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Original Article

Investigating the Association between Gender and Age Distribution with Severity of COVID-19: A Single-Center Study from Southern Iran

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Abstract

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused a highly contagious disease, which led to a pandemic health emergency. However, age distribution and sex, regarding factors affecting the severity of COVID-19, are controversial. Therefore, this study is designed to investigate the effect of gender difference on the severity of COVID-19 infection in the studied age groups.
Methods: Patients with COVID-19 of Valiasr Hospital (Khorrambid, Fars, Iran) from February 20, 2020, to February 20, 2021, are included in this retrospective study. The inclusion criteria were the age of above 15 years old and being residents of Khorrambid. COVID-19 severity was classified as mild and moderate/severe according to the WHO standards. The obtained demographical and clinical data from the patient registry forms were analyzed using SPSS-24; P value <0.05 was considered as the level of significance. Chi-square and independent t-test were used to assess the variables.
Results: Herein, 218 patients were recruited with a mean age of 45.6±17.2 and a relatively equal distribution of men and women population. Out of this population, 23.8% had comorbid diseases, 48.2% had mild, and 51.8% had moderate/severe infections. Our results indicated that male gender and the age range of 25-64 years in men are the most important risk factors associated with the disease severity (P<0.0001).
Conclusions: The current study revealed that the leading risk factor of the disease severity was higher age (≥65 years) in the studied women. Meanwhile, in the men group, this factor was the age range of 25-64 years. These results suggest that further research is required to identify the possible impacts of gender and age on various aspects of the ongoing epidemic.

Keywords: COVID-19, Epidemiology, Gender, Age distribution, Iran

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1. Introduction

In December 2019, a pneumonia outbreak in Wuhan, China, was caused by a group of acute respiratory illnesses with an unknown origin (1), which was highly contagious; it rapidly spread over the world (2). The mentioned disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is associated with human severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) (3).

In February 2020, the World Health Organization (WHO) formally modified the name of the disease from SARS-CoV-2 to coronavirus disease 2019 (COVID-19). WHO has pointed out that COVID-19 is a threatening emergency of pandemic proportions and a massive burden on public health, communities, and the economy (4, 5). This virus might finally lead to death with harsh influenza-like symptoms that can range from a mild disease to a serious lung injury and even organ failure (4). COVID-19 spreads by person-to-person transmission through droplets, airborne particles, discharge of fecal matters, and direct contact with infected individuals. It has an incubation period of approximately 1 to 14 days (6, 7).

The majority of patients affected by COVID-19 had mild/moderate disease, and dyspnea was often encountered within a week. In severe cases, critical conditions, including acute respiratory failure, metabolic acidosis, coagulopathy, and septic shock were also developed (8).

Early determination of the risk factors for critical conditions is required in order to recognize the major clinical and epidemiological features, facilitate supportive treatment, and expedite admittance to the intensive care unit (ICU).

Older patients and those with specific

underlying medical disorders, such as diabetes, obesity, immunocompromised status, as well as pulmonary, cardiac, or renal failure are currently known to be further threatened by the disease. The aforementioned risk factors could lead to hospitalization and mortality (9, 10).

Data from Global Health 50/50, a globally recognized organization that stimulates gender equality in healthcare, demonstrates that males account for a much higher percentage of COVID-19 mortality than females worldwide. The data from the Bulletin of Integrated Surveillance (2020) showed that males in Italy die at a rate approximately twice that of women (17.1 vs. 9.3%). Similar findings were reported from other countries, namely China, Belgium, Denmark, Greece, Netherlands, Spain, and the Philippines (11). Liu and colleagues (12) found that the elderly male population (>70 years) had a significantly higher rate of SARS-CoV-2 positivity, considering only age as a risk factor.

A greater recorded incidence in the elderly and a lower observed incidence in children and adolescents have been the hallmarks of the pandemic despite the predicted initial widespread sensitivity to a new pandemic virus, such as SARS-CoV-2. However, recent data showed that adjusting for testing frequency provides a clear picture of the age-specific risk of SARS-CoV-2 infection, revealing that males at a younger age are an underappreciated group at higher risk of SARS-CoV-2 infection (13).

