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Factors associated with coronavirus disease 2019 infection severity among a sample of Lebanese adults: Data from a cross-sectional study

Elissar El-Hayek[1] | Georges-Junior Kahwagi[1,2] | Nour Issy[1] | Christina Tawil[1] | Nabil Younis[1] | Rony Abou-Khalil[1] | Madonna Matar[2,3] | Souheil Hallit[3,4,5]

[1]Department of Biology, Faculty of Arts and Sciences, Holy Spirit University of Kaslik-Jounieh, Jounieh, Lebanon

[2]Faculty of Medicine and Medical Sciences, Holy Spirit University of Kaslik (USEK), Jounieh, Lebanon

[3]Internal Medicine Department, Division of Infectious Diseases, Notre Dame Des Secours University Hospital, Jbeil, Lebanon

[4]Research Department, Psychiatric Hospital of the Cross, Jal Eddib, Lebanon

[5]Psychology Department, College of Humanities, Effat University, Jeddah, Saudi Arabia

Correspondence
Elissar El-Hayek, Department of Biology, Faculty of Arts and Sciences, Holy Spirit University of Kaslik-Jounieh, Jounieh, Lebanon.
Email: elissarhayek@usek.edu.lb

Abstract

Background and Aims: Identification of factors responsible for severe illness related to coronavirus disease 2019 (COVID-19) could help in the early management of patients with high risk, especially in developing countries with poor medical care systems. To date, no data have been published concerning the factors associated with COVID-19 severity in Lebanon. In this study, we aimed at investigating the relation between sociodemographic variables, health status, and the clinical outcomes of COVID-19 in a sample of Lebanese adults.

Methods: In our cross-sectional study, 1052 patients (563 male and 489 female, with the median age of 42.83 ± 17.88 years), tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) between January and March 2021, were recruited from a hospital in Byblos, Lebanon. Basic demographic data, medical history, clinical data, and selfreported symptoms related to COVID-19 were collected. Clinical classification of COVID-19 severity was carried out according to the WHO interim guidance on May 27, 2020. Multi and bivariate regression analysis were performed.

Results: When comparing patients with moderate symptoms versus mild, the results showed that older age (aOR = 1.05; 95% CI: 1.03–1.06) and having dyslipidemia (aOR = 1.89; 95% CI: 1.01–3.49) were significantly associated with higher odds of having moderate symptoms. When comparing patients with severe symptoms versus mild, older age (aOR = 1.08; 95% CI: 1.06–1.10), higher body mass index (aOR = 1.09; 95% CI: 1.04–1.15) and having respiratory diseases (aOR = 2.57; 95% CI: 1.03–6.36) were significantly associated with higher odds of having severe symptoms, whereas female gender (aOR = 0.56; 95% CI: 0.32–0.98) was significantly associated with lower odds of having severe symptoms compared to males. Finally, when comparing patients with severe symptoms versus moderate, older age (aOR = 1.03; 95% CI: 1.01–1.05) was found to be significantly associated with higher odds of having severe symptoms.

Conclusion: Identification of risk factors may contribute to a better understanding of the COVID-19 pathogenesis and provide clinical reference for early prognosis and management of patients.

KEYWORDS

epidemiology, infectious diseases, public health, respiratory medicine

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) is an ongoing global pandemic caused by the severe acute respiratory syndrome corona-virus 2 (SARS-CoV-2). SARS-CoV-2 is a novel strain of coronavirus. It was first reported from Wuhan, Hubei province, China, in December 2019 and was declared a global pandemic by the World Health Organization on March 11, 2020 (www.who.int).

