Cross-sectional Study

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Predictors of all-cause mortality in hospitalized COVID-19 patients taking corticosteroids: a multicenter retrospective cross-sectional study

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Introduction: Despite the recommendations to avoid using corticosteroids systematically for hospitalized coronavirus disease of 2019 (COVID-19) patients, healthcare professionals used personalized treatments, including corticosteroids, as adjuncts to treat their patients due to their limited access to treatment options. This study aims to evaluate the use of corticosteroids among hospitalized COVID-19 patients with all-cause mortality as the primary outcome and to assess the predictors of all-cause mortality associated with the characteristics of the patients and the corticosteroid regimens adopted.

Methods: A multicenter retrospective study was performed over three months targeting 422 COVID-19 patients from six hospitals in Lebanon. Data were collected from patients' medical charts retrospectively and covered a period of one year (September 2020–August 2021).

Results: The study sample included 422 patients, predominantly males, with 59% of cases classified as severe or critical cases. Dexamethasone and methylprednisolone were the most used corticosteroids. Around 22% of the patients died during hospitalization. After adjusting for covariates, performing a polymerase chain reaction before admission increased the mortality rate by 424% compared to doing it at hospital admission (aHR 4.24, 95% CI 1.35–13.3), with 18.11 times higher mortality rate among critical cases (aHR 18.11, 95% CI 9.63–31.05). Exposure to side effects from corticosteroids increased the mortality rate by 514% compared to others (aHR 5.14, 95% CI 1.28–8.58). In particular, the mortality rate among patients having hyperglycemia dropped by 73% compared to others (aHR 0.27, 95% CI 0.06–0.98).

Conclusion: Corticosteroids are frequently used in treating hospitalized COVID-19 patients. The all-cause mortality rate was higher among older and critical cases and lower among smokers and those treated for more than 7 days. Research exploring the safety and efficacy of corticosteroids is required to allow better in-hospital management of COVID-19 cases.

Keywords: all-cause mortality, corticosteroids, COVID-19, hospitalized, predictors

Introduction

With the emergence of the coronavirus disease of 2019 (COVID-19) pandemic, the number of cases increased globally despite the measures taken to contain the virus[1]. The impact of COVID-19 on all-cause mortality varies by country and region, depending on factors such as population demographics, healthcare capacity, and public health response. Many health system policies, and environmental sustainability issues, were introduced during lockdown across countries, with increased municipal and medical waste[2]. The efficiency of countries' responses to the crisis varied, with no apparent relationship between developing and developed countries, or in different health systems[3]. The pandemic has also indirectly affected mortality, such as disruptions to healthcare services, mental health impacts, and an increased risk of other illnesses due to reduced access to healthcare or social distancing measures[4,5]. In general, areas with high rates of COVID-19 transmission and limited healthcare resources have experienced higher rates of all-cause mortality during the pandemic[6]. The healthcare system faced many limitations, such as drug and health professional shortages, a lack of hospital beds, and a lack of uniform case management guidelines[7]. Accordingly, the associated all-cause mortality increased, and the health infrastructure was negatively affected[8]. Mortality rates

HIGHLIGHTS

- Performing a polymerase chain reaction before admission increased the mortality rate by 424% compared to doing it at hospital admission.
- Around 18 times higher mortality rate among critical cases.
- Exposure to side effects from corticosteroids increased the mortality rate by 514% compared to others.
- The mortality rate among patients having hyperglycemia dropped by 73% compared to others.

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increased with the severity of the cases (50% of critical cases and 15% of severe cases)[9]. These rates are higher in low-income and middle-income countries, possibly due to the unpreparedness of the health system and scarcity of resources[10]. Moreover, in a limited-capacity country such as Lebanon, the socioeconomic and environmental drivers of the pandemic need to be mitigated[11], due to its concurrence with an economic crisis and a blast.

Guidelines for managing COVID-19 patients were published and included clinical and practical recommendations[12,13]. Different medications are used and vary between countries and patients[14]. Among others, corticosteroids are recommended as adjuncts in treating COVID-19 patients namely severe cases and those requiring hospitalization[15]. A meta-analysis published in 2020 highlighted the beneficial role of corticosteroids in the recovery of patients, including those on mechanical ventilation[16]. Nevertheless, recent research recommended avoiding the administration of corticosteroids in nonsevere patients due to their association with all-cause mortality and increased length of hospital stay[17]. Responses to corticosteroid treatment can vary with the dosage, administration time, and treatment duration[18]. Patients receiving a course of corticosteroids for more than 7 days and those taking it in the 48 h following the development of symptoms had greater survival rates than those receiving a shorter course[15,19].

The Lebanese Society of Infectious Diseases and Clinical Microbiology recommended avoiding using corticosteroids systematically due to the lack of scientific evidence[20]. Nonetheless, during the pandemic, healthcare professionals in Lebanon faced several challenges limiting their access to medicines and to the available treatment options in addition to many dilemmas such as prioritization of patients and hospitalization of critical cases only[4,21]. As a result, personalized treatments, including corticosteroids, were provided despite the lack of clinical efficacy support[22]. Risk prediction models for mortality were previously explored[23], but these risks were not assessed in patients taking corticosteroids. Previous research assessed mortality associated with hospitalized COVID-19 patients, but only a few evaluated all-cause mortality solely among patients taking corticosteroids[19,24]. Meta-analyses confirmed a beneficial effect of corticosteroids on short-term mortality and the need for mechanical ventilation[16,25]. Nevertheless, knowledge gaps exist in terms of assessing vulnerable populations and their characteristics, which can lead to differences in efficiency[3]. This study aims to evaluate the use of corticosteroids among hospitalized COVID-19 patients with all-cause mortality as the primary outcome and to assess the predictors of all-cause mortality associated with the characteristics of the patients and the corticosteroid regimens adopted.