Gender difference and age distribution, as factors in association with susceptibility and severity of the infectious disease, have been reported for several other types of viruses (14, 15). However, the association of gender difference and age distribution with the severity of COVID-19 infection is still controversial. Therefore, the present work was conducted to investigate the epidemiological and clinical characteristics of patients with confirmed COVID-19 and the effect of gender difference on the severity of COVID-19 infection in a population from southern Iran.

2. Methods

2.1. Participants and Place

This retrospective study included patients from Valiasr Hospital (Khorrambid county, Fars province, Iran) from February 20, 2020, to February 20, 2021. Khorrambid is located in the north of Fars province, Iran, with an estimated population of 26933 in 5,556 families according to the recent census. Its climate is cold and dry, with an average annual temperature of 10°C. It has a 28-bed active hospital, which is the only center for patients with COVID-19 in Khorrambid; it does not have an ICU or imaging facilities. Furthermore, it lacks sufficient staff and facilities. All the patients diagnosed with COVID-19 were successfully included in this study.

2.2. Sample Size Calculation and Data Collection

According to similar studies (16, 17) and the following formula, the total sample size was set at 180, with 80% power to detect the difference between men and women population, at a two-sided significance level of α=0.05.

$$n = \frac{\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2 (\sigma_1{}^2 + \sigma_2{}^2)}{(\mu_1 - \mu_2)^2}$$

where n denotes the required sample size in each group, μ_1 is the mean age of men (μ_1=44.8), μ_2 is the mean age of women (μ_2=38.9), μ_1-μ_2 is the difference between them (μ_1-μ_2=5.9), σ_1 is the standard deviation of the male group (σ_1=15.2), and σ_2 is the standard deviation of the female group (σ_2=12.7).

The conventional standard z-value at a significance level of 0.05 is Z/2, which equals 1.196. Z_β is equal to 0.84, which is the typical z-value for the power of 80. Additionally, we will include a 10% general study-time dropout assumption (due to the incomplete registration of patient information). To calculate the adjusted sample size, the total expected sample size was divided by one minus the proportion expected to decrease (0.10 in this case). Accordingly, 180 was divided by 0.9 to obtain an adjusted sample size for the possible attrition rate in this study (200 subjects).

Finally, 218 participants were recruited, who were classified based on "Age Categories, Life Cycle Groupings" (18), as follows [Children (00-14 years) were excluded from the study]: 1) Youth (15-24 years), 2) Adults (25-64 years), and 3) Seniors (65 years and over). Each age category was also studied based on gender (male and female).

All the available data, including epidemiological, demographical, clinical, and paraclinical data, along with treatment and outcome information, were obtained from the patient's medical folders using a data-gathering form after the final diagnosis of COVID-19. Moreover, the patients with missing file information were excluded from the study. A physician performed all the physical examinations. To affirm the suspected cases, real-time polymerase chain reaction (RT-PCR) was used for the laboratory confirmation of COVID-19.

2.3. Definition

Based on the WHO guidelines, the Chinese diagnostic and treatment plan for SARS-CoV2 classified the COVID19 severity as mild, moderate, and severe. Mild symptoms without pneumonia on imaging were diagnosed as mild type whereas the respiratory tract symptoms and pneumonia on the imaging were considered as moderate types. The severe type was identified with shortness of breath, respiratory rate ≥30 per minute, low blood oxygen saturation ≤93%, PaO_2/FiO_2 ratio below 300, and/or lung infiltrate >50% within 24 to 48 hours. All the mild cases were suggested to have a 14-day home quarantine and supportive care with no anti-viral, antibiotics medication, laboratory, or imaging; they were nonetheless followed by clinical manifestation. All the moderate types of patients were admitted to the hospital in isolation units. A chest x-ray and some laboratory tests were done for them. If appropriate, they received anti-viral treatment and added antibiotics therapy (as their chest x-ray finding). After they were stable, they were discharged and continued their treatment