The current classification of coronaviruses recognizes 39 species in 27 subgenera, five genera and two subfamilies that belong to the family *Coronaviridae*, suborder *Cornidovirineae*, order *Nidovirales*, and realm *Riboviria*.[1] SARS-CoV-2 belongs to the subfamily of *Coronavirinae*, genus *Betacoronavirus* that includes two other zoonotic viruses, the SARS-CoV and the Middle East respiratory syndrome coronavirus (MERS-CoV), introduced to humans earlier in the twenty-first century.[2] SARS-CoV-2 differs from the SARS-CoV and the MERS-CoV in term of disease spectrum and transmission efficiency.[1] SARS-CoV-2 can cause symptoms ranging from mild to moderate upper-respiratory tract illnesses, like the common cold to more severe and even fatal multiorgan dysfunction.[3] Previous research showed that COVID-19 is associated with thrombosis,[4] neuropsychiatric complications,[5] kidney, heart, and liver dysfunctions.[6–8]

The COVID-19 pandemic has spread quickly, as of February 2021, more than 5 million confirmed deaths attributed to COVID-19 in the world have been reported (WHO Coronavirus [COVID-19] Dashboard | WHO Coronavirus [COVID-19] Dashboard With Vaccination Data). Besides being one of the deadliest in history, the COVID-19 pandemic has produced an exceptional global socioeconomic crisis.

Early management of symptomatic subjects at high risk of developing severe forms of COVID-19 has shown to reduce efficiently the numbers of hospitalizations and intensive care admission, decreasing thereby the related costs sustained by public health systems.[9]

Numerous studies have revealed that the clinical outcomes of SARS-CoV-2 infection in term of disease severity and related death are influenced by multiple comorbidities such as hypertension,[10] dyslipidemia,[11] diabetes,[12] obesity,[13] chronic kidney diseases,[14] respiratory diseases,[15] and cardiovascular diseases.[16] Demographics such as age and gender are also known to be associated with COVID-19 severity.[10,17,18] Additional studies are needed indeed to better identify risk factors responsible for severe and critical illness or even death related to COVID-19 in different races and populations. Understanding these factors could help in the early identification and management of patients with high risk, especially in developing countries with poor medical care systems.

Lebanon, with a population density of around 6 million, is considered as one of the smallest countries in Western Asia. The COVID-19 pandemic has caused devastating socioeconomic damages in Lebanon, given the critical economic and political situation that the country is passing through since the end of 2019. Lebanon had reported over 546,000 confirmed cases and 7867 deaths as of July 2021 (Lebanon: WHO Coronavirus Disease [COVID-19] Dashboard With Vaccination Data | WHO Coronavirus [COVID-19] Dashboard With Vaccination Data). To date, no data have been published concerning the factors associated with the severity of COVID-19 in Lebanon. In this study, we aimed at investigating the association between sociodemographic variables, health status and the clinical outcomes of COVID-19, and illness severity in a sample of Lebanese adults.

2 | METHODS

2.1 | Patient recruitment and data collection

This cross-sectional study included 1052 patients (563 male and 489 female, with the median age of 42.83 ± 17.88 years) who were tested positive for SARS-CoV-2 at Notre Dame Des Secours (NDS) Hospital or affiliated outpatient clinics between January and March 2021. Testing was performed on nasopharyngeal specimens using real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR). Samples were collected by registered nurses with special training in the proper collection and handling of the specimen. The study was approved by the institutional review board of NDS hospital. Oral consent had been sought from each participant at the beginning of the telephone surveys.

Basic demographic data (including age and gender), medical history (including body mass index (BMI), tobacco use, alcohol consumption and pre-existing comorbidities), clinical data, and selfreported symptoms related to COVID-19 were collected for all patients identified to have a positive SARS-CoV-2 test. These data were taken either from health records for inpatients or by conducting telephone surveys for outpatients.

2.2 | Patient classification

Clinical classification of COVID-19 severity was carried out according to the WHO interim guidance originally published under the title

"Clinical management of COVID-19: interim guidance, May 27, 2020."[14] Patients tested positive for SARS-CoV-2 were classified into four categories: (1) Asymptomatic are people without any reported clinical symptom; (2) Patients with mild disease are symptomatic meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia; (3) Patients with moderate disease have clinical signs of pneumonia but no signs of severe pneumonia, including $SpO_2 \geq 90\%$; (4) patients with severe and critical disease include patients with severe pneumonia, including $SpO_2 < 90\%$, acute respiratory distress syndrome (ARDS), Sepsis and septic choc.

