Epidemiological Risk Factors for Acquiring Severe Coronavirus Disease 2019 (COVID-19): A Prospective Cohort Study

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Abstract

Objective: We aimed to determine epidemiological risk factors associated with acquiring severe COVID-19 in patients requiring hospitalization. ***Methods***: A prospective cohort study was conducted using a questionnaire comprised of six close-ended questions to identify potential risk factors for severe COVID-19. Using COVID-19 associated illnesses and complications (pneumonia, ARDS, need for mechanical ventilation, acute kidney failure, cardiac failure and thromboembolic events), we derived an index variable to measure the severity of COVID-19 in patients. ***Results:*** 143 confirmed adult COVID-19 patients were included, of whom 62% (n=89) were male and 38% (n=54) female of an average age of 50.6 (SD = 16.5) years. Our study found that being a female, working at the health care facility, being a healthcare worker, attending a mass gathering within the last 14 days, attending a gathering with 10 persons or less and being admitted to a hospital, were associated with increased risk of developing severe COVID-19. However, at

the multivariant analysis, the only risk factor associated with severe COVID-19 was working at a health care facility (OR=33.42, *p=0.029*). ***Conclusions:*** Intervention directed to control risk factors associated with acquiring severe COVID-19 should be a core priority for all countries, especially among high risk occupations and workplaces including working at a health care facility. A risk based approach to prioritize vaccination among these high risk individuals should be supported to strengthen implementation of non-pharmaceutical interventions.

Keywords: COVID-19; severity index; risk factors; hospitalized patients; Oman.

Introduction

The devastating impact of severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) continues to be felt globally for more than a year since it was first reported in Wuhan China. [1] As of the end of March 2021 more than 129 million individuals have been infected with the virus causing more than 2,778,619 deaths.[2] Oman has documented 156,883 (3,072/100,000 population) COVID-19 cases with 1,662 deaths with a fatality rate of (1.1%).[3] The first two cases were reported by the governorate of Muscat (Province), the capital of Oman, and were associated with a trip to the Islamic Republic of Iran.[4,5]

COVID-19 vaccines and the non-pharmaceutical interventions (NPIs), have the potential to prevent serious infections, hospitalizations and death. However, in order for the vaccines to be effective, countries will need to achieve herd immunity by vaccinating more than 70% of the population.[6] For many countries, the process may take two or three years. Therefore, without the wide availability of vaccines, the mainstay approach to control the transmission of the virus are the NPIs including social distancing, hand hygiene, use of face masks, restriction of social gatherings, lock downs and early detection of cases and quarantine. In hospitals, patients are

generally managed by providing supplemental oxygen, antibiotics for secondary bacterial infection and dexamethasone to control the hyperinflammatory response. Remdesivir and tocilizumab have been also advocated for the management of hospitalized patients with moderate and severe COVID-19 respectively.[7]

Over a one-year period, epidemiological investigations into COVID-19 outbreaks have revealed that the factors influencing acquisition risk vary from one context to another. However, several local factors appear in many well-established patterns that can be identified and avoided when well-studied that are influenced by contact patterns, environmental factors and socio-economic inequalities.[8,9] Transmission can take place in any setting but some settings facilitate greater risk of acquistion due to a combination of environmental and behavioural factors. Therefore, understanding the behavioral and demographic characteristics of patients with COVID-19 infection and potential risk factors for acquisition of COVID-19 during the 2 weeks before illness onset, as well as the epidemiological risk factors for severe illness leading to hospiatlization , could help significantly in the efforts to reduce community transmission. [5,10-12]

To our knowledge, there is a paucity of literature describing the community transmission risk factors for severe COVID-19 specifically in Oman. Therefore, the aim of our study is to determine epidemiological risk factors associated with the potential acquisition of severe COVID-19 and hospitalization, in order to manage and reduce transmission in the community and the health care setting and to enforce control measures.

