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Large variations in disease severity, death and ICU admission of 2993 patients infected with SARS-CoV-2: The potential impact of genetic vulnerability

Halah Mohammed Farajallah^a, Sara Khamis AlSuwaidi^a, Shatha Mohammad AlSuwaidi^a, Ghada AlAhmdani AlAli^a, Amani Salem AlZubaidi^a, Frederick Robert Carrick^{b,c,d}, Mahera Abdulrahman^{e,*}

^a Primary Healthcare Sector, Dubai Health Authority, Dubai, United Arab Emirates

^b Centre for Mental Health Research in association with University of Cambridge, Cambridge, UK

^c University of Central Florida College of Medicine, Orlando, FL USA MGH Institute for Health Professions, Boston, MA, USA

^d Carrick Institute, Cape Canaveral, Florida, USA

^e Health Informatics and Smart Health Department, Health Regulation Sector, Dubai Health Authority, Dubai, United Arab Emirates

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ABSTRACT

Background: The COVID-19 pandemic has had an immeasurable impact, affecting healthcare systems, the global economy, and society. Exploration of trends within the existing COVID-19 data may guide directions for further study and novel treatment development. As the world faces COVID-19 disease, it is essential to study its epidemiological and clinical characteristics further to better understand and aid in its detection and containment.

Methods: We aimed to study the clinical characteristics of patients infected with COVID-19 in Dubai, a multi-national Society.

Results: Our findings demonstrate that during the first wave of the COVID-19 epidemic, age, gender, and country of origin were associated with more severe cases of COVID-19, higher risk for hospitalization and death. Male individuals between 41 and 60 years of age from India had the most significant hospitalization and death predictor ($p = .0001$). The predictors for COVID-19 related deaths were slightly less than UAE Nationals by individuals from GCC ($p = .02$) that were followed closely behind by Pilipino ($p = .02$) and Arabs ($p = .001$).

Conclusion: The vulnerability of individuals to infection and in the spectrum of COVID-19 symptoms remains to be understood. There are large variations in disease severity, one component of which may be genetic variability in responding to the virus. Genomics of susceptibility to COVID-19 infection and the wide variation in clinical response to COVID-19 in patients should become active investigation areas.

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Introduction

Humanity faces extreme public health challenges in contemporary history when dealing with the disease caused by a new type of coronavirus, called coronavirus disease 2019 – COVID-19.

In early 2020, a novel coronavirus was isolated and named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The World Health Organization named the disease coronavirus disease 2019 (COVID-19) and subsequently declared it a pandemic due to the widespread infectivity and high contagion rate. The COVID-19 outbreak has become a pandemic threatening global health, undermining the global economy, and destabilizing societies across the world [2]. It has been well established that at the onset of the disease, the main manifestations of COVID-19 are fatigue, fever, dry cough, myalgia, and dyspnea, with less typical symptoms being nasal congestion, headache, runny nose, sore throat, vomiting, and diarrhea [3]. Severe patients often have dyspnea or hypoxemia one

* Corresponding author.

E-mail addresses: hfarajallah@dha.gov.ae (H.M. Farajallah), SarMAISuwaidi@dha.gov.ae (S.K. AlSuwaidi), SMAlSuwaidi@dha.gov.ae (S.M. AlSuwaidi), goalali@dha.gov.ae (G.A. AlAli), ASAlzubaidi@dha.gov.ae (A.S. AlZubaidi), Drfrccarrick@post.harvard.edu (F.R. Carrick), marad@dha.gov.ae (M. Abdulrahman).