2.3 | Statistical analysis

The Statistical Package for the Social Sciences (SPSS) software v.23 was used for all statistical analyses. The means and standard deviations (SD) were used for normally distributed data, whereas the median and interquartile ranges were used for non-normally distributed variables. Two-sided statistical tests were conducted to check the variables associated with the severity of the COVID-19 infection. The Chi-square test was used to compare between categorical variables, whereas the ANOVA test was used to compare between three and more means. A multinomial regression was conducted, taking the classification of COVID-19 infection as the dependent variable. Several backward logistic regressions were also done, taking the categories of the COVID-19 infection as a dependent variable two by two. Independent variables entered in the model were those that showed a $p < 0.2$ in the bivariate analysis. $p < 0.05$ was deemed significant.

3 | RESULTS

A total of 1052 patients were included in this paper. The mean age was 42.83 ± 17.88 years, with 53.5% males. The majority of the patients were classified as having mild COVID-19 infection (76.4%). The sociodemographic characteristics of the participants are summarized in Table 1. Out of 1052 patients, 83 (7.89%), 825 (78.42%), 65 (6.18%), and 79 (7.51%) were identified respectively as asymptomatic, having mild, moderate, and severe/critical illness. 108 (9.7%) patients required hospitalization, 12 (1.1%) patients were admitted to the intensive care unit (ICU), 8 (0.8%) required intubation and 8 (0.8%) patients died. Nearly all intubated patients died.

3.1 | Bivariate analysis

A higher percentage of females had mild COVID-19 infection. A higher percentage of patients who had anemia and immuno-suppression had moderate COVID-19 infection. A higher percentage of patients who had hypertension, cardiovascular problems,

TABLE 1 Sociodemographic and other characteristics of the patients ($N = 1052$).

Variable	N (%)
Gender	
Male	563 (53.5%)
Female	489 (46.5%)
Smoking	
No	615 (58.5%)
Yes	437 (41.5%)
Patients' classification of COVID-19 infection	
Asymptomatic	83 (7.9%)
Mild	825 (78.4%)
Moderate	65 (6.2%)
Severe/critical	79 (7.5%)
Other characteristics related to the severity of COVID-19	
Patients requiring conventional oxygen therapy	116 (11.0%)
Patients requiring hospitalization	108 (9.7%)
Patients admitted to intensive care unit (ICU)	12 (1.1%)
Patients requiring Intubation	8 (0.8%)
Death	8 (0.8%)
Age (in years) (mean ± SD)	42.83 ± 17.88
Body mass index (kg/m²)	
Median	25.53
Interquartile ranges	
25th	22.76
50th	25.53
75th	28.73

Abbreviation: SD, standard deviation.

dyslipidemia, diabetes, cancer, and kidney diseases had severe/critical COVID-19 infection. Higher means age and BMI were also found in those who had severe/critical COVID-19 infection (Table 2).

3.2 | Multivariable analysis

A multinomial regression was conducted, taking the patients' classification of COVID-19 as the dependent variable and the asymptomatic group as the reference one. When comparing those with mild infection versus asymptomatic, the results showed that older age (aOR = 0.94; 95% CI: 0.92–0.96), higher BMI (aOR = 0.88; 95% CI: 0.82–0.95) and having respiratory diseases (aOR = 0.06; 95% CI: 0.01–0.50) had lower odds of having mild disease (Table 3, Model 1).

TABLE 2 Bivariate analysis of factors associated with the patients' classification of COVID-19 infection.