Methods

Study design

A multicenter retrospective study was performed over a period of three months, collecting data retrospectively from one year (September 2020–August 2021) of hospitalized COVID-19 patients from six hospitals in Lebanon. This work has been reported in line with the strengthening the reporting of cohort, cross-sectional and case-control studies in surgery (STROCSS) criteria[26].

Study sample and sample size calculation

Adults patients admitted to the hospital after a confirmed COVID-19 infection, irrespective of the stage and severity of the disease, were included in the study. Only those receiving corticosteroids as a treatment were in the study sample, with no preferences based on race or ethnicity. Ten percent of total confirmed cases were recruited every month from each of the six hospitals as follows: hospital 1 (30.8%), hospital 2 (25.4%), hospital 3 (22.7%), hospital 4 (10.9%), hospital 5 (7.8%), and hospital 6 (2.4%). All the included hospitals were public university hospitals, distributed in six governorates of Lebanon. They all followed the same guidelines the Ministry of Public Health provided for managing COVID-19 patients and were required to report mortality and survival daily.

EpiInfo software calculated the required sample size with a power of 80%, a 5% margin of error, and a 95% CI. The expected proportion of the population was set at 0.5, given that the prescription of corticosteroids among hospitalized COVID-19 patients has yet to be studied in Lebanon. This yielded a minimum sample size of 384 patients. To allow better control for confounding, 422 patients were targeted (+ 10% of the minimum sample). Moreover, to reduce selection bias, random sampling schemes were adopted where every unit in the population has a chance to be selected.

Data collection

The data were collected using a uniform data collection form. Three clinical pharmacists were responsible for data collection extracted retrospectively from patients' medical records. The study sample was randomly selected after fulfilling the criteria for selection. Data completion took an average of 25 min per patient and was filled in the different hospitals.

General characteristics of the patients

The data collection form included questions about the general characteristics of the participants (sex, age (18–40, 41–65, > 65), the governorate of residence, height, weight, and smoking status). Furthermore, the admission floor (internal medicine or ICU) was also registered in addition to the length of stay in the hospital (from admission to discharge/death date).

COVID-19 related variables

This section collected information about the characteristics of the COVID-19 infection. The reported symptoms were collected, such as fever, dyspnea, fatigue, insomnia, cough, and headaches (Fig. 1). Information about whether or not the patient did a real-time polymerase chain reaction (PCR) test and whether it was done before or during the admission process was also registered. Patients were classified as critical (septic shock, sepsis, mechanical ventilation, or vasopressor therapy), severe (oxygen saturation $\leq 90\%$, respiratory rate > 30 breaths/min or the existence of signs of severe respiratory distress), and nonsevere cases (absence of any signs of severe or critical COVID-19)[27].

Medical history of the patients

The number of comorbidities (none, one, two, or more than two) and their types (diabetes, hypertension, coronary artery disease, dyslipidemia, heart failure, chronic kidney disease, chronic

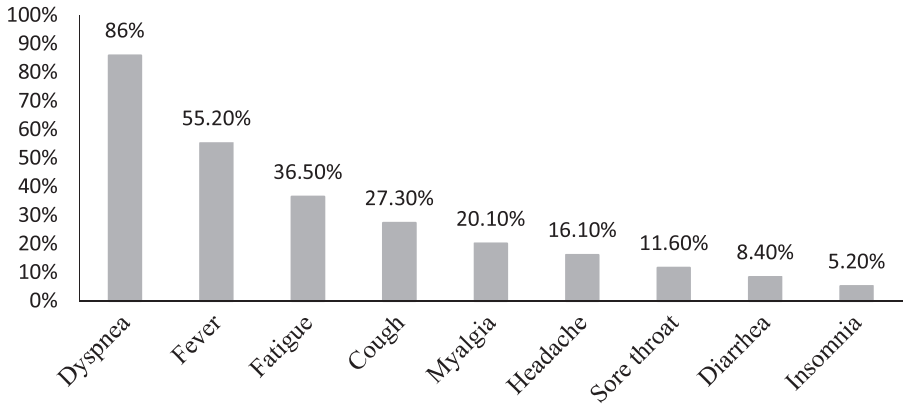

Figure 1. Reported symptoms at admission.

obstructive pulmonary disease, asthma, and cancer) were collected in this part (multiple answers were allowed).

Corticosteroids regimen characteristics

The name and the number of corticosteroid drugs prescribed to the patients during their hospitalization were recorded in this part. The dosage of each type of corticosteroid was classified as low, moderate, or high based on the recommendations of the American Society of Health-System Pharmacists in assessing evidence for COVID-related treatments[28]. The duration of treatment was classified as 7 days or less or more than 7 days based on a meta-analysis performed in 2021[15]. Side effects such as hyperglycemia, superinfection, gastrointestinal bleeding, and muscle weakness were also collected in this part.

Ethical considerations

The research protocol and data collection tool were reviewed and approved by the hospital's institutional review board on 13 October 2021 (reference: CRU329) and from the direction and medical comity of the other five hospitals where the study was conducted. The data were completely anonymous and non-identifiable; storage of the data follow-up university general data protection regulation guidelines. Findings were considered for research purposes only, and no financial incentives were provided.

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS Inc.) Version 27. Based on the values of the skewness (-0.211) and kurtosis (0.057), the data were normally distributed and converged to their expected values[29]. The age of the patients, height, weight, BMI, length of hospital stay, and duration of treatment with corticosteroids are presented using means and SD. In contrast, categorical variables are presented using frequencies and percentages. Bivariate analyses were conducted by taking all-cause mortality as the independent variable and the general characteristics of the patients, the medical history, and the corticosteroid regimen characteristics as dependent variables. χ^2/Fisher exact tests were used to compare percentages between associate categorical variables. Survival was calculated using the Kaplan–Meier method and the log-rank test, using as exposures the general and clinical characteristics of the patients. Univariate and multivariate Cox proportional hazards models were run, producing Hazard Ratios (HR) with a 95% CI. Independent variables were only selected if they had P values <0.20 in the bivariate analysis. A P-value <0.05 was considered statistically significant.