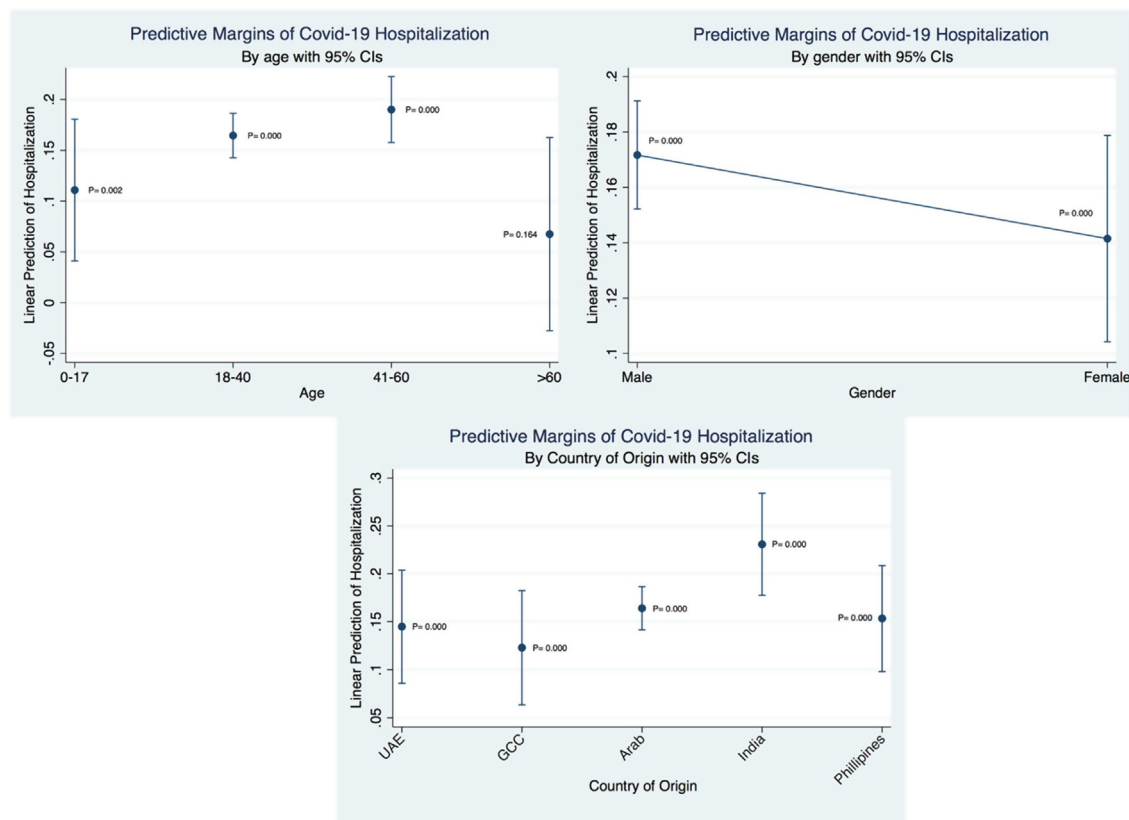


Fig. 1. Predictive margins of COVID-19 hospitalization by age, gender, and country of origin are presented.

week after onset, after which septic shock, acute respiratory distress syndrome (ARDS), difficult-to-correct metabolic acidosis, and coagulation dysfunction develop rapidly. Of note, severe and critical patients can also present with a low fever, or even no apparent fever, while mild patients show only low fever, mild fatigue, and no pneumonia [4,5]. These asymptomatic or mild cases are challenging, as they can spread COVID-19 between individuals.

Although severe lung injury has been described at all ages, in some high-risk individuals, such as the elderly or those affected by multi-morbidities, the virus is more likely to cause severe interstitial pneumonia, ARDS, and subsequent multi-organ failure, which are responsible for severe acute respiratory failure and high death rates [6]. It is now evident that not all infected patients develop a severe respiratory illness; the reason for this is currently not apparent. Moreover, very little is understood about inter-individual genetic differences in the immune response to this virus.

Like global patterns, the number of confirmed cases in the United Arab Emirates (UAE) has also increased. The UAE was the first country in the Middle East to report a confirmed case, announced on January 29, 2020, and linked to a family of Chinese tourists traveling from Wuhan, China, the virus epicenter [7]. As of November 9, 2020, the total number of confirmed cases has reached 142,143, according to the Ministry of Health and Prevention, with a daily average increase of around 514 cases countrywide.