	Classification of COVID-19 infection				
Variable	Asympto-matic (N = 83)	Mild (N = 825)	Moderate (N = 65)	Severe/critical (N = 79)	p
Gender					**0.01**
Male	54 (65.1%)	420 (50.9%)	38 (58.5%)	51 (64.6%)	
Female	29 (34.9%)	405 (49.1%)	27 (41.5%)	28 (35.4%)	
Smoking					0.06
No	44 (53.0%)	473 (57.3%)	42 (64.6%)	56 (70.9%)	
Yes	39 (47.0%)	352 (42.7%)	23 (35.4%)	23 (29.1%)	
Chronic inflammatory diseases					0.14
No	83 (100.0%)	818 (99.2%)	63 (96.9%)	77 (97.5%)	
Yes	0 (0%)	7 (0.8%)	2 (3.1%)	2 (2.5%)	
Hypertension					**<0.001**
No	74 (89.2%)	726 (88.0%)	45 (69.2%)	38 (48.1%)	
Yes	9 (10.8%)	99 (12.0%)	20 (30.8%)	41 (51.9%)	
Cardiovascular diseases					**<0.001**
No	81 (97.6%)	793 (96.1%)	57 (87.7%)	60 (75.9%)	
Yes	2 (2.4%)	32 (3.9%)	8 (12.3%)	19 (24.1%)	
Respiratory diseases					0.17
No	81 (97.6%)	763 (92.5%)	59 (90.8%)	70 (88.6%)	
Yes	2 (2.4%)	62 (7.5%)	6 (9.2%)	9 (11.4%)	
Dyslipidemia					**<0.001**
No	74 (89.2%)	743 (90.1%)	46 (70.8%)	52 (65.8%)	
Yes	9 (10.8%)	82 (9.9%)	19 (29.2%)	27 (34.2%)	
Diabetes					**<0.001**
No	75 (90.4%)	780 (94.5%)	53 (81.5%)	55 (69.6%)	
Yes	8 (9.6%)	45 (5.5%)	12 (18.5%)	24 (30.4%)	
Anemia					0.005
No	83 (100.0%)	816 (98.9%)	61 (93.8%)	78 (98.7%)	
Yes	0 (0%)	9 (1.1%)	4 (6.2%)	1 (1.3%)	
Cancer					**<0.001**
No	81 (97.6%)	822 (99.6%)	61 (93.8%)	74 (93.7%)	
Yes	2 (2.4%)	3 (0.4%)	4 (6.2%)	5 (6.3%)	
Immunosuppression					**<0.001**
No	81 (97.6%)	825 (100.0%)	63 (96.9%)	78 (98.7%)	
Yes	2 (2.4%)	0 (0%)	2 (3.1%)	1 (1.3%)	
Thyroid problems					0.81
No	80 (96.4%)	802 (97.2%)	62 (95.4%)	76 (96.2%)	
Yes	3 (3.6%)	23 (2.8%)	3 (4.6%)	3 (3.8%)	

TABLE 2 (Continued)

Variable	Classification of COVID-19 infection				
	Asympto-matic (N = 83)	Mild (N = 825)	Moderate (N = 65)	Severe/critical (N = 79)	p
Rheumatoid diseases					0.38
No	82 (98.8%)	816 (98.9%)	63 (96.9%)	79 (100.0%)	
Yes	1 (1.2%)	9 (1.1%)	2 (3.1%)	0 (0%)	
Chronic kidney diseases					**<0.001**
No	83 (100.0%)	825 (100.0%)	61 (93.8%)	69 (87.3%)	
Yes	0 (0%)	0 (0%)	4 (6.2%)	10 (12.7%)	
Neurological diseases					0.07
No	83 (100.0%)	805 (97.6%)	64 (98.5%)	74 (93.7%)	
Yes	0 (0%)	20 (2.4%)	1 (1.5%)	5 (6.3%)	
Age	39.15 ± 19.51	40.33 ± 16.13	55.13 ± 18.03	63.43 ± 15.05	**<0.001**
Body mass index	25.28 ± 4.40	25.68 ± 5.16	27.21 ± 4.62	28.43 ± 4.42	**<0.001**

TABLE 3 Multinomial regression taking the patients' classification of COVID-19 as the dependent variable.

