



RESEARCH ARTICLE

Clinical characteristics and predictors of the duration of hospital stay in COVID-19 patients in Jordan [version 1; peer review: 1 approved with reservations, 1 not approved]

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V1 First published: 10 Dec 2020, 9:1439
<https://doi.org/10.12688/f1000research.27419.1>
 Latest published: 10 Dec 2020, 9:1439
<https://doi.org/10.12688/f1000research.27419.1>

Abstract

Background: On March 11th, 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) as a global pandemic. Healthcare systems in low- and middle-income countries may face serious limitations during a pandemic, for which understanding the predictors of prolonged hospital stay are crucial in decreasing the mortality rate. The aim of this study was to investigate the predictors of increased length of hospitalization among COVID-19 patients.

Methods: In this prospective study, we investigated the effect of presenting symptoms and laboratory investigations on the duration of hospitalization of 131 COVID-19 patients at a tertiary hospital in Jordan from March 17th to April 9th, 2020.

Results: Patients median age was 24 years [interquartile range (IQR): 8-39], of which 67 (51.15%) were males and 64 (48.85%) were females. Smokers had shorter in-hospital stay (OR: -3.52; 95% CI: -6.73 to -0.32; P=0.03). Taste loss (OR: 5.1; 95% CI: 1.95 to 8.25; P<0.01) and chills or rigors (OR: 4.08; 95% CI: 0.73 to 7.43; P=0.02) were the symptoms significantly associated with increased in-hospital stay, while those who had malaise (OR: -4.98; 95% CI: -8.42 to -1.59; P<0.01) and high white blood cell (WBC) count (OR: -0.74; 95% CI: -1.31 to -0.17; P=0.01) had faster recovery.

Conclusions: Our study found that the most common presenting

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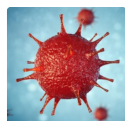
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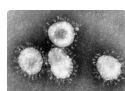
symptoms of COVID-19 are cough, malaise, and headache. Smoking, presenting with malaise or elevated WBCs were associated with shorter hospital stay, while loss of taste and chills or rigors at presentation were associated with a longer in-hospital stay.

Keywords

COVID-19, SARS-CoV-2, symptoms, smoking, Hydroxychloroquine.



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Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

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How to cite this article: Alqassieh RS, Bsisu IK, Al-Sabbagh MQ *et al.* **Clinical characteristics and predictors of the duration of hospital stay in COVID-19 patients in Jordan [version 1; peer review: 1 approved with reservations, 1 not approved]** F1000Research 2020, 9:1439 <https://doi.org/10.12688/f1000research.27419.1>

First published: 10 Dec 2020, 9:1439 <https://doi.org/10.12688/f1000research.27419.1>

Introduction

In December, China reported a group of pneumonia cases of unknown etiology that were later identified to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)^{1,2}. On March 11th, 2020, the World Health Organization (WHO) categorized coronavirus disease 2019 (COVID-19) as a global pandemic³. Patients with COVID-19 frequently present with a cluster of different respiratory symptoms, including fever, chills, cough, shortness of breath, sore throat, and new loss of taste and/or smell within 2 to 14 days after exposure in most cases⁴.

Coronaviruses belong to viral family *Coronaviridae* (order *Nidovirales*) and include viruses approximately 26–32 kilobases in size with a positive-sense single-stranded RNA genome (+ssRNA)⁵. The *Coronaviridae* family contains four genera, one of which is the *Betacoronavirus* genus, which SARS-CoV-2 belongs to⁶.

Initial assessments of the epidemiologic characteristics and transmission dynamics showed that the basic reproductive number (R_0), which is defined as the expected number of additional cases that can directly be generated by one case in a population susceptible to infection on average over the course of its infectious, range from 2.2 to 3.58^{7,8}, with the potential for asymptomatic transmission being a major concern for most of previous investigations.