<https://www.mohap.gov.ae/en/AwarenessCenter/Pages/COVID19-Information-Center.aspx>. UAE, and particularly Dubai, is a society with a multi-ethnicity component. People from different genetic backgrounds are living in the same geographic place. As the world faces this new infectious disease, it is essential to study its epidemiological and clinical characteristics further to understand better why COVID-19 has different susceptibility and severity on different individuals with dissimilar genetic backgrounds. An enormous rush of research and studies is being published around

the globe. The Middle East and specifically the Gulf region were found to be short with this regard and still require more efforts in that area as the burden of this disease continues to increase, which is why this study was found to be of particular necessity and importance. In this study, we summarize and present the epidemiological and clinical characteristics of COVID-19 positive patients in the Emirate of Dubai, aiming to gain more information to understand the prevalence, clinical manifestations better, and risk factors for COVID-19 severity and mortality in the UAE compared to the published global patterns.

Methods

Study design and participants

This descriptive retrospective study was conducted on all patients who attended primary healthcare centers in Dubai Health Authority (DHA) from Feb 2020 to April 2020 and were diagnosed with COVID-19 (tested positive through Coronavirus PCR pharyngeal or nasopharyngeal swabs).

Study procedure

Data was recruited from DHA's Electronic medical records (Salama).

Study design (evaluation tools)

Demographic information, clinical characteristics, exposure information, lab results, and Chest x-ray of each patient were collected, reviewed, and analyzed by different independent researchers. Both UAE citizens (UAE nationals) and expatriates were included in this study. The related data were double-checked and insert into the study tool indepen-

dently. Data that were missing were omitted. The severity of COVID-19 was considered as per Dubai health authority guideline for COVID-19 https://www.dha.gov.ae/en/HealthRegulation/Documents/National_Guidelines_of_COVID_19_1st_June_2020.pdf.

Data analysis and statistics

All collected data were entered into STATA version 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.) for statistical analysis. Descriptive statistics were computed for the socio-demographic variables. The total clinical data and outcome were determined using the Chi-square test, and statistical significance was recorded for non-parametric data. For all analyses, alpha (α) was set at 0.05. A multiple regression model was fitted to explore the possible predictors of COVID-19 symptoms, hospitalization, and death.

Ethics statement

The institutional review boards approved the Dubai Health Authority Dubai (Approval # DSREC-06/2020.09). Aggregate reporting of data assured to enhance confidentiality and accurate reporting by the patient’s data. The investigators guaranteed the anonymity of the data by coding the dataset.

Results

Overall, 37,716 COVID-19 tests were carried out in the Dubai Health Authority from February to April 2020, out of which 11,538 were positive. We randomized our sample by simple randomization method using an online computerized system: www.stattrek.com/statistics/random-number-generator.aspx#error. Medical data of 2993 COVID-19 patients were then accessed, and almost the majority were diagnosed during contact tracing of case-patients (1878, 63%). The majority of our patients were between 18 and 40 years, male, non-UAE national, residing in the UAE, non-healthcare workers (Table 1). Most of the patients did not need hospitalization (2637, 88%) or Intensive care unit (ICU) admission (2845, 95%), and only eight have died (Table 2). Interestingly, most of our patients did not have any symptoms (1601, 53%), and those with symptoms 987 (80%) had a resolution. The most common symptoms on admission were fever (66%), cough (55%), sore throat (35%), and headache (27%). Only 151 (12%) of the 2993 patients had dyspnea, and diarrhea was rather uncommon (3%). Chest radiography showed no abnormality in 2854 (89%) of the 2993 patients. only 313 (10%) of patients had comorbid conditions, and only 1% had risky behavior such as smoking or drinking alcohol (Table 3).