	p	aOR	95% CI
Model 1: Mild versus asymptomatic[a]			
Age	**<0.001**	0.94	0.92–0.96
Body mass index	**0.001**	0.88	0.82–0.95
Respiratory diseases (yes vs. no[a])	**0.01**	0.06	0.01–0.50
Model 2: Moderate versus asymptomatic[a]			
Age	**<0.001**	0.94	0.92–0.96
Body mass index	**0.004**	0.93	0.88–0.98
Gender (females vs. males[a])	0.07	1.68	0.96–2.92
Respiratory diseases (yes vs. no[a])	**0.04**	0.39	0.16–0.93
Model 3: Severe/critical versus asymptomatic[a]			
Age	0.11	0.98	0.96–1.01
Body mass index	0.27	0.96	0.90–1.03
Respiratory diseases (yes vs. no[a])	0.21	0.60	0.27–1.33

Note: Numbers in bold indicate significant *p*-values; Pseudo R^2 = 23.8%; variables entered in the model: smoking, hypertension, cardiovascular problems, respiratory diseases, dyslipidemia, diabetes, immunosuppression, cancer, gender, age, body mass index.
Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.
[a]Reference group.

When comparing patients with moderate symptoms to those asymptomatic, the results showed that older age (aOR = 0.94; 95% CI: 0.92–0.96), higher BMI (aOR = 0.93; 95% CI: 0.88–0.98) and having respiratory diseases (aOR = 0.39; 95% CI: 0.16–0.93) were significantly associated with lower odds of having moderate symptoms (Table 3, Model 2). We should note that respiratory

diseases include asthma (17 patients), chronic obstructive pulmonary disease (COPD) (four patients), and respiratory allergies (61 patients).

Finally, none of the variables was significantly associated with having severe symptoms (Table 3, Model 3).

When comparing patients with moderate symptoms versus mild, the results showed that older age (aOR = 1.05; 95% CI: 1.03–1.06) and having dyslipidemia (aOR = 1.89; 95% CI: 1.01–3.49) were significantly associated with higher odds of having moderate symptoms (Table 4, Model 1).

When comparing patients with severe symptoms versus mild, the results showed that older age (aOR = 1.08; 95% CI: 1.06–1.10), higher BMI (aOR = 1.09; 95% CI: 1.04–1.15) and having respiratory disease (aOR = 2.57; 95% CI: 1.03–6.36) were significantly associated with higher odds of having severe symptoms, whereas female gender (aOR = 0.56; 95% CI: 0.32–0.98) was significantly associated with lower odds of having severe symptoms compared to males (Table 4, model 2).

Finally, when comparing patients with severe symptoms versus moderate, the results showed that older age (aOR = 1.03; 95% CI: 1.01–1.05) was significantly associated with higher odds of having severe symptoms (Table 4, Model 3).

3.3 | Symptoms experienced by the patients after COVID-19 infection

The most common symptoms experienced by the patients after COVID-19 infection were respiratory symptoms including cough, sore throat, nasal congestion, runny nose and pneumonia (59.7%), myalgia (57.0%), loss of smell and/or taste (50.2%), headache (49.3%), and fever (37.2%).

The full description of all symptoms are summarized in Table 5.

Those with mild disease experienced myalgia the most (68.8%), followed by respiratory disease (60%), headache (59.2%), loss of smell

TABLE 4 Backward logistic regression taking the patients' classification of COVID-19 as the dependent variable.