Results

General characteristics of the patients

Table 1 represents the general characteristics of the study participants. The sample included more males (59.0%) than females (41.0%). The mean age of the patients was 63.6 (15.6) distributed as follows: 10.0% of them were between 18 and 40 years of age, 40.8% were between 41 and 65 years, and 49.1% were older than 65 years. Participants were distributed between the six governorates, with Mount Lebanon (48.3%) and Beirut (38.2%) accounting for the highest percentages. The mean BMI was 28.0 (4.7). Most of the patients (70.9%) were admitted to the internal medicine floor, and the rest (29.1%) were in the ICU with a mean length of hospital stay of 7.7 (3.8) days. All patients tested positive for COVID-19, of which 92.4% did a PCR test during hospital admission (75.2%) or before the admission date (24.8%). Forty-one percent of cases were classified as nonsevere, 32.7% as severe, and 26.3% as critical cases.

The reported symptoms at admission are illustrated in Figure 1. Most patients reported having dyspnea (86.0%) and a fever (55.2%). Fatigue and cough were reported by 36.5 and 27.3% of patients, respectively. Furthermore, around 20% reported myalgia as one of their symptoms, while headache was reported by only 16.1%. Nevertheless, sore throat (11.6), diarrhea (8.4), and insomnia (5.2%) were less reported by the patients.

Medical history and corticosteroid regimen characteristics

Table 2 presents the patients' medical history and the characteristics of corticosteroid regimens. Regarding the number of comorbidities, 23.4% of patients had no comorbidities, 27.5% had one and two comorbidities, respectively, and 21.6% had more than two comorbidities. The most reported comorbidities were hypertension (58.4%), diabetes (30.6%), and coronary artery diseases (30.6%), while chronic obstructive pulmonary disease (4.5%), asthma

Table 1

Distribution of the general characteristics of the patients

	Total ($N=422$)
	Frequency (%)
Sex	
Male	249 (59.0)
Female	173 (41.0)
Age (years)	63.6 ± 15.6
18–40	42 (10.0)
41–65	172 (40.8)
> 65	207 (49.1)
Governorate of residence	
Beirut	161 (38.2)
Mount-Lebanon	204 (48.3)
South	36 (8.5)
North	2 (0.5)
Bekaa	13 (3.0)
Nabatiyeh	6 (1.4)
BMI (kg/m^2)	28.0 ± 4.7
Admission floor	
Internal medicine	299 (70.9)
ICU	123 (29.1)
Length of hospital stay (days)	7.7 ± 3.8
Smoking status	
Yes	55 (13.3)
PCR test done	
Yes	399 (92.4)
Before admission	99 (24.8)
During admission	300 (75.2)
Severity of cases	
Nonsevere	173 (41.0)
Severe	138 (32.7)
Critical	111 (26.3)

Results are given in terms of frequency (percentage) or Mean ± SD.
PCR, Polymerase Chain Reaction.

Table 2

Medical history and corticosteroid regimen characteristics

	Total ($N=422$)
Medical history	**Frequency (%)**
Comorbidities	
None	99 (23.4)
One	116 (27.5)
Two	116 (27.5)
More than two	91 (21.6)
Hypertension	246 (58.4)
Diabetes Mellitus	129 (30.6)
Coronary artery disease	92 (21.8)
Dyslipidemia	35 (8.3)
Heart failure	23 (5.5)
Chronic kidney disease	21 (5.0)
COPD	19 (4.5)
Asthma	18 (4.3)
Cancer	14 (3.3)
Corticosteroids regimens	Frequency (%)
Number of corticosteroids used	
One	359 (85.1)
Two	63 (14.9)
Type of corticosteroids	
Dexamethasone	275 (65.2)
Methylprednisolone	187 (44.3)
Prednisone	22 (5.2)
Hydrocortisone	3 (0.7)
Dosage	
High	149 (35.3)
Moderate	178 (42.2)
Low	95 (22.5)
Duration of treatment	5.8 ± 3.7
≤7 days	352 (83.4)
>7 days	70 (16.6)
Side effects ($N=86$)	
Yes	86 (23.7)
Hyperglycemia	67 (77.9)
Superinfection	32 (37.2)
Gastro-intestinal bleeding	2 (2.4)
Muscle weakness	1 (1.2)

Results are given in terms of frequency (percentage) or Mean ± SD.
COPD, Chronic Obstructive Pulmonary Disease.

(4.3%), and cancer (3.3%) were the least reported. Most of the patients (85.1%) were treated with only one type of corticosteroids and around 15% were treated with two types. Among the different types of corticosteroids, dexamethasone (65.2%) and methylprednisolone (44.3%) were mostly used. Regarding dosage, 35.3% were treated with a high dosage, 42.2% with a moderate dosage, and only 22.5% with a low dosage of corticosteroids. Most patients (83.4%) were treated for less than or equal to 7 days. Around 24% of patients had side effects with hyperglycemia (77.9%), and superinfection (37.2%) was mostly reported.

