



Predictors of COVID-19 Patients' Hospitalization Costs: A Cross-Sectional Study from Iran

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Abstract

Background: One of the important issues in managing COVID-19 is the correct, principled and timely provision of health services. To achieve this goal, full attention to its economic dimensions is important. The aim of the present study was to estimate direct medical costs of COVID-19 cases and its predictors at a referral hospital in Shahroud, Northeast of Iran.

Methods: This descriptive-analytical cross-sectional study was performed on all confirmed cases with COVID-19 infection who were hospitalized in the referral hospital in Shahroud, Northeast of Iran, between February 20, 2020, and May 23, 2020. A total of 744 confirmed cases were hospitalized during this period. Analyses were conducted on data from 697 patients who survived at admission and had complete records, with final status recorded as discharged or deceased. The bottom-up costing approach was applied to calculate direct medical costs. Univariate analyses were performed using Mann-Whitney U test, Friedman test, and Spearman correlation test. Also, quantile regression was applied in the multivariate analysis. A significance level of 0.05 was used for all statistical tests.

Results: A total of 697 patients were included in the analysis. The mean (SD) of the costs was US\$ 965.8 (1477.2) with the median (IQR) of US\$ 493.7 (366.5, 880). Of the studied patients, 120 (17.2%) were admitted to the ICU, with the mean (SD) and median (IQR) costs of US\$ 2894.6 (2644.6) and US\$ 2129.9 (1212.6, 3895.7), respectively. The highest mean costs were observed for bed and hoteling (42.5% of total costs) and for medications and supplies (34.5%). Age, diabetes, cardiovascular disease, other comorbidities, and patients' intubation had a significant association with the length of stay and the costs of hospitalization in the univariate analysis. The quantile regression results identified that male gender, cardiovascular disease, patients' intubation, and length of stay all were predictors of the patients' hospitalization costs.

Conclusions: The results of the present study showed that clinical management of COVID-19 inpatients incurs a significant financial burden to the healthcare system. Diseases severity was the only modifiable factor which increased the hospitalization costs at its different levels. Mitigating the incidence and severity of the disease through adherence to the health protocols, increasing vaccination coverage, and early diagnosis and timely treatment of patients can play an important role in reducing costs and effective use of health care resources in the management of COVID-19.

Keywords: COVID-19, Hospitalization costs, Iran, Quantile regression.

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Introduction

Coronavirus is one of the main pathogens that primarily targets the human respiratory system. Previous coronavirus outbreaks include Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV) as the cause of severe lower respiratory tract infection in humans, which is recognized as a major threat to general human health¹. The third outbreak of Coronavirus disease SARS-CoV-2 began from China, and the effects of the disease were most widespread there. Then the disease has spread to many other countries, the scope and severity of the disease vary from asymptomatic or mild to severe. A significant proportion of patients with obvious evidence of clinical infection have severe disease². The new corona virus-2019 is transmitted through droplets, close contact, aerosols, and possibly fecal-oral transmission, and patients in the incubation period can transmit the virus to others^{3,4}. Also, the incubation period of this virus was announced as 5 days with an average range of 4 to 7 days⁵⁻⁸.

The mortality rate of COVID-19 is changing and the number of recovered cases is increasing. The mortality rate of the new coronavirus is significantly lower than that of the SARS-CoV (approximately 9.6%) and the MERS-CoV (approximately 35.2%)^{3,5,9} and the rate of transmission of the disease is between 2.5 to 3.5^{10,11}. The spread of the new coronavirus disease is more rapidly than SARS-CoV and MERS-CoV¹². According to the WHO, from 3 January 2020 to 17 September 2021, 5,378,408 confirmed cases of COVID-19 were reported, of which 116,072 cases were died¹³.

One of the important issues in managing COVID-19 is the correct, principled and timely provision of health services, one of the true manifestations of social justice. To achieve this goal, full attention to its economic dimensions is important¹⁴. The increasing growth of health system costs around the world, especially costs related to disease diagnosis and treatment, is



such that it has become one of the main concerns of managers and decision makers of the health systems. According to the results of the World Bank study in developing countries, hospitals are considered as the most important and costly components of health systems and this issue is very important and vital and should be considered¹⁵. In the analysis of treatment costs, direct treatment costs, indirect costs and intangible costs are usually included. Direct treatment costs include the costs of the formal care, including costs related to nurses or medical staff, medicine, equipment, diagnostic tests, amenities and surgical supplies, non-medical direct costs are ancillary costs incurred by patients or their companions for medical and therapeutic purposes and include ancillary equipment, travel and transportation, accommodation and food^{16, 17}. Intangible costs include pain and discomfort. High direct costs of hospitalization, the payment of costs is of particular importance to individuals and organizations. In fact, recognizing these costs prevents the health, human capital and of course the economy of the country from being affected by the shock caused by coronavirus disease^{18, 19}.