Table 1: Demographic and epidemiologic characteristics of our 2019-nCoV patients based on severity status

Patients' characteristics	Overall (n=218)	Disease severity		P value
		Mild (n=105)	Moderate/severe (n=113)	
Age, years, mean (median)	45.6±17.2 (42.00)	37.8±16.5	65.3±18.4	<0.0001
15-24	30 (13.8)	25 (83.3)	5 (16.7)	
25-64	99 (45.4)	57 (57.6)	42 (42.4)	
≥65	89 (40.8)	23 (25.8)	66 (74.2)	
Gender (women)	108 (49.5)	69 (63.9)	39 (36.1)	<0.0001
Weight, kg, mean (median)	64.8±15.1 (63.70)	59.5±18.6	74.6±9.2	<0.0001
BMI, kg/m^2	25.3±7.3	22.5±11.6	28.3±7.2	<0.0001
Coexisting Condition	52 (23.8)	18 (34.6)	34 (65.4)	0.027
Hypertension	25 (48.1)	7 (28.0)	18 (72.0)	
Diabetes	20 (38.5)	7 (35.0)	13 (65.0)	
Peritoneal dialysis	3 (5.7)	1 (33.3)	2 (66.7)	
Others	4 (7.7)	3 (75.0)	1 (25.0)	
Blood Group				
O	73 (33.5)	48 (65.7)	25 (34.3)	0.003
A	51 (23.4)	20 (39.2)	31 (60.8)	0.153
B	46 (21.1)	12 (26.1)	34 (73.9)	0.008
AB	29 (13.3)	15 (51.7)	14 (48.3)	0.695
Rh positive	138 (63.3)	70 (50.7)	68 (49.3)	0.329
Missing	19 (8.7)	10 (52.6)	9 (47.4)	0.811
Occupation				
Employee/Worker	86 (39.4)	40 (46.5)	46 (53.5)	0.781
Self-employed/Farmer	48 (22.0)	23 (47.9)	25 (52.1)	0.999
Housekeeper	55 (25.2)	26 (47.3)	29 (52.7)	0.999
Student	24 (11.1)	19 (79.2)	5 (20.8)	0.002
Missing	5 (2.3)	3 (60.0)	2 (40.0)	0.674
Education				
Illiterate & Primary school	39 (17.9)	20 (51.3)	19 (48.7)	0.725
Less than high school	21 (9.6)	8 (38.1)	13 (61.9)	0.366
High school graduate	126 (57.8)	56 (44.4)	70 (55.6)	0.218
Bachelor degree	14 (6.5)	8 (57.2)	6 (42.8)	0.585
Master degree or higher	12 (5.5)	9 (75.0)	3 (25.0)	0.075
Missing	6 (2.7)	4 (66.7)	2 (33.3)	0.432

Data are expressed as mean±SD and n (%).

as at-home quarantine. Our severe/critical cases were transferred to Shiraz hospital (center of the province) and immediately admitted to ICU.

2.4. Statistical Analysis

Statistical analysis of the data was performed via SPSS-24 for windows. Quantitative data are represented by the mean and standard deviation or median while qualitative data are reported as number (presentage). Chi-square, Fisher's exact test, independent t-test, and Mann-Whitney U test were used to assess the variables. P value<0.05 was considered as the level of significance.