The first identified case of COVID-19 in Jordan was on March 2nd, 2020, a returning traveler two weeks prior to quarantine procedures⁹. On March 13th, a wedding ceremony led to a large outbreak of COVID-19 cases in northern Jordan¹⁰, after which a strict lockdown took place and five tertiary hospitals were selected to provide medical care for patients suspected or diagnosed COVID-19 cases^{9,10}.

Healthcare systems in low- and middle-income countries may face serious limitations in capacity and accessibility during a pandemic, leading to worse clinical outcomes and an increase in mortality rate¹¹. Therefore, the aim of this study is to investigate the predictors of increased length of hospitalization among COVID-19 patients, in order to provide evidence-based public health outbreak response strategies for COVID-19 and future pandemics.

Methods

Study design

In this prospective observational investigation, we reviewed COVID-19 patients who were admitted to the isolation center at Prince Hamza Hospital (PHH), which is a tertiary hospital in Amman, the capital of the Hashemite Kingdom of Jordan. We included Jordanian patients above the age of 18 years who were diagnosed with COVID-19 and admitted to the isolation center of PHH. The diagnosis of COVID-19 was made after the collection of nasopharyngeal swabs using Xpert® sample collection kit (catalog number XPRSARS-COV2-CE-10, Cepheid, Sunnyvale, CA, USA)¹² at the emergency department of five tertiary hospitals in Amman, after which positive cases were transferred to the isolation center at PHH. The data

collection took place between March 17th till April 9th, 2020, during which all of the 131 patients admitted to PHH with the primary diagnosis of COVID-19 were included in our investigation, representing 40.4% of the total 324 cases diagnosed with COVID-19 in Jordan during the study's timeframe. None of the patients were not eligible, declined to be enrolled, or withdrew from the study, and the study was reported in accordance with the STROBE statement (<https://www.strobe-statement.org/>). It is noteworthy that, in Jordan, all patients diagnosed with COVID-19 were admitted to hospital during the study's timeframe, regardless of the severity of their illness.

Data collection

Based on semi-structured interviews by anesthesia and intensive care resident physicians, the demographic data, smoking habit, and past medical history of patients were documented directly from the patients during medical history taking. Moreover, we documented the current presenting symptoms, including cough, shortness of breath, chest pain, fever, chills/rigors, sweating, malaise, myalgia, headache, diarrhea, abdominal pain, palpitations, loss of taste, loss of smelling, nasal congestion, and rhinorrhea. Furthermore, baseline vital signs and laboratory investigations were collected, and whether the physician started the patient on hydroxychloroquine as a treatment. All patients were followed-up daily from admission till discharge from the hospital after clinical resolution and having negative test results.

Ethical approval

The study protocol was approved by the Institutional Review Board (IRB) committee of The Hashemite University (No. 1/10/2019-2020). Written informed consent was obtained from all patients prior to participation in the study. All patients were able to withdraw from the investigation at any time without affecting their care. No identifying information were obtained from the patients, and all collected data were used solely for statistical analysis.

Statistical analysis

Statistical analysis was performed using **STATA** (Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). The total sample number comprised of 131 patients. The association between the categorical baseline variables and the length of hospitalization was studied using Mann Whitney-U test for the dichotomous variables and Kruskal-Wallis test for the rest of the poly chotomous variables. Data were reported as medians with interquartile range (IQR) as they were non-normally distributed ($P < 0.01$ for the Shapiro-Wilk test).

A Linear regression analysis was used to examine the factors predicting the length of hospitalization. Baseline characteristics, presenting symptoms, and laboratory results at day of presentation were first analyzed using univariable linear regression analysis. Then, only significant variables were fitted into the final multivariable linear regression analyses. We reported the regression coefficients with their level of significance; p-value and 95% confidence intervals (95% CI). The p-value of statistical tests was two-sided, and statistically significant results were defined as those with a p-value < 0.05 .