While several studies have been conducted worldwide on the costs of COVID-19 disease²⁰⁻²³, only one study estimated the economic burden of COVID-19 in Iran²⁴. However, in this study factors associated with the costs have not been assessed. Therefore, the present study was conducted with the aim of estimating hospitalization (direct medical costs) associated with the management of COVID-19 cases and its predictors at referral hospital in Shahroud, northeast of Iran. Furthermore, the quantile regression technique was used to obtain more detailed information on the association between costs and its predictors.

Materials and Methods

This descriptive-analytical cross-sectional study was performed on all confirmed cases with COVID-19 infection who have been hospitalized in the referral hospital in Shahroud, Northeast of Iran. The study data were extracted from COVID-19 registry system and patients' medical electronic records in the Hospital Information System (HIS). HIS provides a source of information on medical, administrative, financial, and service issues. COVID-19 registry system is an electronic data record included demographic, medical, and general information. We merged data from two sources of COVID-19 registry system and HIS. Study population is patients who were being hospitalized due to a confirmed infection of COVID-19 based on the two diagnostic methods of reverse transcription-polymerase chain reaction (RT-PCR) or Computed Tomography Scan (CT scan).

744 confirmed cases of COVID-19 were admitted to the hospital between February 20, 2020 and May 23, 2020. We used data from 697 patients who were survived at the time of admission and their information were recorded completely in the HIS and COVID-19 data registry system as a patient with a final status of discharged or dead.

The bottom-up costing approach was applied to calculate direct medical costs of the patients. In this approach, the costs of hospitalization were break down to the cost items which their information were collected through the patient bills in the HIS. All cost figures were initially recorded in Iranian Rials (IRR) and were subsequently converted to U.S. dollars using the 2021 Purchasing Power Parity (PPP) exchange rate published by the World Bank (1 USD=50488.17 IRR)²⁵. This approach was adopted to enhance international comparability and to provide a more realistic representation of economic burden by adjusting for differences in price levels between Iran and other countries.

Total costs of hospitalization for COVID-19 patients was calculated through summing up of the cost items including: bed and hoteling costs (for general, Intensive Care Unit (ICU), Coronary Care Unit (CCU), Post-CCU, and temporary beds), fees for medical procedures (visits, counselling, surgery, therapeutic and other medical procedures), diagnostic and laboratory tests (chest X-ray, chest CT scan, other imaging services, RT-PCR, and other laboratory tests), medication and supplies (antibiotics and antivirals, other medications, and medical supplies).

The study covariates were gender, age (≥ 40 years, < 40 years), having diabetes (yes, no), cardiovascular disease (yes, no), other comorbidities (yes, no), intubation (yes, no), risk of mortality (1.5%, 9.2%, and 22%), and length of stay (days). Other comorbidities consisted of cancer, chronic respiratory disease, asthma, chronic kidney disease, chronic liver disease, and autoimmune disorders (including systemic lupus erythematosus and rheumatoid arthritis). Risk of mortality evaluated based on the: confusion, uremia, respiratory rate, blood pressure, age ≥ 65 years (CURB-65 index), a validated criteria which predicts the risk of mortality in community-acquired pneumonia²⁶. The index was calculated based on the patients' confusion status, respiratory rate ≥ 30 breaths/min, blood pressure (systolic < 90 mmHg or diastolic ≤ 60 mmHg), age ≥ 65 years, and blood urea nitrogen level > 19 mg/dL (> 7 mmol/L). If a patient had each of these conditions took one point and the total score of the patients could range from 0 to 5. Risk of mortality for patients with the total score of 0-1, 2, and ≥ 3 was considered to be 1.5%, 9.2%, and 22%, respectively.

Univariate analyses were performed to explore how the medical costs and patients' length of stay changed across patients' demographic and clinical characteristics using Mann-Whitney U test, Friedman test, and Spearman correlation test.