A multilinear regression model predicting COVID-19 hospitalization by age, gender, and country of origin was statistically significant ($p < .001$). We calculated the predictive margins from the linear regression model. Individuals between 41 and 60 years of age ($p = .000$), males ($p = .0001$), and individuals from India ($p = .0001$) had the most significant predictor of hospitalization (Fig. 1). A multilinear regression model predicting death due to COVID-19 by age, gender, and country of origin was statistically significant ($p < .001$). Individuals between 41 and 60 years of age had the most significant predictor of death from COVID-19 infection ($p < .001$), followed by ages 18–40 years of age ($p = .001$). Males were predicted to die from COVID-19 infection ($p = .001$) more than females (Fig. 2). When analyzing the nationality correlations, individuals from India that contracted COVID-19 were predicted to have the highest death rate ($p < .001$); out of 6 death cases, three were from India.

The predictors for COVID-19 related deaths were slightly less than UAE Nationals by individuals from GCC ($p = .025$) that were followed closely behind by Pilipino ($p = .02$) and Arabs ($p = .001$) (Fig. 3). Individuals between 41 and 60 years of age ($p = .001$), males

Table 3

Clinical characteristics of the study population. DM: Diabetes Mellitus, HTN: Hypertension, CVD: CardioVascular Disease, CLD: Chronic Lung Disease, CKD: Chronic Kidney Disease.

Clinical characteristics	All patients (n = 2993)P atients with symptoms (n = 1231)
Fever > 38°	816 (66)
Cough	673 (55)
Sore throat	436 (35)
Headache	338 (27)
Fatigue	211 (17)
Dyspnea	151 (12)
Pneumonia	111 (9)
ARDS	8 (1)
Rhinorrhea	59 (5)
Chest pain	44 (4)
Nausea or Vomiting	31 (3)
Chills	33 (3)
New olfactory/taste disorder	36 (3)
Diarrhea	31 (3)
Abdominal pain	25 (2)
Wheeze	4 (0.2)
Abnormal chest x-ray	139 (11)
Mechanical ventilation/intubation	7 (1)
Abnormal EKG	2 (0.1)
Medical condition (DM, HTN, CVD, CLD,313 (10)	
CKD, immunosuppression, disability, autoimmune, etc.)	
Risky behavior (smoking, alcohol, illicit39 (1) drugs)	

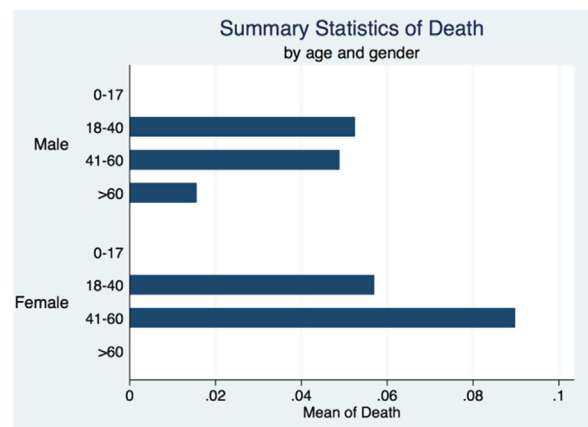


Fig. 2. Summary of death due to COVID-19 by age and gender is presented.

($p = .001$), and People with an Arab Country of origin had a more significant predictive margin of having symptoms than all other countries of origin ($p = .001$) had the most significant predictability of having symptoms after COVID-19 infection (Fig. 4).

Discussion

The global health and economic consequences of the COVID-19 pandemic are severe. It has been reported that progression into critical cases could happen within 3–10 days in 10%–20% of cases [8]. Although many therapies have been suggested, there are no specific options capable of treating COVID-19 disease or preventing SARS-CoV-2 infection. The only viable intervention and proven to decrease the contagion rate seems to be strict quarantine measures for the general population. The possibility of a second wave of SARS-CoV-2 infections is genuine; hence, preventive measures are essential. It is noteworthy that vaccines against the respiratory syncytial virus (RSV), rhinoviruses, SARS-CoV-1, and MERS-CoV have not yet been successful. Thus, for SARS-CoV-2 (and these other viruses), the medical and scientific communities must intensify

Table 1
Descriptive demographic characteristics of COVID-19 patients (n = 2993).