Association between all-cause mortality and the characteristics of patients, medical history, and corticosteroid regimens

Overall, 92 patients (21.8%) died with a mean mortality days after admission of 8.9 (7.8). The reported causes of death were heart failure (23 patients; 25%), septic shock (21 patients; 22.8%), respiratory failure (20 patients; 21.7%) and pulmonary embolism (17 patients, 18.5%), and 11 patients (12.0%) had other causes of death. The association between all-cause mortality and the characteristics of patients, medical history, and corticosteroid regimens is presented in Table 3. Among mortality cases, nonsmokers (23.4%) represented significantly more cases compared to smokers (10.9%) ($P=0.037$). Patients doing a PCR test before admission (41.4%) had significantly higher all-cause mortality in comparison to those doing it during admission to the hospital (14.3%) ($P<0.001$) and the more severe the cases, the higher the probability of all-cause mortality ($P<0.001$). Patients with no comorbidities (27.3%) or with more than two comorbidities (28.6%) had significantly higher percentages of all-cause mortality compared to those with one (16.4%) or two comorbidities (17.2%) ($P=0.050$). As regards the corticosteroid regimens, patients treated with dexamethasone or methylprednisolone had lower all-cause mortality ($P=0.001$). Furthermore, those treated with corticosteroids for more than 7 days (10.0%) had significantly lower all-cause mortality compared to those treated for 7 days or less (24.1%) ($P=0.009$). Significantly greater all-cause mortality was noted among patients encountering side effects (33.7%) ($P=0.019$), particularly those having a superinfection during their hospitalization (53.1%) ($P=0.003$). Nonetheless, patients having hyperglycemia (26.9%) as a side effect had significantly lower all-cause mortality compared to other patients (57.9%) ($P=0.012$).

Table 3

Association between all-cause mortality and the characteristics of patients, medical history, and corticosteroid regimens

	All-cause mortality ($N=92$)	
	Frequency (%)	*P*
Sex		
Male	54 (21.7)	0.946[a]
Female	38 (22.0)	
Age (years)		
18–40	6 (14.3)	
41–65	38 (22.1)	0.443[a]
>65	48 (23.2)	
Admission floor		
Internal medicine	67 (22.4)	0.638[a]
ICU	25 (20.3)	
Do you smoke?		
Yes	6 (10.9)	**0.037**[a]
No	84 (23.4)	
Did you do a PCR test?		
Yes	84 (21.1)	0.121[a]
No	8 (34.8)	
If yes, when was it done?		
Before admission	41 (41.4)	**<0.001**[a]
During admission	43 (14.3)	
The severity of cases		
Nonsevere	4 (2.3)	
Severe	21 (15.2)	**<0.001**[b]
Critical	67 (60.4)	
Comorbidities		
None	27 (27.3)	**0.050**[a]
One	19 (16.4)	
Two	20 (17.2)	
More than two	26 (28.6)	
Hypertension		
Yes	46 (26.1)	0.068[a]
No	46 (18.7)	
Diabetes Mellitus		
Yes	26 (20.2)	0.587[a]
No	66 (22.5)	
Coronary artery disease		
Yes	22 (23.9)	0.579[a]
No	70 (21.2)	
Heart failure		
Yes	6 (26.1)	0.609*
No	86 (21.6)	
Chronic kidney disease		
Yes	3 (14.3)	0.392[b]
No	89 (22.2)	
COPD		
Yes	5 (26.3)	0.626[b]
No	87 (21.6)	
Number of corticosteroids used		
One	75 (20.9)	0.280[a]
Two	17 (27.0)	
Type of corticosteroids		
Dexamethasone	46 (17.8)	**0.001**[b]
Methylprednisolone	39 (26.4)	
Prednisone	4 (33.3)	
Hydrocortisone	3 (100.0)	
Dosage		
High	29 (19.5)	0.219[a]
Moderate	46 (25.8)	
Low	17 (17.9)	
Duration of treatment		
≤7 days	85 (24.1)	**0.009**[a]
>7 days	7 (10.0)	
Side effects		
Yes	29 (33.7)	**0.019**[a]
No	59 (21.3)	
Hyperglycemia		
Yes	18 (26.9)	**0.012**[a]
No	11 (57.9)	
Superinfection		
Yes	17 (53.1)	**0.003**[a]
No	12 (22.2)	

bold values are statistically significant of *P*-values < 0.05.
Results are given in terms of frequency (percentage). *P*-value detected using.
[a]χ^2test or.
[b]Fisher exact test.
COPD, Chronic Obstructive Pulmonary Disease; PCR, Polymerase Chain Reaction.

Predictors of all-cause mortality among hospitalized COVID-19 patients

A univariate analysis of the predictors of all-cause mortality among the patients is presented in Figure 2 and Table 4. The increase of one year in age was associated with increased all-cause mortality (HR 1.02, 95% CI 1.00–1.03) with no significant variations between age groups (HR 1.12, 95% CI 0.47–2.66) and sexes (HR 1.01, 95% CI 0.67–1.53). Smokers had 60% lower risks of death than nonsmokers (HR 0.40, 95% CI 0.17–0.97). Doing a PCR test before admission increased all-cause mortality risk by 4.22 times more than those who did it during hospital admission (HR 4.22, 95% CI 2.53–7.06). Furthermore, critical cases had a higher mortality risk than severe or nonsevere cases (HR 17.42, 95% CI 9.96–30.46). A significant correlation was also noted between being treated with corticosteroids for more than 7 days and all-cause mortality with a decreased mortality by 65% than those treated for 7 days or less (HR 0.35, 95% CI 0.15–0.79). Encountering side effects from corticosteroids during hospitalization was associated with increased all-cause mortality (HR 1.88, 95% CI 1.11–3.20). Among others, hyperglycemia was associated with 73% lower risks of all-cause mortality (HR 0.27, 95% CI 0.09–0.77) while superinfection increased by 3.97 times these risks (HR 3.97, 95% CI 1.54–10.21). After adjusting for covariates, performing a PCR before admission increased the mortality rate by 424% compared to doing it at hospital admission (aHR 4.24, 95% CI 1.35–13.3), with 18.11 times higher mortality rate among critical cases (aHR 18.11, 95% CI 9.63–31.05). Exposure to side effects from corticosteroids increased the mortality rate by 514% compared to others (aHR 5.14, 95% CI 1.28–8.58). In particular, the mortality rate among patients having hyperglycemia droped by 73% compared to others (aHR 0.27, 95% CI 0.06–0.98).

