeled the association between COVID-19 risk factors and mortality using cox regression and they exposed that the hazard of death is higher among men than women and older age (40). The risk factors of COVID-19 outcome is investigated by Chen et al. among hospitalized patients. It was revealed that the hazard of death increases with age so that cases younger than 65 years old had an almost constant and higher survival probability than older patients (41). The impact of sex on clinical outcomes in cases with COVID-19 was evaluated by Cho et al. They showed a lower survival probability for men in comparison to women. It was also found that one-year older case has 10% more hazard of death. Their subgroup analysis revealed that the adverse effect of male sex and older age is almost the same in different wards (42). Another study by Pen et al. assessed the time course of lung changes at chest CT during recovery from coronavirus disease 2019. In their study, women had 5% more probability of discharge and male sex was associated with longer recovery times, and a higher average morbidity rate (43). Quah et al. demonstrated the mortality rates of patients with COVID-19 in the intensive care unit using a systematic review and it was shown that almost 25% of cases in ICU were deceased and only 18% were discharged. It might be due to the fact that cases with an intensive condition are hospitalized in the ICU-CCU wards. They also revealed that 29% of the ICU patients who died in the Chinese studies did not receive mechanical ventilation and some other countries were struggling with resource constraints so that rationing of ventilators and ICU beds in overwhelmed health systems may postpone the intubation (44). However, this finding might be influenced by the policy of physicians in transferring new cases to the ICU-CCU wards. Usually, new patients in ICU are transferred after someone dies and this might delay the golden time of hospitalization and often decision makers in ICU-CCU wards prefer to delegate ICU treatment to the younger patients as they appeared to have a better chance of survival.

The major strength of this multicenter study is lies in its large sample size which collected from 55 hospitals in city of Tehran. Our study has one major limitation which should be considered before interpreting any findings of the current study; we didn't consider the interaction of age or sex with the risk factors (demographic, clinical, sign and symptom, and drugs) to assess the adjusted effect of sex on the death outcome in different age categories.

Conclusion

In this study, regardless of other risk factors, we found that sex differential effect on COVID-19 mortality varies significantly in different age groups; therefore, appropriate strategies should be designed to protect adult and senior men from this deadly infectious disease. Furthermore, owing to the considerable death rate of COVID-19 patients with negative test results, new policies should be launched so as to increase the accuracy of diagnosis tests.

Abbreviations

CFR: case fatality rate, COVID-19: coronavirus disease 2019, CT: chest computed tomographic, HIS: Health Information System, PCR: polymerase chain reaction, RT-PCR: reverse transcriptase polymerase chain reaction, WHO: World Health Organization

Declarations

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Authors' contributions

MAL, SJ, EZ, PA, FM, MK, AVA, MRT, GM, MRN, and MAP contributed to project conception; GM prepared data cleaning; MAL and FM did the statistical analysis; AVA did the literature review; MAL, PA and FM wrote the manuscript and MAP critically revised the successive drafts. All authors read and approved the final manuscript.

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Availability of data and material

Data would be available by contacting corresponding author and after excluding the personal information of patients.

Ethics approval

The study was approved by Research Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.RETECH.REC.1399.087).

Consent for publication

Not applicable

Conflicts of interest

The authors declare that they have no competing interests.

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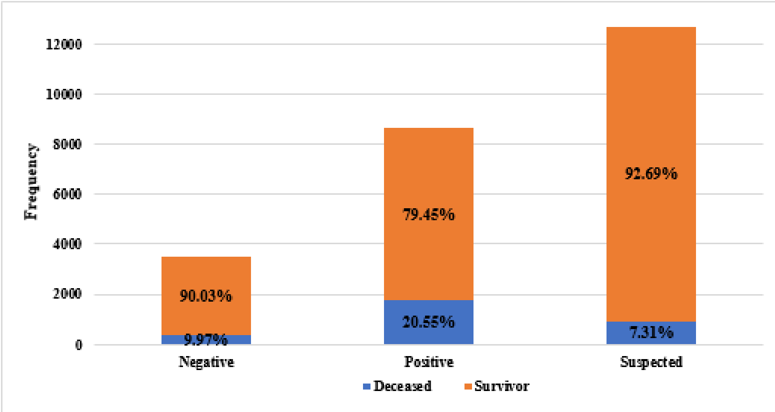
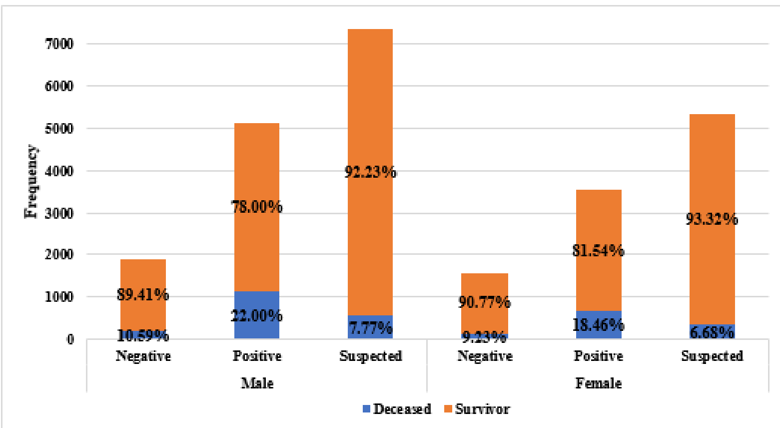
Figures