Variable, n(%)				
Age (Years)	≤17 197 (7)	18–40 1857 (62)	41–60 841 (28)	≥61 98 (3)
Gender	Male 2334 (78)	Female 659 (22)		
Nationality	UAE 284 (9)	Non-UAE 2709 (91)		
UAE residency	Yes 2724 (91)	No 147 (5)	Unknown/Missing 122 (4)	
Healthcare worker	Yes 63 (2)	No 2811 (94)	Unknown/Missing 119 (4)	
If Healthcare worker, occupation	Physician 3 (5)	Nurse 5 (8)	Unknown/Missing 55 (87)	

Table 2
Clinical characteristics of COVID-19 patients (n = 2993).

Variable, n(%)					
Case identification	Clinical evaluation		Routine surveillance	Contact tracing of case-patient	
	546 (18)		569 (19)	1878 (63)	
Pregnancy	Yes	No	Not Applicable (male or women who are not married)	Unknown/Missing	
	13 (0.4)	215 (7)	2593 (87)	172 (5.6)	
Hospitalization	Yes	No	Unknown/Missing		
	218 (7)	2637 (88)	138 (5)		
ICU admission during hospitalization	Yes	No	Unknown/Missing		
	8 (0.3)	2845 (95)	140 (4.7)		
Mechanical ventilation/Intubation	Yes	No	Unknown/Missing		
	7 (0.2)	2833 (95)	153 (4.8)		
Death	Yes	No	Unknown/Missing		
	6 (0.2)	2916 (97)	71 (1.8)		
14 days Exposure	International travel/Cruise ship travel	Contact with known COVID-19 case	Crew member/Workplace exposure	Mass gathering or event	Unknown exposure
	29 (1)	1434 (48)	13 (0)	3 (0)	1514 (51)
Symptoms	Yes	No	Unknown/Missing		
	1231 (41)	1601 (53)	161 (5)		
Symptoms resolution	Yes	No	Unknown/Missing		
	987 (80)	4 (1)	240 (19)		

their drug development studies to discover efficacious therapies and preventive measures. Prevention would include avoidance of viral contamination and possible identification of genetically susceptible subgroups within the human population.

Studies show that all age groups are susceptible to being infected with COVID-19; however, most patients currently affected are between 35 and 55 years [9]. The male gender has been shown to hold a bigger share of COVID-19 infection, at 60% compared to women [10]. Also, adult male patients with established comorbidities are more likely to be affected by the virus. Those most significant were cardiovascular and cerebrovascular diseases, in addition to diabetes. This phenomenon was attributed to the weaker immune functions of these patients [7]. However, low overall comorbidities in infected patients in this study may be due to under-reporting and missing data. Our data showed that critical cases consisted of around 0.3% of the COVID-19 patient population, with a 30-day mortality of 0.2% (Table 2). The number of patients admitted to the (Intensive Care Unit (ICU) was 8 (0.3%); of them, 7 (0.2%) required invasive mechanical ventilation, and 6 (0.2%) had decreased. Therefore, predicting the likelihood of progression to critical cases in non-critical cases and predicting in-hospital

mortality in critical cases became particularly important to the stratified management of patients with COVID-19 in a circumstance of the severe shortage of medical resources during the pandemic. As a convenient and easy-to-detect index, age, nationality, and gender must be obtained and monitored in all clinical settings and databases. Our study showed that individuals between 41 and 60 years of age had the greatest predictability of death from COVID-19 infection ($p < .0001$). Also, nationality and gender were both predictable for higher death, with Indians and males having the highest rate ($p < .0001$ and $p < .0001$ consequently). This is predictable as most UAE laborers are from India, and they have low income and live in labor campuses. The campuses usually are crowded and social distance is not followed as well. Our study shows 0.3% ICU admission, 0.3% ARDS, 4% pneumonia, and 0.2% rate for mechanical ventilation use and death.