Results and discussion

Characteristics of the sample

The median age of included patients was 24 years [interquartile range (IQR): 8-39], of which 67 (51.15%) were males and 64 (48.85%) were females. Of the 131 patients, 29 (22.14%) were smokers. No comorbid conditions at presentation was recorded for 95 patients (72.52%), while 9 (6.87%) had hypertension, 8 (6.11%) had chronic respiratory diseases, and 7 (5.34%) had diabetes mellitus [Table 1¹³].

Presenting symptom of COVID-19

Overall, 74 (57%) patients presented with cough, of which 47 (36%) had dry cough, while 27 (21%) had productive cough. Malaise (n= 62; 47%) and headache (n=59; 45%) were the second and third commonest presenting symptoms, followed by loss of smell (n=54; 41%), loss of taste (n=51; 29%), and diarrhea (n=51; 39%). Only 49 (37%) patients presented with nasal congestion, chills, or rigors, and 48 (37%) presented with myalgia. Of the 131 patients, 42 (32%) had fever at time of presentation [Table 2¹³].

Factors predicting the length of hospital stay

Overall, smokers had shorter in-hospital stay (β : -3.52; 95% CI: -6.73 to -0.32; $P=0.03$). Moreover, taste loss (β : 5.1; 95% CI: 1.95 to 8.25; $P<0.01$) and chills or rigors (β : 4.08; 95% CI: 0.73 to 7.43; $P=0.02$) were the symptoms significantly associated with increased in-hospital stay, while those who had malaise (β : -4.98; 95% CI: -8.42 to -1.59; $P<0.01$) and high white blood cell (WBC) count (β : -0.74; 95% CI: -1.31 to -0.17; $P=0.01$) at presentation had faster recovery. Hydroxychloroquine was not associated with decreasing the duration of hospital stay (β : -2.55; 95% CI: -5.67 to 0.56; $P=0.11$) [Table 3¹³].

Discussion

In spite of the great progress in understanding COVID-19, a therapeutic or preventive solution is yet to be achieved¹⁴. Consequently, better management of medical facilities during the next phase of this pandemic is crucial in improving the outcomes in these patients¹⁵. In the present study, smoker, as well as patients presenting with malaise and elevated WBCs at presentation had shorter hospital stay, while loss of taste and chills or rigors at presentation were associated with lengthier in-hospital stay.

Several previous studies investigated the clinical manifestations of COVID-19. Most common presenting symptoms in most of these studies were fever, cough, dyspnea, malaise and myalgia^{16,17}. Interestingly, it has been suggested that anosmia (loss of smelling sense) and ageusia (loss of taste function) can represent the first or only symptomatology¹⁸, while an investigation from Italy found that 64% mildly symptomatic patients had impaired olfaction¹⁹.

Remarkably, even though multivariable linear regression analyses in the current study did not show significant correlation between demographic factors and the length of in-hospital stay except for smoking habit, an investigation from Germany revealed that those with preexisting respiratory diseases, obese

patients, and those with persistently elevated inflammatory markers are at increased risk of developing acute respiratory distress syndrome (ARDS), which will prolong their hospitalization period²⁰. Moreover, a study conducted in China found that severe cases more frequently had dyspnea, lymphopenia, and hypoalbuminemia, with higher levels of c-reactive protein, d-dimer, lactate dehydrogenase, alanine aminotransferase, ferritin, IL-2R, IL-6, IL-10, and TNF- α ²¹. In the current study, patients with elevated WBCs count had shorter in-hospital stay. Immunocompetent WBCs play a significant role in systemic inflammatory response to infection, with neutrophil-lymphocyte count ratio being significantly higher in mortality cases of community-acquired pneumonia²².