Before fitting the regression model, we checked the outliers of medical cost data. The box plot of the cost data in Figure 1. shows that it contains outliers and is positively skewed (Skewness=5.8) which implies that the ordinary least square (OLS) model is not an appropriate technique to examine the effects of the patients' characteristics on their medical costs.

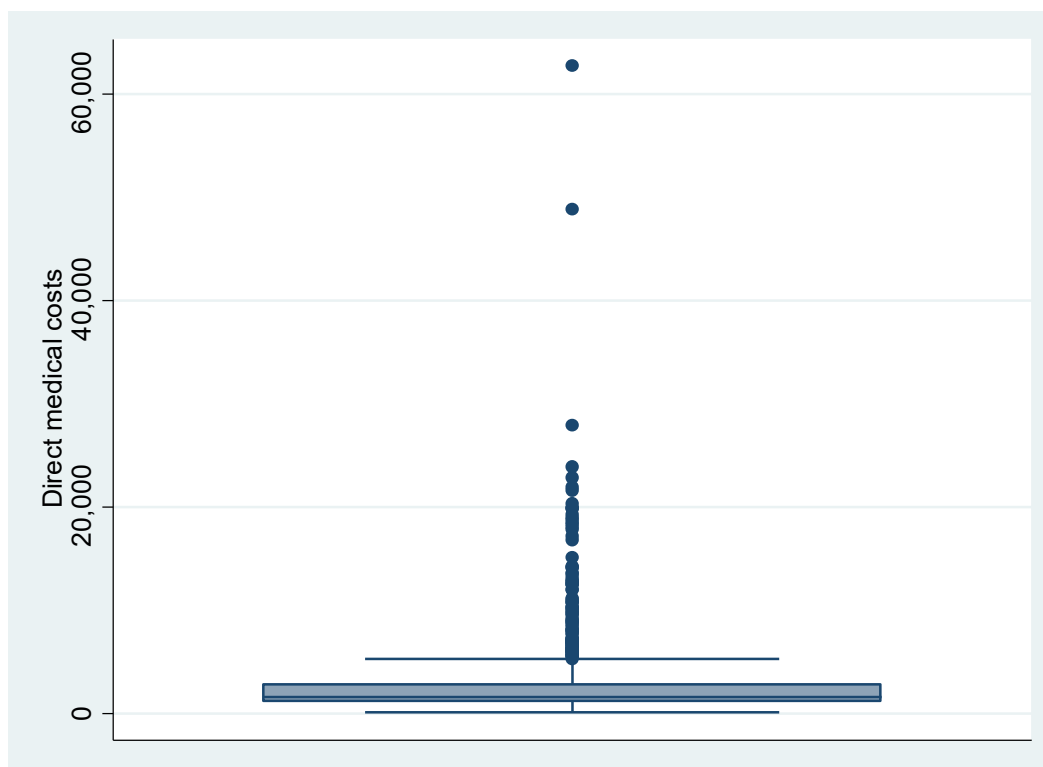


Figure 1. Box plot for COVID-19 patients' direct medical costs

Therefore, we employed a Simultaneous Quantile Regression (SQR) model to assess how predictors affect different levels of hospitalization costs. This model jointly estimates multiple quantiles of the outcome and captures heterogeneity in the associations across the cost distribution.

Given the skewed nature of cost data and the occurrence of negative lower bounds in the 95% confidence intervals of cost estimates in preliminary models, we re-specified the quantile regression by applying a natural logarithmic transformation to the dependent variable (total cost). This approach stabilizes variance, reduces skewness, and ensures that the exponentiated predicted costs remain strictly positive. We also explored the possibility of constrained quantile regression models (restricting coefficients to non-negative values, $\beta \geq 0$); however, these models either failed to converge or yielded unstable estimates. Therefore, the final analysis is based on the unconstrained quantile regression model with log-transformed costs.

The model was fitted to estimate the adjusted effects of the study covariates on the patients' costs, as follows:

$$Q_{\tau|x_i}(\tau|x_i) = x_i^T \beta_{\tau} \quad \tau \in (0, 1)$$

In the equation above, $Q_{\tau|x_i}(\tau|x_i)$ is conditional direct medical cost for i^{th} patient in the τ^{th} quantile. In this

study, we simultaneously estimated the regression coefficients in 10th, 25th, 50th, and 75th quantile points. Therefore, τ took the values of 0.1, 0.25, 0.5, and 0.75. x_i is a vector of covariates for i^{th} patient, and β_{τ} is a vector of estimated coefficients for quantile (τ).