UAE is trying its best to perform screening for at-risk individuals. To date, we had more than 14,137,717 COVID-19 tests being performed, and 142,143 cases were diagnosed as positive; 1437.2 per 100k population. Recovery rate was 1398.2 per 100k population and total death was 514; 5.2 per 100k population; with Case Fatality Rate 0.4% (<https://fcsa.gov.ae/en-us/Pages/Covid19/>

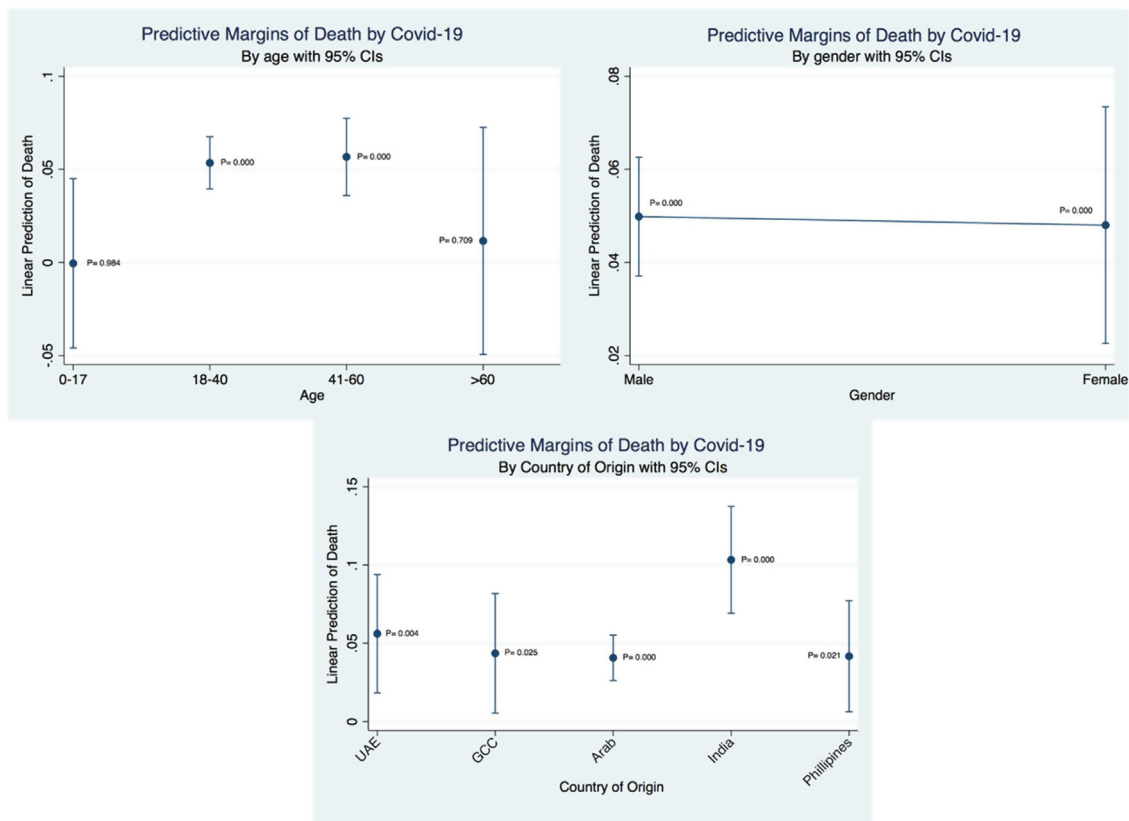


Fig. 3. Predictive margins of death due to COVID-19 by age, gender, and country of origin are presented.

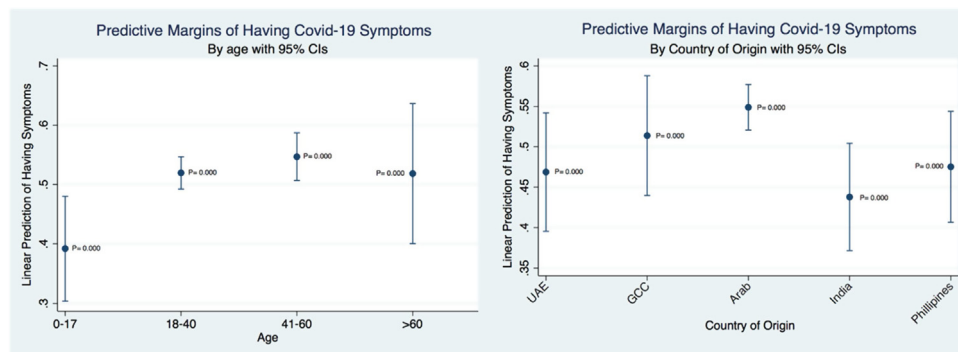


Fig. 4. Predictive margins of having COVID-19 symptoms by age and country of origin are presented.