An interesting finding in our study is that smokers had shorter in-hospital stay, moreover, only 22% of hospitalized COVID-19 patients were smokers. There is a controversy in the current literature about the role of smoking and nicotine in COVID-19^{23,24}. It is postulated that smokers are at higher risk to get respiratory tract infections and develop more severe illness, due to the preexisting bronchopulmonary damage, reduced mucociliary clearance, and the local inflammatory status²³. Some reports, however, showed lower COVID-19 related mortality and morbidity in smokers²⁴. Nicotine, as a cholinergic agonist, inhibits pro-inflammatory cytokines such as TNF, IL-1, IL-6 by binding acetylcholine receptors (nAChR). These cytokines, among the others, might result in the notorious feature of this illness, the cytokine storm. Therefore, it was hypothesized that COVID-19 is a disease of nicotinic cholinergic system. Another supporting observation is that patients with ageusia in our sample had longer in-hospital stay; this sensory disturbance is mainly related to the cholinergic system of the brain, and it might indicate that such patients are having more extensive disease, or technically, nicotinic cholinergic dysfunction^{23,24}. Although it is not wise or acceptable to advice people to smoke, this might shed the light on the promising role of nicotine in preventing and treating COVID-19 infection.

The rapid upsurge in the number of confirmed cases makes the control of the spread of COVID-19 and its treatment challenging²⁵. Several ongoing clinical trials will soon confirm or disprove the usefulness of several candidate medications in treating COVID-19²⁶. Studies investigating the use of hydroxychloroquine were unable to confirm its benefit on in-hospital outcomes of COVID-19 patients²⁷. On the other hand, dexamethasone has shown a decrease in the 28-day mortality among those who were receiving respiratory support, with both of dexamethasone and methylprednisolone being equally effective in treating moderate to severe COVID-19 cases^{28,29}. With no definitive method of prevention or treatment being available to date, precautions should be made in order to control the spread of COVID-19, including proper hand hygiene, isolation of infected or suspected persons in properly ventilated hospitals, social distancing, discouraging large gatherings, and avoiding direct contact with suspected animal reservoir hosts³⁰.

The main limitation of this study is that it did not investigate the predictors of in-hospital mortality of COVID-19 patients.

Table 1. Descriptive characteristics of 131 patients according to the length of their hospital stay.

Variable	Category	Total n (%)	Length of hospital stay Median (IQR)	P value
Total		131(100)	14 (12-19)	
Gender				
	Male	67 (51.15)	14 (12-17)	0.28
	Female	64 (48.85)	16 (12-20)	
Age (years)				
	0-10	38 (29.01)	13 (11-18)	0.67
	11-20	21 (16.03)	14.5 (13-19)	
	21-30	21 (16.03)	13.5 (11-18)	
	31-40	21 (16.03)	16 (12.5-26)	
	41-50	15 (11.45)	15.5 (12-19)	
	Above 50	15 (11.45)	15.5 (12-19.5)	
Comorbidities				
	No Comorbidities	95 (72.52)	14 (11-18)	0.31
	Chronic respiratory diseases	8 (6.11)	13.5 (11.5-20)	0.8
	Ischemic heart disease	2 (1.53)	13.5 (11-16)	0.63
	Diabetes mellitus	7 (5.34)	16.5 (15-18)	0.6
	Hypertension	9 (6.87)	19 (17-20)	0.05
	Drug allergies	3 (2.29)	14 (9-19)	0.6
	Other comorbidities	17 (12.98)	17 (13-19)	0.34
Smoking status				
	Smoker	29 (22.14)	14 (11-17)	0.29
	Non smoker	102 (77.86)	14.5 (12-20)	
ABO blood group				
	A	30 (43.48)	14 (12-19)	0.5
	B	12 (17.39)	16 (13-19)	
	AB	5 (7.25)	13 (12-17)	
	O	22 (31.88)	13 (11-16)	
Hydroxychloroquine				
	Received hydroxychloroquine	63 (48.09)	14 (12-18)	0.56
	Did not receive hydroxychloroquine	68 (51.91)	15 (11-20)	

Table 2. The presenting symptoms of 131 COVID-19 patients.