Discussion

The present study aimed to describe the use of corticosteroids among hospitalized COVID-19 patients and assess the predictors of all-cause mortality associated with the characteristics of the patients and the recommended corticosteroid regimens. The

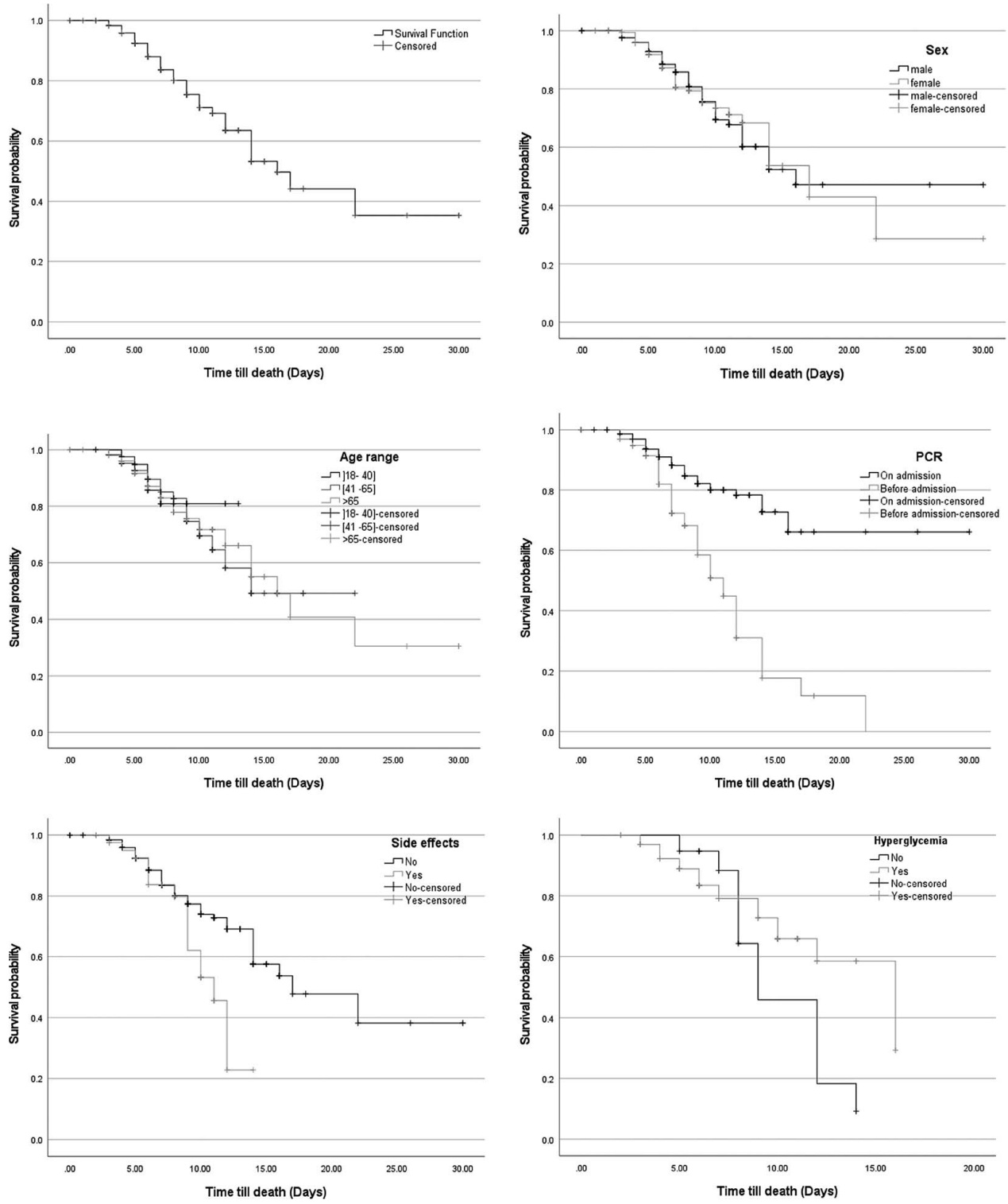

Figure 2. Kaplan–Meier curves for in-hospital mortality by demographic and some clinical data.

study sample was predominantly males. According to a review published in 2021, clinical outcomes showed that males experienced a higher fatality and severity of COVID-19 infection than females, which may explain their hospitalization[30]. Most patients in this study were older than 65 in agreement with observational studies showing that older COVID-19 patients were those more prone to hospitalization[31,32]. Mount Lebanon and Beirut accounted for the highest number of cases in coherence with reports from the Ministry of public health in Lebanon. They can possibly be associated with these governorates having most of