UAE-Covid-19-Updates.aspx). However, one of the major goals for any healthcare service is to prevent death and severe morbidity. It should be the first place people go for information, screening, and testing for COVID-19, only turning to hospitals when necessary. The case was the same in Dubai healthcare systems, as PHC was the first station for the patients with COVID-19 symptoms. There are no registered drugs to treat COVID-19 disease, and a vaccine is not available [11,12]. Management is based mainly on supportive therapy and treating the symptoms, and trying to prevent respiratory failure. Several clinical trials of possible treatments for COVID-19 are underway, based on antiviral, anti-inflammatory, and immunomodulatory drugs, cell therapy, antioxidants, and other therapies [13].

Large differences in outcomes for invasively ventilated patients with COVID-19 have been reported for different countries – e.g., mortality rates for these patients in China [14] were reported to be two times higher than those in Italy [15] and the USA [16] and even within a single country, such as the UK [17]. Several

studies suggest that genetics plays an essential role in making some people more vulnerable than others to SARS-CoV-2, influencing infection efficiency, the immune response to infection, or the severity of COVID-19 symptoms [18–23]. Differences in outcomes motivate urgent comparative research to characterize between-country differences to inform best practice in the context of a surge of cases. Since treatments and vaccines for COVID-19 have not yet been developed, strategies to contain the virus’s spread have been implemented, such as encouraging social distancing and, in the most affected regions, mandatory population confinement [24]. The main objective of adopting such measures is limiting the number of infected people to a threshold at which the healthcare system and services can meet the demand, distributing the total number of cases over time, a phenomenon that has been popularly called flattening the curve [25].

The COVID-19 pandemic has had an immeasurable impact, affecting healthcare systems, the global economy, and society as a whole. Exploration of trends within the existing COVID-19 data

may guide directions for further study and novel treatment development. Our study demonstrates that men in almost every age group have higher test positivity, hospitalization, and death rates. This finding mirrors data from over 50 countries across six continents in which death rates were more significant in men versus women, with an estimated 60% increased risk of severe illness or death [26]. The differences in mortalities among the countries may be explained by genomic variations of susceptibility to SARS-CoV-2 infection and the differences in the prevalence of the comorbid conditions of the patients and overwhelmed healthcare systems.

Conclusions

Our findings demonstrate that during the first wave of the COVID-19 epidemic, age, gender, and country of origin were associated with more severe cases of COVID-19, higher risk for hospitalization and death. It is known that advanced age and pre-existing comorbidities render a person more vulnerable to the more severe health consequences of COVID-19. However, there are large variations in disease severity, one component of which may be genetic variability in responding to the virus. We emphasize that individuals' vulnerability to infection and in the spectrum of COVID-19 symptoms remain to be understood. Genomics of susceptibility to SARS-CoV-2 infection and the wide variation in clinical response to COVID-19 inpatients should become active areas of investigation.

Limitation of study

Limitations of our study include the surveillance-based nature of this evolving dataset. Some data was missing in our dataset, as the study was conducted during a large-scale infectious disease outbreak setting when the healthcare system was overwhelmed by a large number of patients seeking medical care. Nevertheless, given our study size, including population-level adjustments, we can assume our findings are sufficiently powered, generalizable, and externally valid. Although this study is a retrospective cohort study in nature, the results could indicate the context measured. Nevertheless, a more extensive national study with data from all emirates in the UAE is needed for better representative sampling.

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Competing interests

None declared.

Ethical approval

Not required.

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