	p	aOR	95% CI
Model 1: Moderate versus mild[a]			
Age	**<0.001**	1.05	1.03–1.06
Body mass index	0.09	1.05	0.99–1.10
Dyslipidemia (yes vs. no[a])	**0.05**	1.89	1.01–3.49
Nagelkerke R^2 = 14.1%			
Model 2: Severe/critical versus mild[a]			
Age	**<0.001**	1.08	1.06–1.10
Body mass index	**0.001**	1.09	1.04–1.15
Gender (females vs. males[a])	**0.04**	0.56	0.32–0.98
Respiratory diseases (yes vs. no[a])	**0.04**	2.57	1.03–6.36
Dyslipidemia (yes vs. no[a])	0.06	1.77	0.98–3.21
Diabetes (yes vs. no[a])	0.06	1.90	0.97–3.69
Nagelkerke R^2 = 34.8%			
Model 3: Severe/critical versus moderate[a]			
Age	**0.007**	1.03	1.01–1.05
Nagelkerke R^2 = 7%			

Note: Numbers in bold indicate significant *p*-values; variables entered in the model: smoking, hypertension, cardiovascular problems, respiratory diseases, dyslipidemia, diabetes, anemia immunosuppression, cancer, gender, age, body mass index.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

[a]Reference group.

TABLE 5 Description of the symptoms experienced by the patients after COVID-19 infection (N = 1052).

Variable	N (%)
Respiratory symptoms	628 (59.7%)
Dyspnea	168 (16.0%)
Fever	391 (37.2%)
Gastrointestinal symptoms	293 (27.9%)
Loss of smell and/or taste	528 (50.2%)
Confusion	33 (3.1%)
Dizziness	100 (9.5%)
Sleeping disorders	140 (13.3%)
Headache	519 (49.3%)
Loss of consciousness	4 (0.4%)
Neurological manifestations	11 (1.0%)
Ear problems	12 (1.1%)
Ocular problems	31 (2.9%)
Thrombotic complications	5 (0.5%)
Arrhythmia	10 (1.0%)
Myalgia	600 (57.0%)
Skin irritation	12 (1.1%)

and taste (52.3%), fever (38.3%) and gastrointestinal symptoms (GI) including diarrhea, nausea and vomiting (29.8%).

Those with moderate disease experienced respiratory disease the most (83.1%), followed by loss of smell and taste (58.5%), dyspnea (53.8%), fever (49.2%) and GI symptoms (44.6%) and needed conventional oxygen therapy in 44.6% of the times.

Those with severe/critical disease experienced respiratory disease the most (100%) and dyspnea (100%), followed by loss of smell and taste (70.9%), fever (54.4%) and GI symptoms (22.8%); all patients needed conventional oxygen therapy at hospital admission.

4 | DISCUSSION

In the present study, a total of 1052 patients were recruited from a teaching affiliated hospital in Byblos, Lebanon. Among them, 395 patients (37.5%) had at least one comorbidity. Patients were classified according to their COVID-19 severity level using the WHO standards based on clinical outcomes;[19] 7.9% patients were asymptomatic, 78.4% had mild disease, 6.2% had moderate disease and 7.5% had severe or critical illness.

We have focused on identifying the factors that are related to COVID-19 severity, by performing multi and bivariate regression analysis. Age, gender, respiratory and metabolic comorbidities were recognized as risk factors, consistent with most previous studies.[10,17,18]

Our results show that the presence of respiratory diseases including asthma, COPD and respiratory allergies increases the odds of having more severe COVID-19 illness compared to asymptomatic patients. In contrast to COPD that is considered evidently by numerous studies as a high risk factor requiring an aggressive treatment for COVID-19,[20] studies on the relation between asthma, respiratory allergies, and COVID-19 are controversial. At the beginning of the pandemic, US Centers for Disease Control and Prevention (CDC) considered asthma and allergic airway diseases as risk factors for COVID-19 because they can worsen with upper respiratory viral infections (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/asthma.html). However, several recent studies did not find evidence of asthmatic patients being at high risk for COVID-19 infection.[21,22] This may be explained by the decrease in the gene expression of angiotensin-converting enzyme 2 (ACE2), the key cell surface receptor for the virus, in the nose and bronchial cells of allergic airway diseases that may reduce the risk and severity of COVID-19.[23] Further studies should be done to better elucidate the contribution of respiratory diseases in COVID-19 outcomes, taking into consideration the phenotype of the respiratory diseases and the presence of other potential concomitant risk factors (demographic, health, and genetic factors).