Table 4

Predictors of all-cause mortality among hospitalized COVID-19 patients

	Crude model		Adjusted model	
	HR [95% CI]	*P*	aHR [95% CI]	*P*
Age in years (per increase of one year)	1.02 [1.00–1.03]	**0.029**	1.02 [0.97–1.04]	0.107
BMI (kg/m^2) (per increase of one unit)	1.09 [0.95–1.26]	0.216		
Smoking status				
Nonsmokers	Reference		Reference	
Smokers	0.40 [0.17–0.97]	**0.042**	1.09 [0.38–3.12]	0.867
Doing a PCR				
No	Reference			
Yes	0.50 [0.21–1.22]	0.127		
When was the PCR done?				
On admission	Reference		Reference	
Before admission	4.22 [2.53–7.06]	**< 0.001**	4.24 [1.35–13.3]	**0.013**
The severity of cases				
Nonsevere/Severe	Reference		Reference	
Critical cases	17.42 [9.96–30.46]	**< 0.001**	18.11 [9.63–31.05]	**< 0.001**
Number of comorbidities				
None	Reference			
One	0.52 [0.27–0.99]	**0.050**		
Two	0.56 [0.29–1.07]	0.078		
More than two	1.07 [0.57–2.01]	0.842		
Hypertension				
No	Reference			
Yes	0.65 [0.41–1.03]	0.069		
Duration of treatment				
≤7 days	Reference			
>7 days	0.35 [0.15–0.79]	**0.012**		
Side effects				
No	Reference		Reference	
Yes	1.88 [1.11–3.20]	**0.020**	5.14 [1.28–8.58]	**0.021**
Hyperglycemia				
No	Reference		Reference	
Yes	0.27 [0.09–0.77]	**0.015**	0.27 [0.06–0.98]	**0.047**
Superinfection				
No	Reference			
Yes	3.97 [1.54–10.21]	**0.004**		

bold values are statistically significant of *P*-values < 0.05.

Question: Was the patient dead before discharge? The baseline answer is 'No' CI, Confidence interval; HR, Hazard Ratio.

PCR, Polymerase Chain Reaction. Omnibus test ($P < 0.001$), Nagelkerke r square (0.428), Hosmer & Lemeshow ($P = 0.459$).

the hospitals in Lebanon[33]. The most reported symptoms were dyspnea, fever, fatigue, and cough in agreement with other clinical settings[34,35]. Almost 75% of patients did a PCR test during their admission to the hospital and tested positive for COVID-19, possibly since an admission screening plan is adopted in hospitals[36].

Dexamethasone and methylprednisolone were used as adjuncts in the treatment of most patients, in agreement with findings from a systematic review assessing the effectiveness of corticosteroid use in hospitalized COVID-19 patients[37]. Most patients were treated with a moderate or high dose of corticosteroids reported to have a beneficial effect on both recovery and mortality, namely in severe and critical cases[38]. A third of the patients encountered side effects from corticosteroids during their hospitalization, particularly hyperglycemia and superinfection previously outlined in other research targeting hospitalized COVID-19 patients[39]. Moreover, a recent meta-analysis recommended considering corticosteroid therapy only in patients requiring mechanical ventilation since it increased the length of stay in the hospital and the odds of hyperglycemia[40]. Around 22% of the sample died from septic shock, heart failure, respiratory failure, or pulmonary embolism. Similar mortality percentages were noted in a cohort study conducted in China in 2020[41]. In the univariate analysis, all-cause mortality significantly increased per increase in age and among critical cases compared to nonsevere and severe cases. These findings were also reported in a study recently published reporting that deceased patients were frequently older and critical COVID-19 patients[42]. Interestingly, the all-cause mortality rate was lower among nonsmokers than among smokers. This can be attributable to other coexisting factors that could have impacted the outcome of interest. According to a study published in 2020, the overall mortality rate for COVID-19 among nonsmokers was estimated to be around 1.4%[43]. However, this rate varied widely based on age and other health factors. For example, the mortality rate for nonsmokers over the age of 80 was estimated to be over 20%, while the rate for those under the age of 50 was less than 0.1%[43]. A recently published causal mediation analysis

showed that active smokers did not experience worse COVID-19 outcomes during hospitalization compared to nonsmokers, while former smokers had a higher risk of mortality and complications[44]. In this study, the smoking status was only registered, and former smokers could have considered themselves nonsmokers, affecting the all-cause mortality rate. Nevertheless, after adjusting for covariates, smoking was not a significant predictor of all-cause mortality. Mortality significantly decreased if patients had one comorbidity compared to those with none, contrary to previous research[45]. This may possibly be since chronic conditions were known a priori and sought management and evaluation of adverse events in the hospital. Furthermore, being treated with corticosteroids for more than 7 days was a protective factor for all-cause mortality compared to a shorter duration. In agreement, a meta-analysis reported that those who received a course of corticosteroids for over 7 days had higher survival rates than a shorter treatment course[15]. Mortality was significantly higher among patients encountering side effects from their corticosteroid treatment, particularly superinfection. Other research reported bacterial superinfection among almost half hospitalized COVID-19 patients[46]. Nonetheless, contradictory findings regarding all-cause mortality risks associated with superinfection were reported in the literature where in some, survival rates did not differ between patients with or without superinfections[47,48], while in other superinfections were associated with higher risks of in-hospital mortality[48]. A complex web of factors may have also contribute to the COVID-19 pandemic such as air pollution, urbanization, population density, climate change, and global travel[11], which highlights the need for coordinated efforts to address both the immediate and underlying drivers of the crisis.

Strengths, limitations, and conclusion

The study has strengths. The random selection of patients reduced selection bias. Pharmacists were uniformly trained and used the same data collection form and data coding and analysis were performed by a different researcher. The present study is the first multicenter study tackling the predictors of all-cause mortality among hospitalized COVID-19 patients taking corticosteroids. It can therefore provide additional information for managing these cases. It is important to note that hospital mortality rates for COVID-19 can also vary based on the capacity and resources of the healthcare system, as well as the quality of care provided to patients. This study has also limitations. Data were collected retrospectively from the medical charts of the patients, which may possibly not cover all the information of patients such as side effects and reported cause of mortality. No adjustment was performed for the hospitals in the multivariate analysis, which could affect the final outcome since all-cause mortality could vary between hospitals. Findings from this study highlight the importance of integrating clinical pharmacists, nurses, and doctors in the team responsible for COVID-19 patients since their role has been multifaceted and provides vital expertise in medication management, infection control, and public health education.