3. Results

3.1. Demographic and Epidemiologic Characteristics

This study analyzed 218 patients with confirmed 2019nCoV infection from February 20, 2020, to February 20, 2021, in Khorrambid, Fars province, Iran. As represented in Table 1, their mean age was 45.6±17.2 years (median 42.0 years); a significant difference existed between mild and moderate/severe disease severity in terms of the patients' population (P<0.0001). The patients' mean weight was 64.8±15.1 kg (median 63.7 kg); there was a significant difference between the mean weight of the two studied levels of disease severity (P<0.0001). Moreover, the mean BMI of the participants was 25.3±7.3; there was a significant difference between mild and moderate/severe cases in this regard (P<0.0001). The studied men and women were equally infected (P=0.968). However, the disease severity between men and women significantly differed (P<0.0001). Overall, 23.8% of the patients (52 cases) had at least one coexisting medical condition, with hypertension and diabetes at the top of them in the mild and moderate/severe population. Most of our patients (73 cases, 33.5%) had a blood group of O, and 63.3% (138 cases) were Rh+. The B blood group was more closely related to COVID-19 severity whereas blood group O was found to be at a lower risk of COVID-19 severity. The majority of the subjects were employees/workers (86 cases, 39.4%) and housekeepers (55 cases, 25.2%). Among them, 105 (48.2%) had a mild infection, and 51.8% (113 cases) developed the common type that were hospitalized. Almost half of the hospitalized patients (58 cases) presented with severe/critical type and were admitted to ICU. The mean age was 37.8±16.5 years in mild and 65.3±18.4 years in moderate/severe cases. As the obtained data suggest, the severity of the disease is significantly correlated with older age, male sex, higher BMI (P<0.0001), a coexisting disease (P=0.027), and blood group of B (P=0.008).

Based on the three strata of age category, Table 2 summarizes the descriptive characteristics of our 2019-nCoV patients, such as weight, BMI, coexisting conditions, and blood groups.

3.2. Clinical and Laboratory Characteristics

On admission, most patients had cough (one-third of the patients: 75 cases, 34.4%), 31.2% presented with shortness of breath (68 cases), and 24.3% with fever (53 cases). The other observed

Table 2: Descriptive characteristics of our 2019-nCoV patients in each strata of age category

Patients' characteristics	Overall (n=218)	Age distribution (years)		
		15-24	25-64	≥65
Weight, kg, mean (median)	64.8±15.1 (63.70)	48.6±3.6	67.4±6.1	58.3±6.9
BMI, kg/m^2	25.3±7.3	20.3±1.3	26.4±3.5	24.6±6.4
Coexisting Condition	52 (23.8)	5 (9.6)	18 (34.6)	29 (55.8)
Hypertension	25 (48.1)	1 (4.0)	10 (40.0)	14 (56.0)
Diabetes	20 (38.5)	4 (20.0)	7 (35.0)	9 (45.0)
Peritoneal dialysis	3 (5.7)	0 (0.0)	2 (66.7)	1 (33.3)
Others	4 (7.7)	0 (0.0)	2 (50.0)	2 (50.0)
Blood Group				
O	73 (33.5)	29 (39.7)	23 (31.5)	21 (28.8)
A	51 (23.4)	7 (13.7)	26 (51.0)	18 (35.3)
B	46 (21.1)	16 (34.8)	12 (26.1)	18 (39.1)
AB	29 (13.3)	10 (34.5)	8 (27.6)	11 (37.9)
Rh positive	138 (63.3)	39 (28.3)	47 (34.0)	52 (37.7)
Missing	19 (8.7)	7 (36.8)	8 (42.1)	4 (21.1)

Data are expressed as mean±SD and n (%).

symptoms included myalgia, loss of taste/smell, sore throat, fatigue, headache, GI symptom, chills, hoarseness, and anorexia (Table 3). Based on WHO criteria, the difference between mild and moderate/severe disease severity was determined with a temperature higher than 37.3°C, a respiratory rate more than 24 times per minute, and O_2 saturation below 93%; in our study, there were significant differences among all the three criteria (P<0.0001).

3.3. Effects of Gender and Age Distribution on the Severity of COVID-19

Table 4 shows how the age distribution in men and women populations affects the severity of COVID-19. Disease severity was higher in the oldest age group (≥65 years) and noticeably lower in those younger than 24. Moreover, there were differences between disease severity in male and female age groups. It was considerably higher in males aged 25 to 64 years compared with their female peers (25-64 years) (P<0.0001) and the overall population (P=0.018). However, the disease severity is believed to be more correlated with older age in women (P<0.0001).

