Epidemiological Risk Factors for Acquiring Severe COVID-19: Prospective Cohort Study

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ABSTRACT

Objectives: We aimed to determine epidemiological risk factors associated with acquiring severe coronavirus disease 2019 (COVID-19) in patients requiring hospitalization. *Methods*: A prospective cohort study was conducted using a questionnaire comprised of six closed-ended questions to identify potential risk factors for severe COVID-19. Using COVID-19 associated illnesses and complications (pneumonia, acute respiratory distress syndrome, 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:* We included 143 adult patients with confirmed COVID-19 of whom 62.2% (n = 89) were male and 37.8% (n = 54) were female. The average age of the cohort was 50.6±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. The only risk factor associated with severe COVID-19 was working at a health care facility (odds ratio = 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 the implementation of non-pharmaceutical interventions.

The devastating impact of severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) continues to be felt globally 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 coronavirus disease 2019 (COVID-19) cases (3072/100 000 population) with 1662 deaths with a fatality rate of (1.1%).[3] The first two cases were reported by the governorate of Muscat, the capital of Oman, and were associated with a trip to Iran.[4,5]

COVID-19 vaccines and non-pharmaceutical interventions (NPIs) have the potential to prevent serious infections, hospitalizations, and death. However, for the vaccines to be effective, countries must achieve herd immunity by vaccinating > 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 NPIs, including social distancing, hand hygiene, use of face masks, restriction of social gatherings, lockdowns, 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 also been advocated for managing hospitalized patients with moderate and severe COVID-19, respectively.[7]

Over one year, epidemiological investigations into COVID-19 outbreaks have revealed that the factors

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influencing acquisition risk vary from one context to another. However, several local factors appear in well-established patterns that can be identified and avoided when well-studied, influenced by contact patterns, environmental factors, and socioeconomic inequalities.[8,9] Transmission can take place in any setting, but some settings facilitate greater risk of acquisition due to a combination of environmental and behavioral 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 two weeks before illness onset and the epidemiological risk factors for severe illness leading to hospitalization could help significantly in the efforts to reduce community transmission.[5,10–12]

There is a paucity of literature describing the community transmission risk factors for severe COVID-19, specifically in Oman. Therefore, our study aims to determine epidemiological risk factors associated with the potential acquisition of severe COVID-19 and hospitalization to manage and reduce transmission in the community and healthcare settings and enforce control measures.

METHODS

The Royal Hospital is the largest tertiary healthcare facility with nearly 1000 beds, designated for hospitalization of patients with moderate and severe COVID-19.

A prospective cohort study was conducted among patients hospitalized with laboratory-confirmed SARS-CoV-2 infection by real-time polymerase chain reaction at the Royal Hospital, Muscat, Oman. Patients were admitted into a designated isolation ward through the emergency room, general wards, transfers from other hospitals, or transfers (step down) from the intensive care unit (ICU) within the Royal Hospital.

A total of 143 individuals were enrolled from 9 August to 30 November 2020, who could self-report verbally. Pregnant women and patients < 18 were excluded.

The interview was conducted by trained health care workers (HCWs) within 48 hours following the patient's admission to the hospital or ICU transfer. A questionnaire comprising six closed-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 < 300 mm Hg, or infiltrates in > 50% of the lung field.[1,3]

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

Patient characteristics were described using frequencies and percentages for categorical variables and mean and standard deviation for continuous variables. The chi-square test was used to determine a significant relationship between independent variables and the severity of infection. Unadjusted and adjusted logistic model analyses were used to determine measures of association between independent variables (risk factors) and severity of COVID-19 infection. All statistical analysis were done using the R statistical analysis program (R Core Team (2020). R Foundation for Statistical Computing, Vienna, Austria). Tests < 0.050 were statistically significant.

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 member of the study team.

RESULTS

A total of 143 patients were included in the study; 95.8% (n = 137) were Omani citizens and 4.2% (n = 6) were non-citizens. Overall, the cohort consisted of 62.2% (n = 89) males and 37.8% (n = 54) females. The average age of the cohort was 50.6±16.5 years. More than half of the patients (73.4%, n = 105) were residents of Muscat and

Table 1: Demographic and exposure characteristics of the COVID-19 patients.

Variables	n (%)
Age, mean ± SD, years	50.6 ± 16.5
Gender	
Male	89 (62.2)
Female	54 (37.8)
Nationality	
Citizen	137 (95.8)
Non-citizen	6 (4.2)
Place of residence	
Muscat	105 (73.4)
Other governorates (provinces)	38 (26.6)
Occupation	
Working in a healthcare facility	7 (4.9)
Healthcare worker	136 (95.1)
Disease exposures	
Traveling within last 14 days	17 (11.9)
Contact with COVID-19 case within last 14 days	
Home	42 (29.4)
Workplace	11 (7.7)
Hospital	9 (6.3)
Contacting with COVID-19 cases with < 2 meter space	
Family member	50 (35.0)
Co-workers	11 (7.7)
Friends	15 (10.5)
Working outside their homes within the last 14 days	
Daily	30 (21.0)
2–3 times a week	11 (7.7)
Once a week	7 (4.9)
Never	93 (65.0)

SD: standard deviation.