Corticosteroids are frequently used in the treatment of hospitalized COVID-19 patients. Drug types and duration of treatment differed between hospitals. All-cause mortality rate were higher among older and critical cases and lower among those treated for more than 7 days. Moreover, encountering side effects namely superinfections increased all-cause mortality rate among patients treated with corticosteroids. Further investigations exploring the safety and efficacy of corticosteroids are required to allow better in-hospital management of COVID-19 cases. Previous studies reported the use of corticosteroids in managing COVID-19 patients, with only a few that linked the general and clinical characteristics of patients with all-cause mortality and have inferred that hospital-related complications may play a role in these findings. This study can help provide evidence supporting this hypothesis, clarifying the need to further assessment of corticosteroid use in COVID-19 patients.

Ethical approval

Ethical approval for this study (CRU329) was provided by the institutional review board of Ain Wazein Medical Village, Ain Wazein, El-Chouf, Lebanon, PO Box: 1503-2010/02 on October 13th, 2021.

Consent

Written informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

V.M. and A.A.S.: methodology, data curation, project administration, writing-original draft; G.H.: conceptualization, formal analysis, validation and writing-original draft; D.G.: data curation and writing-original draft; A.Y.: conceptualization, methodology, and writing-original draft; S.A.: conceptualization, data curation, methodology, writing-review and editing.

Conflicts of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Data availability statement

Datasets are available upon reasonable request.