Methods

Study Setting

Oman is one of the 22 countries within the Eastern Mediterranean Region (EMR) of the World Health Organization (WHO) with a population of nearly 5 million out of whom approximately 43% are foreign-born individuals (non-citizen). The Royal Hospital (RH) is the largest tertiary healthcare facility with nearly 1000 beds that has been designated for hospitalization of patients with moderate and severe COVID-19.

Study Design

A prospective cohort study was conducted among patients hospitalized with laboratory confirmed SARS-CoV-2 infection by real time polymerase chain reaction (RT- PCR) at the Royal Hospital, Muscat, Oman. Patients were admitted into a designated isolation ward through Emergency Room (ER), general wards, or transfers from other hospitals or transfers (step down) from the Intensive Care Unit (ICU) within the same hospital.

Study sample and population

A total of 143 individuals were enrolled during the period August 9th, 2020 through November 30th , 2020, who were able to self-report verbally. Pregnant women and patients younger than 18 were excluded.

Data Collection

The interview was conducted by trained health care workers (HCWs) within 48 hours following the patient's admission to the hospital or transfer from the ICU . A questionnaire comprising six close-ended questions was used to identify potential exposure risk factors for COVID-19. The questionnaire, collected data on: demographic characteristics (sex, age, place of residency, and nationality), clinical presentation, contact and exposures history in the 14 days before symptoms onset, features of severe COVID-19 and COVID-19 complications. For epidemiologic purposes, severe COVID-19 in adults is defined as dyspnea, a respiratory rate of 30 or more breaths per

minute, a blood oxygen saturation of 93% or less, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Pao_2:Fio_2) of less than 300 mm Hg, or infiltrates in more than 50% of the lung field.[13]

Using COVID-19 complications that included severe illness (severe pneumonia and ARDS), need for mechanical ventilation, acute renal failure, cardiac failure and thromboembolic events, we developed an index score variable to measure the severity of COVID-19 in hospitalized patients. Patients having at least one of severe illnesses or complications were classified as being severe, otherwise not severe.

Statistical Analysis

Patient characteristics were described using frequencies and percentages for category variables, mean and standard deviation for continuous variables. Chi-square test was used to determine significant relationship between independent variables and severity of infection. Unadjusted and adjusted logistic model analysis were used to determine measures of association between independent variables (risk factors) and severity of COVID-19 infection. All statistical analysis and tests were done using the R statistical analysis program at a significance level, alpha of 0.05.

Ethical Approval

The study was approved by the Royal Hospital Ethical Committees (SRC#26/2020). Consent was obtained from all patients willing to participate in the study by a qualified member of the study team.

Results

Patient demographic and clinical characteristics

A total of 143 patients were included in the study, of those, 95.8% (n=137) were Omani citizens

and 4.2% (n=6) were non-citizens. Overall, the sample consisted of 62.2% (n=89) male and 37.8% (n=54) female, with an average age of 50.6 (SD = 16.5, Range = 69) years. More than half of the patients 73.4% (n=105) were residents of Muscat governorate and 26.6% (n=38) were from other governorates. Approximately 4.9% (n=7) of patients were health care workers (HCWs)[Table 1].

Table1. Demographic and exposure characteristics of the COVID-19 patients

Variables	n(%)
Gender	
Male	89 (62.2)
Female	54(37.8)
mean (SD) age, years	50.6(16.5)
Nationality	
Citizen	137(95.8)
Non-Citizen	6(4.2)
Place of Resident	
Muscat	105(73.4)
Other governorates (provinces)	38(26.6)
Occupation	
Working in health care facility	7(4.9)
Health care worker	136(95.1)
Disease Exposures	
Travelling within last 14 days	17(11.9)
Contact with COVID-19 case within last 14 days	
at home	42 (29.4)
at work place	11 (7.7)
at the hospital	9 (6.3)
Contacting with COVID-19 cases with less than 2 meter space	
member of family	50(35.0)
co-workers	11(7.7)
friends	15(10.5)
Working outside their homes within the last 14 days	
dialy	30(20.1)
2-3 times a week	11(7.7)

	once a week	7(4.9)
	never	93(65.0)

Of the total number of patients diagnosed with COVID-19, 29.4% (n=42) were admitted or stepped down from the ICU, while 24.5% (n=35) required mechanical ventilation, MV. The associated COVID-19 illnesses/complications were as follow: severe pneumonia 14.0% (n=20), ARDS 13.3% (n=19), acute renal failure 10.0% (n=14), cardiac failure 3.5% (n=5) and thromboembolic events 1.4% (n=2).