Our data reveals that dyslipidemia increases the odds of having moderate disease compared to asymptomatic patients and those with mild disease. This result is in accordance with several previous studies suggesting that dyslipidemia could play a role in the severity of COVID-19, especially in male patients with older age and hypertension.[11,24] Metabolic disorders are actually known to compromise the adaptive immune response lowering the tolerability to viral infections.[25,26]

In our study, diabetes was significantly associated with higher odds of having severe disease compared to mild, in agreement with a meta-analysis showing that diabetes is associated with a twofold increase in severity of COVID-19, as compared to nondiabetics.[27] Similarly, numerous evidence suggest that diabetes is associated with physiological and structural abnormalities in lung tissues that could exacerbate the lung injury during infections.[28,29] Rahman et al. have shown that hyperglycemia and COVID-19 have a synergistic inflammatory effect that could be due to a common differential gene expression pattern between COVID-19 and diabetes, suggesting the involvement of biological processes and pathways commonly dysregulated.[30]

In addition to diabetes, we have found that higher BMI was also significantly associated with higher odds of having more severe forms of COVID-19. These results suggest an association of metabolic comorbidities with adverse outcomes of COVID-19. Obesity is actually a major health problem that could trigger a series of other disorders, including hypertension, cardiovascular disease, diabetes mellitus, and chronic kidney disease.[31] A meta-analysis done by Popkin et al. reveals that the odds of hospitalization and mortality is significantly higher in obese people infected with COVID-19 when compared to nonobese patients.[32] This increased risk of severe illness is related to higher rates of metabolic and cardiovascular complications.[33] Furthermore, obesity is characterized by a chronic systemic inflammation that could contribute to the pathogenesis of COVID-19.[34,35]

According to bivariate analysis (Table 2), a higher percentage of patients who had hypertension and cardiovascular diseases had severe/critical COVID-19 infection. However, multivariate analysis showed that these factors are not significantly associated with COVID-19 severity. This result is in disagreement with previous reports suggesting that hypertension and cardiovascular diseases were significantly associated with ICU admission in COVID-19 patients.[36] Hence the need to study hypertension and cardiovascular burden among a larger cohort of Lebanese COVID-19 patients.

Concerning demographic factors, our finding are in accordance with previous studies showing that older age and male gender are significantly associated with higher odds of having more severe forms of COVID-19. In fact, a global COVID-19 meta-analysis done by Peckham et al. has identified the male sex as a risk factor for death and ICU admission, highlighting the influence of the gender on COVID-19 outcomes and its implication in clinical management.[37] While males and females have comparable susceptibility to SARS-CoV-2, males are more prone to having higher levels of severity and mortality, which is similar to the feature of SARS 2003 and

MERS.[38,39] The mechanism underlying these gender differences in term of COVID-19 outcomes is not yet clearly understood. It can be partly explained by the higher expression of proinflammatory cytokines and chemokines in males.[40] Fagone et al. have suggested that differences in female and male responses to SARS-CoV-2 infection could be related to the different roles of androgen receptor (AR) and estrogen receptor 1 (ESR1) in innate and adaptive immune regulations. While AR is involved in the recruitment of neutrophils and macrophages by increasing the expression of chemotactic factors such as the neutrophil chemotactic factor CXCL1 and the dendritic cell chemotactic factor CCL20 in the human epithelial lung cells, ER is involved in the enhancement of interferon production and antiviral response.[41] In addition, it has been shown that IL-6 receptor, the main actor in the cytokine storm, is expressed at higher levels in lung epithelial cells in males compared to females. These findings suggest that males are more disposed to cytokine storm that can lead to the worsening of COVID-19 outcomes[40,42,43] and that estrogen receptor modulators could be considered as potential drugs to treat COVID-19.[41] Furthermore, a study done by Song et al. show that the cell type-specific expression of the ACE2 receptor in type II alveolar epithelial cells is higher in males than in females,[44] which could be involved in the increased vulnerability of the male respiratory system to SARS CoV-2 infection.