4. Discussion

We investigated the epidemiology and clinical characteristics of 218 patients with COVID-19 in

Table 3: Clinical and laboratory characteristics in our 2019-nCoV patients

Patients' characteristics	Overall (n=218)	Disease severity		P value
		Mild (n=105)	Moderate/severe (n=113)	
Symptoms				
Cough/dry cough	75 (34.4)/43 (19.7)	26 (24.8)/16 (15.2)	49 (43.4)/27 (23.9)	<0.0001
Shortness of breath	68 (31.2)	28 (26.7)	40 (35.4)	0.189
Fever	53 (24.3)	6 (5.7)	47 (41.6)	<0.0001
Myalgia	39 (17.9)	10 (9.5)	29 (25.7)	0.002
New loss of taste/smell	56 (25.7)	25 (23.8)	31 (27.4)	0.642
Sore throat	28 (12.8)	13 (12.4)	15 (13.3)	0.999
Fatigue	106 (48.6)	39 (37.1)	67 (59.3)	0.001
Headache	37 (17.0)	15 (14.3)	22 (19.5)	0.368
Nausea or vomiting	34 (15.6)	5 (4.8)	29 (25.7)	<0.0001
Diarrhea	29 (13.3)	4 (3.8)	25 (22.1)	<0.0001
Chills	11 (5.0)	8 (7.6)	3 (2.6)	0.124
Hoarseness	8 (3.7)	3 (2.8)	5 (4.4)	0.723
Anorexia	21 (9.6)	5 (4.8)	16 (14.2)	0.022
Some Laboratory Characteristics				
Temperature, °C	37.4±0.6	36.7±0.5	37.7±0.8	<0.0001
<37.3	165 (75.7)	99 (94.3)	66 (58.4)	
≥37.3	53 (24.3)	6 (5.7)	47 (41.6)	
Respiratory Rate, /min	19.6±2.1	19.5±2.1	23.0±2.5	<0.0001
>24	103 (47.2)	24 (22.8)	79 (69.9)	
O_2 Saturation, %	93.8±4.9	95.1±1.4	82.5±2.1	<0.0001
<93	112 (51.4)	32 (30.5)	80 (70.8)	

Data are expressed as mean±SD and n (%).

Table 4: Effects of gender distribution on the severity of COVID-19 in each strata of age category

Age distribution (years) \ Gender		Overall (n=218)	Female (n=108)	Male (n=110)	P value
15-24	Mild	25 (11.5)	13 (52.0)	12 (48.0)	0.999
	Moderate/severe	5 (2.3)	3 (60.0)	2 (40.0)	
	P value	<0.0001	0.010	<0.0001	
25-64	Mild	57 (26.1)	50 (87.7)	7 (12.3)	<0.0001
	Moderate/severe	42 (19.3)	5 (11.9)	37 (88.1)	
	P value	0.018	<0.0001	0.003	
≥65	Mild	23 (10.5)	14 (60.9)	9 (39.1)	0.334
	Moderate/severe	66 (30.3)	31 (46.9)	35 (53.1)	
	P value	<0.0001	<0.0001	0.037	

the southern region of Iran. The main findings revealed that the male gender and the age range of 25 to 64 years were the most significant risk factors associated with disease severity in the male population. The association between higher age and disease severity, however, was more evident among females.

Our patients had a mean age of 45.6±17.2 years (median 42.0 years) with a similar number in both genders. They were younger than the patients in similar studies; for instance, patients' median age was 45.0 to 62.0 years, with an average of 52.9 to 55.5 in several studies in China (1, 5, 19-23) while in a paper in New York, the median age was 63 years (24) and in Turkey, it was 55.8 (25). The average age of 53.8 to 55.5 years have been reported in Iran (26, 27).

In this study, high percentage of patients had a coexisting disease, with the majority having hypertension and diabetes mellitus; this is in line with other studies (1, 5, 20-24, 26).