Disease Exposures

Of the 143 patients who provided an exposure history, 11.9% (n=17) reported to have travelled domestically within the past 14 days. A total 29.4% (n=42) had got in contact with a case of COVID-19 within 14 days at home, 7.7% (n=11) at work and 6.3% (n=9) at the hospital. Defined as close contact (being in contact with COVID-19 case for more than 10 minutes within two meters or less), about 35.0% (n=50) were with a family member, 7.7% (n=11) with a co-worker and 10.5% (n=15) with a friend. Twenty one percent (n=30) of the COVID-19 infected patients worked outside their home on a daily basis, 7.7% (n=11) worked away from home 2-3 times a week, 4.9% (n=7) worked out of home once a week and 65.0% (n=93) never worked out of their home in the preceding 14 days prior to the infection [**Table 1**].

Exposure risk factors for severe COVID-19

Out of 66 patients with severe COVID-19, several risk factors were identified to be significant. Being female (n=31; 51.7%; *p=0.01*), attending a mass gathering within the last 10 days (n=18; 30.0%; *p*=0.017), attending a gathering with 10 person or less (n=18; 30.0%; *p=0.034*), being admitted at a hospital within the last 14 days (n=38; 63.3%; *p=0.027*) displayed potential risks for acquisition of severe infection and were significantly different from patients with less severe

infections. However, working at a healthcare facility (n=23; 39.0%; *p=0.053*) displayed a marginal potential risk.[**Table 2**].

Table 2. Bivariate analysis of associated factors for COVID-19 severity among patients

Associated Factor		Total	Severity	Non-severity	*P*-value
		N=143	N=66	N=77	
Age group					0.202
	18-34	24	7(11.7)	17(22.1)	
	35-50	45	19(31.7)	26(33.8)	
	> 51	68	34(56.7)	34(44.2)	
Gender					0.010
	Male	84	29(48.3)	55(71.4)	
	Female	53	31(51.7)	22(28.6)	
Contact history and disease exposure					
Travelling within last 14 days		17	10(16.7)	7(9.1)	0.283
Health care worker		6	5(17.2)	1(2.1)	0.053
worked in health care facility		39	23(39)	16(21.3)	0.041
Staying with an isolated COVID diagnosis patient		57	30(51.7)	27(35.1)	0.078
Attending mass gathering in the last 14 days		18	13(22.4)	5(6.7)	0.017
Attend gathering with less than 10 person		28	18(30)	10(13.5)	0.034
Admited at hospital within the last 14 days		71	38(63.3)	33(42.9)	0.027

Our unadjusted logistic regression analysis showed that females (OR 2.67; 95% CI 1.33-5.49; *p=0.006*), working in the health care facility (OR 9.58; 95% CI 1.44-189.23; *p=0.044*), being a healthcare worker (OR 2.36; 95% CI 1.11-5.11; *p=0.027*), attending a mass gathering in the past 14 days (OR 4.04; 1.42-13.32; *p*=0.013), gathering with 10 persons or less (OR 2.74; 95% CI

1.17-6.73; *p=0.022*), admission to a hospital (OR 2.30; 95% CI 1.16-4.65; *p*=0.018) were significantly associated with increased severe COVID-19 disease [**Table 3**].