A



B

Figure 1

The distribution of deceased cases among negative, positive and suspected patients with COVID-19 in A) total patients, B) by gender (The proportion of deceased patients in negative group was significantly higher than in suspected group)

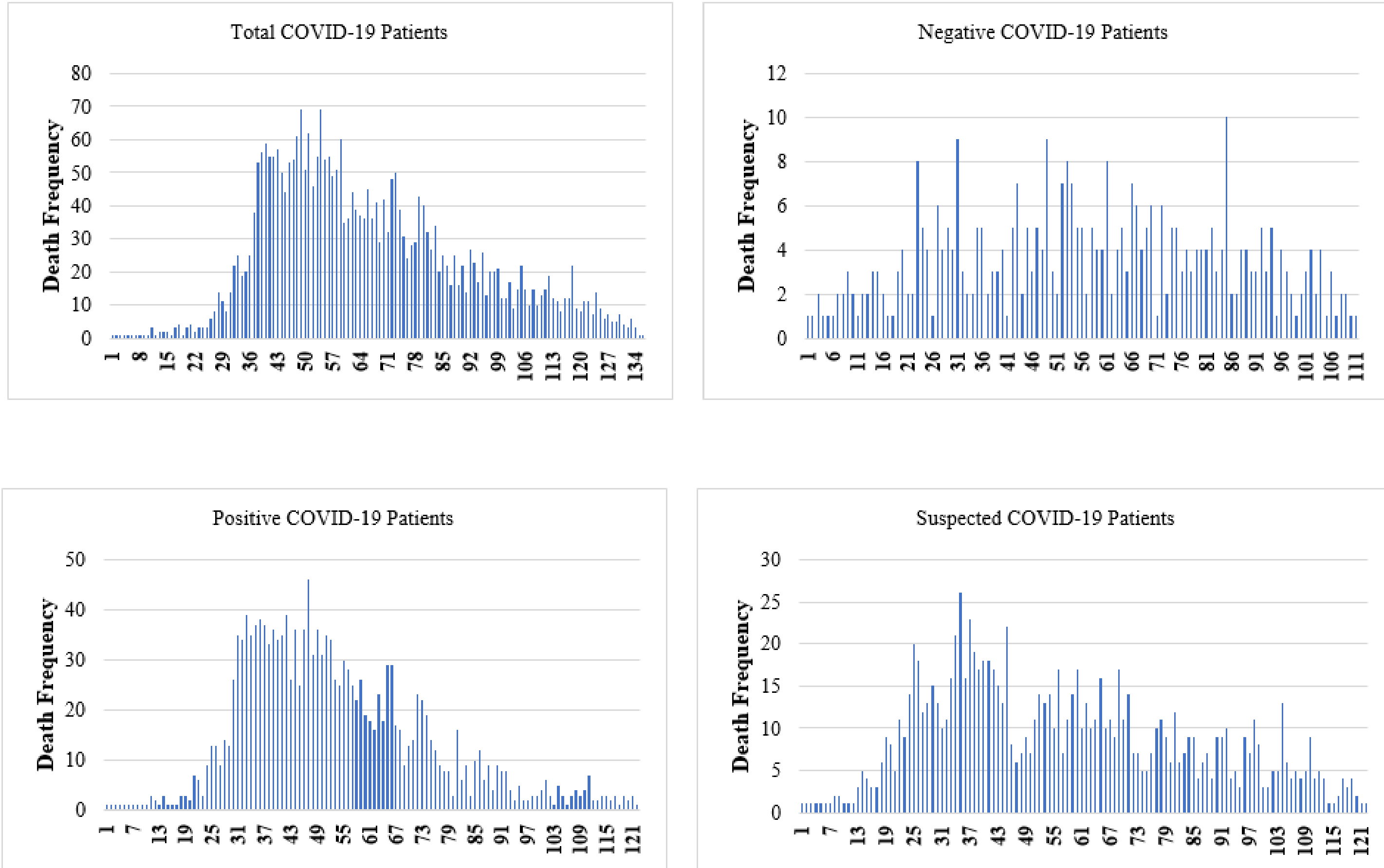


Figure 2