26.6% (n = 38) were from other governorates. Approximately 4.9% (n = 7) of patients were HCWs [Table 1].

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. The associated COVID-19 illnesses/complications were as follows: 14.0% severe pneumonia (n = 20), 13.3% ARDS (n = 19), 10.0% acute renal failure (n = 14), 3.5% cardiac failure (n = 5), and 1.4% thromboembolic events (n = 2).

Of the 143 patients who provided an exposure history, 11.9% (n = 17) reported domestic travel within 14 days. A total 29.4% (n = 42) had 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. Close contact was defined as being in contact with an individual with COVID-19 for > 10 min within two meters or less: 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 daily, 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].

Out of 60 patients with severe COVID-19, several risk factors were identified to be significant. Being female (n = 31; 51.7%; p = 0.010), attending a mass gathering within the last 10 days (n = 13; 21.7%; p = 0.017), attending a gathering with 10 people 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, being a HCW (n = 23; 38.9%; p = 0.041) displayed a marginal potential risk [Table 2].

Unadjusted logistic regression analysis showed that females (odds ratio (OR) = 2.67; 95% confidence interval (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 HCW (OR = 2.36; 95% CI: 1.11–5.11; p = 0.027), attending a mass gathering in the past 14 days (OR = 4.04; CI: 1.42–13.32; p = 0.013), gathering with 10 people 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].

Moreover, the adjusted multivariate logistic regression analysis shows 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 over 51 years showed increased odds of severe infection, it was not statistically significant [Table 3].

DISCUSSION

Patients with severe COVID-19 are at increased risk of morbidity and mortality. Our study has identified

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

Associated factor	Total N = 137	Severity n = 60	Non-severity n = 77	p-value
Age group, years				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				
Traveling within last 14 days	17	10 (16.7)	7 (9.1)	0.283
Worked in a healthcare facility	6	5 (8.3)	1 (1.3)	0.053
Healthcare worker	39	23 (38.3)	16 (20.8)	0.041
Staying with an isolated COVID diagnosis patient	57	30 (50.0)	27 (35.1)	0.078
Attending mass gatherings in the last 14 days	18	13 (21.7)	5 (6.5)	0.017
Attend gathering with < 10 people	28	18 (30.0)	10 (13.0)	0.034
Admitted to hospital within the last 14 days	71	38 (63.3)	33 (42.9)	0.027

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

Variables	Non-severity n (%)	Severity n (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age group, years				
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 a healthcare 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)
Healthcare 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 gatherings				
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 people 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)	
Admitted 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)	

OR: odds ratio; CI: confidence interval.

several risk factors associated with the acquisition of severe COVID-19 and its complications. Females, HCWs, attending mass gatherings, and gathering with 10 people or less were significantly associated with severe COVID-19. On adjusted multivariate analysis working at a healthcare facility

was the only significant risk factor associated with severe COVID-19.

Several reports from retrospective cohort studies in France[13] and China[14] demonstrated that being male was significantly associated with severe COVID-19. On the contrary, our study revealed females were associated with a 1.07-times increased risk of severe COVID-19 despite more males being hospitalized. This finding agrees with several other studies where a higher attack rate was observed in females rather than males.[15–18] Furthermore, Gebhard et al,[19] explored and assessed differentials that exist not only by gender but also by gender roles in the social and economic spheres of life. These differences may be due to the typical female role as caregivers within families 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 more likely to have serious illness, this result was not statistically significant in this cohort, probably due to the relatively small sample size. However, the OR of having severe disease among the 30–51 and > 51 age groups was 1.77 and 2.43, respectively, confirming that severe COVID-19 was seen in older patients rather than those aged 18–34 years. This is consistent with the findings of a multi-center observation study conducted in 18 hospitals designated for COVID-19 patients in Malaysia, which revealed that over half of serious cases were among those aged 51 years old and above.[22]

In this cohort, attending mass gatherings (OR = 4.04; 95% CI: 1.42–13.32; $p = 0.013$) or a gathering of 10 people 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 the 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 involving 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 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 banning gatherings.

Our findings based on unadjusted logistic regression analysis showed that gatherings are associated with COVID-19 severity regardless of the number of people. Moreover, these findings bring out the differences, indicating that mass gatherings increased the odds of severe COVID-19 by four times. In contrast, 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 the 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, comorbidities, 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 an increased possibility of infection.[29] Our findings show that 40.0% of the patients reported being in close contact with an index patient in quarantine/isolation. Of those, over 51.0% 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 healthcare 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 non-medical HCWs. 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 worth explaining the differences in increased ORs. HCWs are more exposed due to their frequent bedside visits to patients, caring for patients with severe conditions, and the number of hours they spend with patients. Several 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] Those results are more confirmatory but less predictive because of failure to focus on important transmission risk factors and comorbidities that in most cases exacerbate the worsening disease among COVID-19 patients.

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 exposure vary across populations and countries.

CONCLUSION

The study sought to determine risk factors associated with COVID-19 patients' hospitalization and the potential transmissibility and severity to inform control measures. Being a female, working at a healthcare institution, attending mass gatherings within the last 10 days prior to the onset of the disease, 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 HCWs should be included in the triage scale to identify potential severe COVID-19 illness early.

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