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References

[1] Lau H, Khosrawipour V, Kocbach P, *et al*. Internationally lost COVID-19 cases. J Microbiol Immunol Infect 2020;53:454–8.
[2] Sarkodie SA, Owusu PA. Global assessment of environment, health and economic impact of the novel coronavirus (COVID-19). Envi, Develop Sustainab 2021;23:5005–15.
[3] Pereira MA, Dinis DC, Ferreira DC, *et al*. A network data envelopment analysis to estimate nations' efficiency in the fight against SARS-CoV-2. Exp Syst App 2022;210:118362.
[4] Hatem G, Goossens M. Health care system in Lebanon: a review addressing health inequalities and ethical dilemmas of frontline workers during COVID-19 pandemic. BAU. Journal - Health Wellbeing 2022;5: 1–11.
[5] Hatem G, Ghamloush S, Chami AA, *et al*. Impact of the COVID-19 pandemic on pharmacy practice and on the provision of pharmaceutical care: a cross-sectional study among community pharmacists. J Med Access 2023;7:27550834231161145.
[6] Sepandi M, Taghdir M, Alimohamadi Y, *et al*. Factors associated with mortality in COVID-19 patients: a systematic review and meta-analysis. Iran J Public Health 2020;49:1211.
[7] Peiffer-Smadja N, Lucet JC, Bendjelloul G, *et al*. Challenges and issues about organizing a hospital to respond to the COVID-19 outbreak: experience from a French reference centre. Clin Microbiol Infect 2020;26: 669–72.
[8] Bilinski A, Emanuel EJ. COVID-19 and excess all-cause mortality in the US and 18 comparison countries. JAMA 2020;324:2100–2.
[9] El Falou S, Trad. F. Forecast analysis of the COVID-19 incidence in Lebanon: prediction of future epidemiological trends to plan more effective control programs. in 2021 Sixth International Conference on Advances in Biomedical Engineering (ICABME). 2021. IEEE.
[10] Al-Raeei M. The COVID-19 basic reproductive ratio using SEIR model for the Middle East countries and some other countries for two stages of the disease. Bull Nat Res Centre 2021;45:1–7.
[11] Wu T. The socioeconomic and environmental drivers of the COVID-19 pandemic: a review. Ambio 2021;50:822–33.
[12] Nielsen Jeschke K, Bonnesen B, Hansen EF, *et al*. Guideline for the management of COVID-19 patients during hospital admission in a non-intensive care setting. Eur Clin Respir J 2020;7:1761677.
[13] Bornstein SR, Rubino F, Khunti K, *et al*. Practical recommendations for the management of diabetes in patients with COVID-19. lancet Diab Endocrinol 2020;8:546–50.
[14] Tobaiqy M, Qashqary M, Al-Dahery S, *et al*. Therapeutic management of patients with COVID-19: a systematic review. Infection Prevention in Practice 2020;2:100061.
[15] Chaudhuri D, Sasaki K, Karkar A, *et al*. Corticosteroids in COVID-19 and non-COVID-19 ARDS: a systematic review and meta-analysis. Intensive Care Med 2021;47:521–37.
[16] Sterne JAC, Murthy S, Diaz JV, *et al*. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA 2020;324:1330–41.
[17] Chen Z, Yin X, Tan X, *et al*. Effectiveness of systemic corticosteroids therapy for nonsevere patients with COVID-19: a multicenter, retrospective, longitudinal cohort study. Value Health 2022;25:709–16.
[18] Meduri GU, Annane D, Confalonieri M, *et al*. Pharmacological principles guiding prolonged glucocorticoid treatment in ARDS. Intensive Care Med 2020;46:2284–96.
[19] Awada S, Hatem G. Assessment of all-cause mortality and need for mechanical ventilation among COVID-19 patients taking corticosteroids in the intensive care unit. J Comm Med and Pub Health Rep 2023;4.
[20] Moghnieh R, Mokhbat J, Bizri A, *et al*. The Lebanese Society of Infectious Diseases and Clinical Microbiology (LSIDCM) guidelines for the management of COVID19. 2020.
[21] Hatem G, Navasardyan N, Lahoud E, *et al*. Predictors of substitution to generic drugs and physicians' perceived exclusivity of substitution: A cross sectional survey among physicians. J Gen Med 2022;19:1741134 3221107569.
[22] Coccolini F, Cicuttin E, Cremonini C, *et al*. A pandemic recap: lessons we have learned. World J Emerg Surg. 2021;16:1–8.
[23] Bertsimas D, Boussioux L, Cory-Wright R, *et al*. From predictions to prescriptions: A data-driven response to COVID-19. Health Care Manag Sci 2021;24:253–72.
[24] Awada S, Abbas N, Mahmoud V, *et al*. All-Cause Mortality in Type 2 Diabetes Patients Hospitalized for COVID-19 and Treated with Corticosteroids: A Single Center Cross-Sectional Study. Clin Diabetol 2023;12:112–22.
[25] Van Paassen J, Vos JS, Hoekstra EM, *et al*. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. Crit Care 2020;24:1–22.
[26] Mathew G, Agha R, Albrecht J, *et al*. Strocss 2021: strengthening the reporting of cohort, cross-sectional and case-control studies in surgery. Int J Surg Open 2021;37:100430.
[27] Bhimraj A, Morgan RL, Shumaker AH, *et al*. Infectious Diseases Society of America Guidelines on the treatment and management of patients with coronavirus disease 2019 (COVID-19). Clin Infect Dis 2020:ciaa478.
[28] pharmacists, A.S.o.H.-S. Assessment of Evidence for COVID-19-Related Treatments. 2021; Available from: https://www.fip.org/files/content/priority-areas/coronavirus/mo-resources/ASHP-COVID-19-Evidence-Table-03-21-20.pdf
[29] Hatem G, Zeidan J, Goossens M, *et al*. Normality testing methods and the importance of skewness and kurtosis in statistical analysis. BAU J-Sci Technol 2022;3:7.
[30] Mukherjee S, Pahan K. Is COVID-19 gender-sensitive? J Neuroimm Pharmacol 2021;16:38–47.
[31] Fried MW, Crawford JM, Mospan AR, *et al*. Patient characteristics and outcomes of 11 721 patients with coronavirus disease 2019 (COVID-19) hospitalized across the United States. Clin Infect Dis 2021;72:e558–65.
[32] Berenguer J, Ryan P, Rodríguez-Baño J, *et al*. Characteristics and predictors of death among 4035 consecutively hospitalized patients with COVID-19 in Spain. Clin Microbiol Infect 2020;26:1525–36.
[33] Health, M.o.P., *Monitoring of COVID-19 Infection In Lebanon*. 2021.
[34] Casas-Rojo JM, Antón-Santos JM, Millán-Núñez-Cortés J, *et al*. Clinical characteristics of patients hospitalized with COVID-19 in Spain: Results from the SEMI-COVID-19 Registry. Revista Clínica Española (English Edition) 2020;220:480–94.
[35] Alimohamadi Y, Sepandi M, Taghdir M, *et al*. Determine the most common clinical symptoms in COVID-19 patients: a systematic review and meta-analysis. J Prev Med Hyg 2020;61:E304.
[36] Kirshblum SC, DeLauter G, Lopreiato MC, *et al*. Screening testing for SARS-CoV-2 upon admission to rehabilitation hospitals in a high COVID-19 prevalence community. PM&R 2020;12:1009–14.
[37] Wagner C, Griesel M, Mikolajewska A, *et al*. Systemic corticosteroids for the treatment of COVID-19. Cochrane Database Syst Rev 2021;8: CD014963.
[38] Cano EJ, Fonseca Fuentes X, Corsini Campioli C, *et al*. Impact of corticosteroids in coronavirus disease 2019 outcomes: systematic review and meta-analysis. Chest 2021;159:1019–40.
[39] Fusina F, Albani F, Granato E, *et al*. Effect of corticosteroids on mortality in hospitalized COVID-19 patients not receiving invasive mechanical ventilation. Clin Pharmacol Therap 2021;109:1660–7.
[40] Zhou F, Deng J, Heybati K, *et al*. Efficacy and safety of corticosteroid regimens for the treatment of hospitalized COVID-19 patients: a meta-analysis. Future Virol 2022;17:463–89.
[41] Albani F, Fusina F, Granato E, *et al*. Effect of corticosteroid treatment on 1376 hospitalized COVID-19 patients. *A cohort study* medRxiv 2020.
[42] Li J, Luo H, Deng G, *et al*. Multidimensional evaluation of all-cause mortality risk and survival analysis for hospitalized patients with COVID-19. Int J Med Sci 2021;18:3140.
[43] Vardavas CI, Nikitara K. COVID-19 and smoking: a systematic review of the evidence. Tob Induc Dis 2020;18:20.
[44] Le Guen CL, Muir KC, Simons M, *et al*. The impact of smoking status and smoking-related comorbidities on coronavirus disease 2019 patient outcomes: a causal mediation analysis. Nicot Tobacco Res 2023;25:331–8.

[45] Günster C, Busse R, Spoden M, *et al*. 6-month mortality and readmissions of hospitalized COVID-19 patients: a nationwide cohort study of 8,679 patients in Germany. PLoS One 2021;16:e0255427.
[46] Cataño-Correa JC, Cardona-Arias JA, Porras Mancilla JP, *et al*. Bacterial superinfection in adults with COVID-19 hospitalized in two clinics in Medellín-Colombia, 2020. PLoS One 2021;16:e0254671.
[47] Søvik S, Barratt-Due A, Kåsine T, *et al*. Corticosteroids and superinfections in COVID-19 patients on invasive mechanical ventilation. J Infect 2022;85:57–63.
[48] Pulakurthi YS, Pederson JM, Saravu K, *et al*. Corticosteroid therapy for COVID-19: a systematic review and meta-analysis of randomized controlled trials. Medicine 2021;100:e25719.