Table 3. Multivariate analysis for risk factors of COVID-19 severity among patients

		Non-Severity n(%)	Severity n(%)	Unadjusted OR(95%CI)	Adjusted OR(95%CI)
Age group					
	18-34	17(70.8)	7(29.2)		
	35-50	26(57.8)	19(42.2)	1.77(0.63-5.37, p=0.289)	
	> 51	34(50.0)	34(50.0)	2.43(0.92-6.97, p=0.082)	
Gender					
	Male	55(65.5)	29(34.5)		
	Female	22(41.5)	31(58.5)	2.67(1.33-5.49, p=0.006)	
Working in health care facility					
	No	46(65.7)	24(34.3)		
	Yes	1(16.7)	5(83.3)	9.58(1.44-189.23, p=0.044)	33.42(1.92-1386.88, p=0.029)
Medical Health care worker					
	No	59(62.1)	36(37.9)		
	Yes	16(41.0)	23(59.0)	2.36(1.11-5.11, p=0.027)	
Mass gathering					
	No	70(60.9)	45(39.1)		
	Yes	5(27.8)	13(72.2)	4.04(1.42-13.32, p=0.013)	
Gathering with 10 person or less					
	No	64(60.4)	42(39.6)		
	Yes	10(35.7)	18(64.3)	2.74(1.17-6.73, p=0.022)	
Admited to hospital					
	No	44(66.7)	22(33.3)		

	Yes	33(46.5)	38(53.5)	2.30(1.16-4.65, p=0.018)

Moreover, the adjusted multivariate logistic regression analysis show that, working at a health care facility (OR=33.42; 95% CI 1.92-1386.88; *p=0.029*) was significantly associated with severe COVID-19 infection. Incidentally, being female was only marginally significantly associated. Although, being older than 51years showed increased odds of severe infection, it was not statistically significant [**Table 3**].

Discussions

Patients with severe COVID-19 are at increased risk of morbidity and mortality. Our study has identified a number of risk factors that are associated with acquistion of severe COVID-19 and it's complications. Females, being a healthcare worker, attending a mass gathering and gathering with 10 persons or less were significantly associated with severe COVID-19. On adjusted multivariate analysis working at a health care facility was the only significant risk factor associated with severe COVID-19.

Several reports from retrospective cohort studies in France[14] and China [15] demonstrated that being male was significantly associated with severe COVID-19. In contrary, this study revealed an association between females and increase risk of severe COVID-19 by 2.67 times despite more males were hospitalized. This finding is in agreement with several other studies where a higher attack rate was observed in females rather than males [16-18]. Furthermore, Gebhard et al [19] explored and assessed differentials that exist not only by gender, but also by gender roles played in the social and economic spheres of life. This difference in attack rate based on gender roles, may be due to reasons such as: female role as caregivers within the family that potentially

require closer contact and longer contact period with the index cases [16,20] and in most cases females comprise a large proportion of HCWs.[21] Therefore, implementation of preventive measures to protect females from infection and prioritizing them for vaccination are essential . On multivariate logistic regression analysis, the effect of gender on severity of COVID-19 was not significant.

Although patients over the age of 51 are most likely to have serious illness, this result was not statistically significant in this cohort, probably due to the relatively small sample size. However, it was shown that the odds ratio of having severe disease among age groups 30-51 and age group above 51 was 1.77 and 2.43 respectively. Thus, confirming that severe COVID-19 was seen in the older patients than those aged 18-34 years. This is consistent with the findings of a multi-centre observation study conducted in 18 hospitals designated for COVID-19 in Malaysia which revealed that over half of the serious cases were among age 51-year-old and above.[22]

In this cohort, attending a mass gathering (OR 4.04; 95% CI 1.42-13.32, p=0.013) or a gathering of 10 persons or less (OR 2.74; 95% CI 1.17-6.73; *p=0.022*) was significantly associated with severe COVID-19. Mass gatherings bring people into proximity, in environments that are conducive for transmission of infections.[23] The risk of infection is magnified if the disease is particularly contagious as is the case with COVID-19 and its new variants.[24] Moreover, in mass gatherings people tend to lower their guard on NPIs measures and this could potentially increase the likelihood of transmission. In a large retrospective cohort study involved 7700 close contacts of confirmed COVID-19 cases in Singapore, close physical proximity and increased duration of verbal interaction were independent risk factors for transmission among both household and non-household contacts.[25] These findings confirm the importance of NPIs that has been adopted by countries such as social distancing, universal masking and panning gatherings.