To avoid over fitting, multicollinearity of the study covariates was also checked. The value of VIF for all of the study covariates and the mean VIF were <1.2 and 1.1, respectively, indicating that there was no multicollinearity problem. All the study analyses were performed using Stata software version 14 and a significance level of 0.05 was used for all statistical tests.

Results

According to the results of Table 1, total direct medical costs for 697 COVID-19 inpatients was US\$ 673186.9 with the mean (SD) of 965.8 (1477.2). The median (IQR) cost of hospital care was 493.7 (366.5, 880), which was almost half of its mean. Of the studies patients, 120 (17.2%) were admitted to the ICU. Total costs for these patients was US\$ 347357.3, with the mean (SD) and median (IQR) of US\$ 2894.6 (2644.6) and US\$ 2129.9 (1212.6, 3895.7), respectively.

The highest mean costs were observed for bed and hoteling (42.5%) and for medications and supplies (34.5%), followed by



medical procedures (13.6%), and diagnostic and laboratory tests (9.4%).

Table 2 represents the descriptive statistics of patients' length of hospital stay and direct medical costs by their characteristics.

Table 1. Direct medical costs breakdown for hospitalized patients with COVID-19 disease in Shahroud, Iran

Cost items	Cost (\$)	Mean±SD (\$)	% of Total cost
General	174614.00	250.52 (204.60)	25.94
ICU	105114.80	150.81 (578.64)	15.61
CCU	3485.75	5.00 (49.94)	0.52
Bed & hoteling	230.43	0.33 (4.54)	0.03
Temporary	2094.37	3.00 (21.13)	0.31
Psychiatric	379.65	0.55 (11.70)	0.06
Sum	285919.10	410.21 (648.60)	42.47
Chest X-ray	1069.26	1.53 (4.10)	0.16
Chest CT scan	9861.50	14.15 (10.43)	1.46
Other imaging services	6516.98	9.35 (28.83)	0.97
RT-PCR	19862.08	28.50 (24.50)	2.95
Other laboratory tests	25859.63	37.10 (40.55)	3.84
Sum	63169.44	90.63 (68.19)	9.38
Other medical procedures	91749.15	131.63 (194.08)	13.63
Antibiotics and antivirals	55471.10	79.59 (102.39)	8.24
Other medications	105090.20	150.78 (550.80)	15.61
Medical supplies	71788.00	103.00 (257.83)	10.66
Sum	232349.30	333.36 (740.08)	34.51
Total costs	673186.90	965.84 (1477.18)	100

Abbreviations: \$, US dollar; ICU, Intensive care unit; CCU, Coronary care unit; CT, computer technology; RT-PCR, Reverse transcription-polymerase chain reaction

† Cost items were adjusted for PPP (purchasing power parity) exchange rates

Table 2. Hospital length of stay and direct medical costs of the hospitalized patients with COVID-19 pneumonia by their characteristics in Shahroud, Iran

Characteristics	N (%)	Length of stay Mean (SD)	P-value	Cost Mean (SD)†	P-value
Gender	Female 308 (44.19)	7.82 (7.15)	0.322	971.53 (1769.52)	0.275
	Male 389 (55.81)	7.05 (5.09)		961.33 (1198.6)	
Age (years)	<40 116 (16.64)	6.23 (5.72)	0.001	913.33 (1773.82)	0.016
	≥40 581 (83.36)	7.62 (6.14)		976.32 (1412.07)	
Diabetes	No 521 (74.75)	7.12 (5.76)	0.014	904.18 (1294.36)	0.012
	Yes 176 (25.25)	8.20 (6.94)		1148.34 (1911.92)	
Cardiovascular disease	No 467 (67.00)	6.78 (5.37)	<0.001	808.06 (1194.09)	<0.001
	Yes 230 (33.00)	8.63 (7.20)		1286.18 (1891.18)	
Other comorbidities	No 542 (77.76)	7.04 (5.76)	0.004	953.87 (1579.14)	<0.001
	Yes 155 (22.24)	8.64 (7.01)		1007.66 (1048.47)	
Intubation	No 657 (94.26)	7.22 (5.63)	0.042	837.21 (1064.64)	<0.001
	Yes 40 (5.74)	10.20 (10.98)		3078.49 (3875.50)	
Risk of mortality	1.5% 234 (33.57)	7.46 (5.71)		961.15 (1521.53)	
	9.2% 310 (44.48)	7.23 (5.78)	0.996	879.15 (1459.52)	0.827
	22% 153 (21.95)	7.61 (7.21)		1148.64 (1436.43)	