In agreement with our results, a general population cohort study of 470,034 participants conducted in UK has shown that overall, participants aged ≥75 years were at 13-fold mortality risk compared with those <65 years.[45] This study reveals that the presence of additional comorbidities in older people explained 39.3% of the age-related excess risk. On the other hand, participants aged ≥75 without additional risk factors were at fourfold risk compared with all participants aged <65 years.[45] Thus, older age can be considered as an independent risk factor for COVID-19 severity and mortality. This can be explained by two biological phenomena occurring during aging: the gradual decline in innate and adaptive immune functions called immunosenescence and the chronic increase in systemic inflammation called inflamma-ging.[46,47] These two malfunctions contribute to the onset of an overactive, yet ineffective alert signaling and pathogen clearance.

Respiratory illness is the most common reported clinical manifestation of COVID-19 among our patients. Other frequent extra-pulmonary symptoms have also been noted such as myalgia, loss of smell and/or taste, headache, and gastrointestinal symptoms. The death rate reported in this study is lower than the national one (1.4%) (www.moph.gov.lb), this could be explained by the socio-economic inequalities in health and health care access between the different Lebanese areas and by the low number of severe cases in our sample. This wide spectrum of symptoms ranging in severity from mild to severe illness is consistent with previous reports.[48,49] COVID-19 caused by SARS-CoV-2, which was initially considered as a respiratory disease, is now recognized as a complex disease affecting many body systems including the gastrointestinal, cardiovascular, neurological and renal systems.[48] Although the pathophysiology of these multisystem manifestations is not yet clearly

characterized, they could be partly caused by the direct viral tissue damage, mediated by the expression of the ACE2 receptor in multiple extra-pulmonary tissues[48] and the activation of PI3K/Akt/mTOR pathway, a key cell signaling pathway regulating various important cell functions.[50] Other plausible mechanisms include endothelial damage, thromboinflammation, and dysregulation of immune responses.[4,48,51,52,53]

5 | LIMITATIONS

The major limitation of our study is the absence of laboratory and radiologic data, which may also be important prognostic factors. Unfortunately, no other national data are available to compare our results with. A selection bias is also possible since the data was collected from one hospital only, hindering the generalization of the findings. Accurate information could not be disposed for some treatments, especially for the outpatients that were contacted by phone. Contraceptive pills intake was not reported by the authors. This information could give insights related to the difference in COVID-19 vulnerability between males and females, which could be addressed in future studies. Further studies should be conducted on a bigger cohort of COVID-19 patients in the Lebanese population to investigate the implication of other potential risk factors.

6 | CONCLUSION

In conclusion, we identified six factors associated with COVID-19 severity in a sample of the Lebanese population: older age, male gender, chronic respiratory diseases, dyslipidemia, diabetes, and obesity. These factors may contribute to a better understanding of the COVID-19 pathogenesis and provide clinical reference for early prognosis and management of patients.

AUTHOR CONTRIBUTIONS

Elissar El-Hayek: Conceptualization; methodology; project administration; supervision; writing—original draft. **Georges-Junior Kahwagi**: Conceptualization; investigation; resources; writing—original draft. **Nour Issy**: Conceptualization; investigation; writing—original draft. **Christina Tawil**: Conceptualization; investigation; writing—original draft. **Nabil Younis**: Conceptualization; investigation; writing—original draft. **Rony Abou-Khalil**: Conceptualization; supervision; writing—review and editing. **Madonna Matar**: Conceptualization; resources; writing—review and editing. **Souheil Hallit**: Conceptualization; formal analysis; methodology; supervision; writing—original draft.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

TRANSPARENCY STATEMENT

Elissar El-Hayek affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ORCID

Elissar El-Hayek http://orcid.org/0000-0002-5336-3636
Madonna Matar http://orcid.org/0000-0003-4870-8879

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