Our findings based on unadjusted logistic regression analysis showed that gatherings,regardless of the number, are associated with COVID-19 severity. Moreover, these findings clearly bring out the differences, showing that mass gatherings increased the odds of severe COVID-19 by four times whereas, gatherings with 10 people or less increased the chances of severe symptoms by almost three times compared to those who did not get involved in any gatherings. This difference, though small, has epidemiological implications as to possibility of COVID-19 re-infection in large gatherings and if so whether severity implies higher viral loads. A few studies have confirmed that indeed viral loads have a positive correlation with COVID-19 severity.[26,27] Some of the other factors that influence transmission in settings of mass gatherings include: prevalence and transmission pattern of COVID-19 in the community, the extent and duration of social interactions, and the demographic profile of participants.[23,28]

Whereas COVID-19 severity is influenced by host factors such as age, co-morbidities and immune function, the association between the clinical seriousness of index and secondary cases is not fully studied.[25] However, a retrospective cohort study showed that close contact between adults and those exposed to index cases with dry cough symptoms was associated with increased possibility of infection.[29] Our findings show that forty percent of the patients reported being in close contact with an index patient in quarantaine /isolation. Of those, over fifty one percent had a severe infection. Further, this risk of infection was significantly higher in adults aged at least 60 years.[22,30,31]

In this study, patients working at a health care facility had increased odds of developing severe disease by at least nine times compared to patients who did not work at a health care facility. Additionally, being a medical HCW increased the odds of acquiring severe illness by over two times compared to those who are non medical healthcare workers. These findings are consistent

with an observational and prospective cohort study using the UK and US COVID-19 Symptom Study, which indicated that frontline HCWs were 12 times more likely to be tested positive after a multivariable adjustment.[32] Although, both of these factors yielded statistically significant results with severity of COVID-19, it is worthy to explain the differences in increased odds ratios. It is not doubtable that medical healthcare workers are more exposed due to their frequent bedside visits to patients,caring of patients with severe conditions as required by their occupation and the number of hours they spend with patients. A number of potential factors have been postulated as the underlying reason for the increase in risk among HCWs. These include poor compliance with personal protective equipment, high risk exposure to infected patients, overwork, performing aerosol-generating procedures, poor infection control practices and pre-existing comorbidities .[32-35]

The uniqueness of our study can be attributed to the index of severity developed as an outcome variable. Most recent studies have only used some clinical factors to measure COVID-19 severity.[36-38] Whereas, that approach may work, its results are more confirmatory, but less predictive because of failure to focus on important transmission risk factors as well as co-morbidities that in most cases exacerbate the worsening disease among COVID-19 patients.

Limitations

There were some limitations in the study. Firstly, the nature of the retrospective study inevitably resulted in recall bias. Secondly, the transmission risk factors identified in this cohort might be more specific to the hospitalized population studied and cannot be generalized. Thirdly, the relatively small number of the cohort and exclusion of children and pregnant women could have underestimated the effects of certain modes of transmission. However, clinicians are strongly

encouraged to study these variables for their relevant populations, as lifestyle and exposures can vary across populations and countries.

Conclusions

The study sought to determine risk factors associated with hospitalization in COVID-19 patients, the potential transmissibility and severity so as to inform control measures. Being a female, working at healthcare institution, attending a mass gathering within the last 10 days prior to the diseases onset, gathering with 10 people or less during the last 14 days, and being admitted at a hospital within the last 14 days may identify individuals at high risk of severe COVID-19. At a hospital level, the highlighted healthcare workers should be included in the triage scale for early identification of potential severe COVID-19 illness.

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Conflict of interest

The authors declare no conflict of interest.

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