Most of our patients had a blood group of O and were Rh^+. There were significant results about the association between blood group and characteristics of COVID-19 patients. It was shown that blood group B was more susceptible to the disease severity, but the Rh factor did not make any significant difference. These findings are in agreement with some previous studies (28).

Most cases herein had a cough, shortness of breath, and fever on admission. Similar to our study, the three most common symptoms in other studies were fever, cough, and shortness of breath/gastrointestinal symptoms/fatigue (5, 19, 21-23, 27, 29-32).

Additionally, many papers worldwide showed that the male gender was more prominent among the infected patients (1, 5, 13, 19-21, 24-26). A meta-analysis study on 3062 patients also revealed that a higher proportion of patients were men (29); it was concluded that it was due to the X chromosome protection and sex hormones effect (33).

About 48.2% of the participants presented mild and 51.8% moderate/severe infection. In another similar study, the youngest patients had mild while and the oldest cases had severe infections (30).

Bhopal and Bhopal (34) evaluated a sex ratio over the life course of individuals to determine whether the effects of gender difference on mortality risk of COVID-19 were consistent through all the age groups using national statistics agencies' data by June 21, 2020 (35). The mortality rate in men was more significant than that in women. The male to female sex ratio was not equal in none of the ages. The minimum ratio belonged to children aged 0 to 9 (0.81). The maximum ratio was observed in people aged 60-69 (2.6) (34, 35).

In this regard, Fisman and colleagues (13) showed that testing frequency adjustment develops a new perspective of SARS-CoV-2 infection risk by age, suggesting that younger males are an under-recognized population with a high risk of infection with SARS-CoV-2. Their approach emphasizes the role of younger people, particularly younger men, as silent drivers of virulent infection in older people. Although their findings need to be confirmed in other situations, they provide a straightforward, low-cost approach for calculating real infection risk by age, particularly in areas lacking seroprevalence data.

Moreover, there are considerable sex inequalities in the severe form of COVID-19, with male patients having higher fatality rates than female ones. The incidence of COVID-19 has also been higher in male patients than that in their female counterparts. Female patients have a more sensitive and powerful immune system, explaining this trend. The fundamental explanation for the variable immunological response to COVID-19 is sex hormones, such as estrogens and androgens, which occur in differing available quantities in female and male patients, respectively (36). According to a growing body of evidence, estrogen modulates the immune system, protecting females against severe inflammation and, by extension, severe COVID-19. On the other hand, androgen has been linked to immune cell overactivation, cytokine storm, and severe inflammation, which may predispose male patients to severe COVID-19 (37, 38).

4.1. Limitations

This retrospective research had certain limitations. We were limited in our capacity to account for potential confounders; that is because the data for this study were based on the available database, with the possibility of misclassification and inaccurate coding. Secondly, different research used different definitions of severe disease; the results must be thus cautiously interpreted regarding potential heterogeneity.

Our approach is nevertheless practical since prior research has shown contradictory findings concerning gender differences affecting the severity of COVID-19. We found that age distribution affected disease severity differently in men compared to that in women. Our results revealed that the most significant risk factors associated with disease severity in the male population are the male gender and the age range of 25 to 64 years. However, higher age and disease severity are more closely related in the female population. Further basic and clinical research is required on age, gender, and other predictive variables for future individualized evaluation and therapy.

5. Conclusions

It can be concluded that age- and sex-related differences need to be taken into account in the diagnosis, disease severity, and treatment of patients with COVID-19. The current study transformed our perception of male and female differences; the relationship between them is not completely obvious, and efforts should now be made to comprehend the risk resulting from sex, age, and other factors. The most likely explanations for the observed differences seem to be the risk factors that change with sex and age. These results indicated the necessity of further research for identifying the possible impacts of gender and age on various aspects of the ongoing epidemic.

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Ethical Approval

The study was approved by the local ethics committee of Shiraz University of Medical Sciences with the code of IR.SUMS.REC.1399.069. The goal of the study was explained to the participants and written informed consent was obtained. Also, It was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice principles.

Conflict of Interest: None declared.

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