Symptom	Frequency (%)
Dry cough	47 (36)
Productive cough	27 (21)
Malaise	62 (47)
Headache	59 (45)
Loss of smelling	54 (41)
Loss of taste	51 (39)
Diarrhea	51 (39)
Nasal congestion	49 (37)
Chills/rigors	49 (37)
Myalgia	48 (37)
Fever	42 (32)
Rhinorrhea	33 (25)
Sweating	29 (22)
Shortness of breath	25 (19)
Abdominal pain	25 (19)
Chest pain	19 (15)
Palpitations	10 (8)

Previous studies suggested that older age, high Sequential Organ Failure Assessment (SOFA) score, and elevated d-dimer are associated with poor prognosis^{31,32}. However, upon plotting mortality against the incidence of COVID-19, a significant positive correlation was found, suggesting that mortality is associated with heavier healthcare burden³³. Hence, understanding the predictors of prolonged hospital stay and prognostic factors are crucial in decreasing the mortality of any pandemic. Moreover, we recommend future studies to take into consideration duration and severity of each symptom in order to develop a better understanding of the clinical course of COVID-19. The main strength of our study is that, in Jordan, all COVID-19 patients were hospitalized during the study's timeframe, regardless of the severity of their illness. Therefore, our sample gives a good opportunity to observe the natural progression of COVID-19 under controlled conditions.

Conclusion

Our study found that the most common presenting symptoms of COVID-19 are cough, malaise, and headache. Smoking, presenting with malaise or elevated WBCs were associated with shorter hospital stay, while loss of taste and chills or rigors at presentation were associated with a longer in-hospital stay. Such findings are important in risk stratifying COVID-19 patients according to their presenting symptoms and past medical history. Although it is not wise or acceptable to consider smoking behaviors, future research should shed light on the role of nicotinic receptors in mitigating this illness.

Table 3. Multivariate linear regression analyses of the predictors of the length of hospital stay in 131 Patients.

Characteristic	Subgroups	β coefficient	P value	95% Confidence Interval
Age (years)		0.02	0.73	-0.10 0.14
Smoking		-3.52	0.03	-6.73 -0.32
Hypertension		2.97	0.30	-2.67 8.61
The presenting symptom	Dry cough	2.09	0.17	-.91 5.07
	Chills/rigors	4.08	0.02	0.73 7.43
	Malaise	-4.98	<0.01	-8.42 -1.59
	Loss of taste	5.10	<0.01	1.95 8.25
Laboratory values at presentation	White blood cells (WBC) count	-0.74	0.01	-1.31 -0.17
	Creatinine	0.05	0.04	0.01 0.10
Hydroxychloroquine		-2.55	0.11	-5.67 0.56

Data availability

Underlying data

Harvard Dataverse: Clinical characteristics and predictors of the duration of hospital stay in COVID-19 patients in Jordan. <https://doi.org/10.7910/DVN/SBV1K6>¹³

This project contains the following underlying data:

- Phh data coded-final.tab (Clinical characteristics and predictors of the duration of hospital stay in COVID-19 patients in Jordan)
- Codebook.docx (Data codebook)

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

Acknowledgements

The authors would like to thank healthcare workers and first responders across the globe for their efforts during this pandemic. Moreover, the authors would like to thank the WHO for the great effort they made in response to this pandemic.

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Open Peer Review

Current Peer Review Status:  

Version 1

Reviewer Report 11 June 2021

<https://doi.org/10.5256/f1000research.30300.r86710>

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Omar Soliman Mohamed El-Masry 

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The article titled "Clinical characteristics and predictors of the duration of hospital stay in COVID-19 patients in Jordan" represents an attempt to assess clinical factors that might be associated with COVID-19 patients' hospitalization in Jordan. The article rationale is good, however, it cannot reflect the figure in the whole country as data being taken from five centers and included a limited number of patients. I would suggest revising the title unless the data at this time represents the total number of patients in the whole country.

In the introduction, the authors started to recount history of the beginning of COVID-19 observation in China, but the year was not mentioned (December 2019). Please, add 2019.

The introduction should include a background section on factors reported in the study that might affect patients' hospitalizations that were reported, at least, for similar diseases (MERS, for example). In addition, the authors should discuss the other factors that could affect this parameter; such as comorbidities.