† Adjusted for PPP (purchasing power parity) exchange rates

The mean (SD) and median (interquartile range) of length of stay were 7.4 (6.1) and 6 (4, 8) days, respectively. Results of the Spearman correlation test showed that there was a positive and strength correlation between patients' costs and their length of stay ($r=0.75$, $P\text{-value}<0.001$). As shown in the first column of Table 2, 55.8% of the patients were male and 44.2% were female, and the age of 83.4% of patients was ≥40 years old. The prevalence of diabetes, cardiovascular disease and other comorbidities among hospitalized patients were 25.3%, 33%

and 22.2%, respectively and 54.5% of the patients had at least one comorbidity. Furthermore, 5.7% of the patients were intubated, and the risk of mortality was 1.5%, 9.2%, and 22% in 33.6%, 44.5%, and 22% of the patients, respectively. According to the results presented in the next four columns of the table, age ≥40, diabetes, cardiovascular disease, other comorbidities, and patient intubation were significantly associated with longer hospital stays and higher hospitalization costs.

Table 3 presents the coefficient estimates and percentage changes in direct medical costs derived from quantile regression analysis. The results indicate that, at the 75th quantile, male patients had significantly higher hospitalization costs compared to females, with a 9.9% increase (95% CI: 2.2%, 18.1%). Similarly, at the median (50th quantile), patients with cardiovascular disease incurred significantly higher costs than those without the condition, with a 7.6% increase (95% CI: 0.3%, 15.5%).

Intubation was significantly associated with increased hospitalization costs across the 25th, 50th, and 75th quantiles, with the effect size escalating at higher quantiles. At the 25th quantile, intubated patients incurred 74.6% (95% CI: 3.9,

193.4%) higher costs, rising to 166.2% (95% CI: 111.9, 234.8%) at the median and 190.5% (95% CI: 103.1, 315.6%) at the 75th quantile. This suggests that intubation disproportionately impacts patients with the highest baseline expenditures.

Similarly, longer hospital stays consistently predicted higher costs across all quantiles, with each additional day increasing costs by 10.6% (25th quantile; 95% CI: 8.9, 12.3%), 12.7% (median; 95% CI: 11.3, 14.0%), and 13.6% (75th quantile; 95% CI: 11.6, 15.6%). The strengthening association across quantiles indicates that prolonged hospitalization drives cost escalation most markedly among high-cost patients.

Table 3. Quantile regression results for direct medical costs (coefficients and % change, 95% CI)