The death frequency per day among total COVID-19 patients, negative COVID-19 patients, positive COVID-19 patients and suspected COVID-19 patients

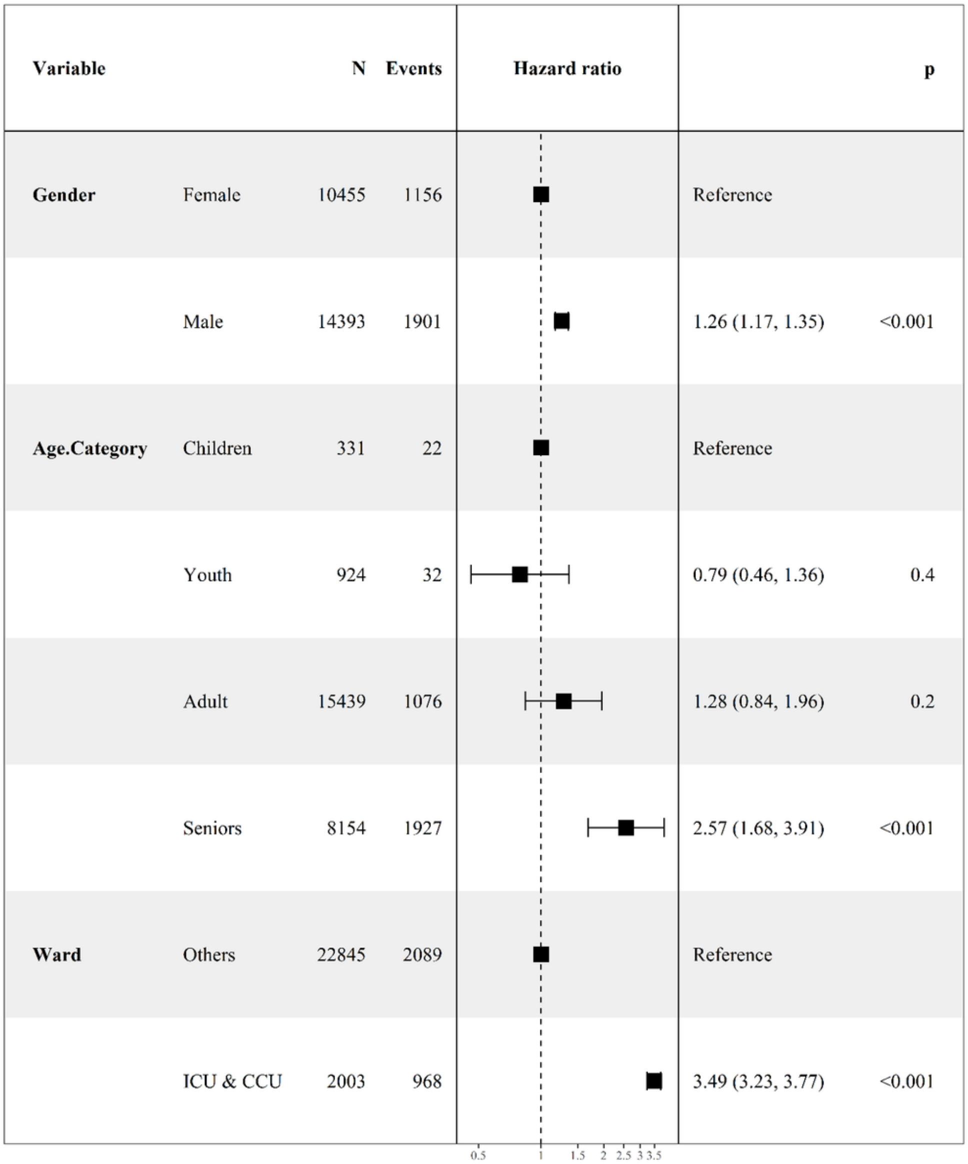


Figure 3

The forest plot for showing the adjusted effect of categorical variables on survival time of patients with COVID-19

Supplementary Files

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