In the material and methods' section, the following sentence "It is noteworthy that, in Jordan, all patients diagnosed with COVID-19 were admitted to hospital during the study's timeframe, regardless of the severity of their illness" needs further clarification; does this mean that those were all COVID-19 patients reported in the whole country? If yes, it would be very early to generalize the findings of the current study and this must be clearly indicated as a limitation.

In the results section, smoking status was not found as a predictor for the length of the hospital stay, which is odd knowing that COVID-19 patients suffer from serious lung problems. Did the author investigate confounding factors with smoking status; such as age, for example? Also, I think calculating odd ratio is not suitable for the study design.

I think the findings were concluded from a premature study, which was conducted at the very

beginning of the Corona crisis; therefore, the conclusions are premature and cannot reflect the logical and the expected conclusions regarding COVID-19. Thus, the study should be revised by including data of a larger sample size to be more representative and provide evidence-based conclusions. Having said that, the study rationale is good and interesting; but when supported with robust design, it will be of more interest to the scientific community and will better reflect the real situation.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical laboratory sciences with a special focus on cancer biology and biomarkers

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 02 June 2021

<https://doi.org/10.5256/f1000research.30300.r85534>

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Denise Battaglini 

Anesthesia and Intensive Care, San Martino Policlinico Hospital, Genoa, Italy

This study investigates the predictors of hospital length of stay in COVID-19 patients in Jordan.

The study is well written and interesting. However, it has a lack of novelty and should be improved. I would suggest to add more information:

1) Hospital length of stay is often made by different wards and eventually ICU. I think it is important to understand which patients were admitted to ICU, if some of them were endotracheally intubated, tracheostomized, if some patients had hemorrhage, thrombosis, infections, other complications, which PaO₂/FiO₂ on admission, if they were non-invasively ventilated (CPAP, NIPPV, High flow), if CPR, D-dimer, previous antibiotic therapy, SOFA on admission, Charlson comorbidity index, steroidal therapy, sedation, analgesia, myorelaxants, etc. and other factors that could have been predictors of hospital stay.

The study aims to investigate only predictors but I believe that there is a lack of some important factors which could have changed patients' clinical course.

I suggest to extend the analysis to other important factors and, if possible to divide between those who survived and those who did not OR those who were admitted to ICU/those who did not.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Intensive care medicine, mechanical ventilation, ARDS, COVID-19, infectious disease, neurocritical care

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 02 Jun 2021

Isam Bsisu, School of medicine, The University of Jordan, Amman, Jordan

We would like to thank Dr. Denise Battaglini for his valuable review, which will enable us to improve the quality of our manuscript.

This study included data collected at the beginning of the pandemic in Jordan, during which all patients diagnosed with COVID-19 were admitted to hospital during the study's timeframe. We agree with the reviewer that the aforementioned laboratory investigations and interventions are important in determining the clinical course, and could have been predictors of hospital stay. Due to the limited number of cases at that time, we were unable to compare between cases in terms of outcomes and ICU admission. For instance, there were only 7 mortality cases related to COVID-19 in the whole country on the last day of patients recruitment, April 9th, 2020. Moreover, this prospective study only documented the laboratory investigations performed at that time, which were done based on their indication and patient's clinical scenario.

The scientific knowledge and clinical practice is dynamically changing during COVID-19 pandemic, and so does the indicated investigations, the guidelines for medical management, and post discharge medical care for cured patients. We understand that this study was conducted and published prior to the two peaks in Jordan. However, it provided unique data in which we can understand the predictors of hospital stay based on one of the most important steps in the clinical practice of any physician, which is history taking and clinical examination. In addition, simple laboratory values can be of great benefit as a predictor. Future studies including patients from the whole country during the two peaks can be conducted (as we will recommend in our discussion section in the updated version 2), and it will surely be of great benefit in understanding the clinical course of the disease and its effect on the hospital stay and clinical outcome.

Competing Interests: No competing interests were disclosed.

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