Characteristics	10th quantile		25th quantile		50th quantile		75th quantile	
	Coefficient (95% CI)	Percent change in cost (95% CI)	Coefficient (95% CI)	Percent change in cost (95% CI)	Coefficient (95% CI)	Percent change in cost (95% CI)	Coefficient (95% CI)	Percent change in cost (95% CI)
Gender (RC: Female)	0.078 (-0.068, 0.224)	8.10 (-6.61, 25.12)	0.032 (-0.021, 0.086)	3.26 (-2.12, 8.94)	0.031 (-0.021, 0.084)	3.18 (-2.11, 8.77)	0.094 (0.022, 0.166)*	9.85 (2.21, 18.06)*
Age (RC: <40 years)	0.035 (-0.144, 0.214)	3.59 (-13.40, 23.91)	0.035 (-0.034, 0.103)	3.52 (-3.36, 10.89)	-0.011 (-0.097, 0.075)	-1.70 (-9.23, 7.83)	0.001 (-0.118, 0.120)	0.07 (-11.15, 12.71)
Diabetes (RC: No)	0.070 (-0.068, 0.207)	7.20 (-6.53, 22.95)	0.017 (-0.044, 0.077)	1.68 (-4.28, 8.01)	-0.017 (-0.074, 0.040)	-1.65 (-7.11, 4.13)	-0.007 (-0.100, 0.087)	-0.67 (-9.55, 9.09)
Cardiovascular disease (RC: No)	0.003 (-0.158, 0.164)	0.32 (-14.60, 17.84)	0.047 (-0.021, 0.114)	4.80 (-2.05, 12.12)	0.074 (0.003, 0.144)*	7.64 (0.30, 15.53)*	0.098 (-0.011, 0.206)	10.25 (-1.12, 22.94)
Other comorbidities (RC: No)	-0.019 (-0.202, 0.165)	-1.86 (-18.31, 17.89)	0.078 (-0.032, 0.187)	8.06 (-3.12, 20.54)	0.051 (-0.022, 0.123)	5.20 (-2.13, 13.08)	0.051 (-0.030, 0.133)	5.27 (-2.99, 14.24)
Intubation (RC: No)	0.286 (-0.176, 0.749)	33.14 (-16.17, 111.46)	0.558 (0.039, 1.077)*	74.64 (3.93, 193.44)*	0.979 (0.751, 1.207)*	166.23 (111.91, 234.8)*	1.067 (0.709, 1.424)*	190.53 (103.12, 315.56)*
Risk of mortality (RC: 1.5%)	-0.070 (-0.201, 0.060)	-6.79 (-18.18, 6.18)	-0.029 (-0.085, 0.026)	-2.89 (-8.11, 2.62)	-0.005 (-0.061, 0.051)	-0.48 (-5.90, 5.25)	-0.037 (-0.121, 0.048)	-3.59 (-11.44, 4.95)
9.2%	-0.220 (-0.465, 0.025)	-19.73 (-37.17, 2.55)	-0.079 (-0.182, 0.024)	-7.59 (-16.60, 2.40)	0.015 (-0.064, 0.094)	1.50 (-6.23, 9.86)	0.058 (-0.067, 0.182)	5.95 (-6.45, 20.00)
Length of stay	0.090 (0.078, 0.102)*	9.42 (8.13, 10.72)*	0.101 (0.086, 0.116)*	10.59 (8.93, 12.28)*	0.119 (0.107, 0.131)*	12.67 (11.33, 14.03)*	0.127 (0.110, 0.145)*	13.58 (11.58, 15.62)*

Abbreviations; CI: Confidence interval, RC: Reference category

*P-value<0.05



Discussion

There are studies estimated the economic burden of COVID-19 in some countries. The present study was aimed to estimate direct medical costs of the COVID-19 inpatients and its predictors using data from a referral hospital in Shahroud, Northeast of Iran. The costs of managing COVID-19 inpatients and the average length of hospital stay were estimated to be US\$ 965.8 and 7.4 days per patient, respectively. We found that medical costs in $\geq 25^{\text{th}}$ quantile points were higher when patients were intubated. The results also showed a direct association between the medical costs and the length of hospital stay, intubation, having cardiovascular disease, and male gender.

Our results showed that the highest percentage of medical costs were related to the bed and hoteling and also medications and medical supplies, whereas diagnostic laboratory tests were accounted to be the less costly items. These findings were in line with the results of other studies^{24, 27}. The higher bed and hoteling costs can be explained by the justification that treatment of COVID-19 patients requires more hospitalization than the other respiratory diseases in order to completely cure the infected people, and to prevent further spread of the disease to the community²⁸. In a study conducted in China, medications had the largest share of COVID-19 inpatients' costs (45.1%)²⁹. One of the reasons for the high cost of medications may be the existence of comorbidities in hospitalized patients. According to the results of various studies, comorbidities were one of the main clinical characteristics of the COVID-19 hospitalized patients^{27, 29-32}, which increase the costs of their treatment^{27, 29, 32}. Having comorbidities can lead to a more severe state of the disease^{33, 34}, the treatment of which requires the use of more medications such as antiviruses, antibiotics, immunomodulators, and other drugs associated with the comorbidities.

The median direct medical costs of COVID-19 inpatients in our study (US\$ 493.7) was lower than an estimated median cost of US\$ 3,045 for managing a hospitalized SARS-Cov-2 patient in the United States³⁵. Furthermore, the average direct medical costs (in US dollars) in our study was 965.8, which reported to be 2,395 in China³⁶, 4,633.4 in India³⁷, and US\$ 1193.7 in Korea³². Differences in currency conversion rates across studies could affect cost comparisons. Since medical costs were originally incurred in local currencies and later converted to US dollars, fluctuations in exchange rates may contribute to observed discrepancies. Furthermore, international variations in hospitalization protocols, discharge policies, and healthcare financing structures significantly influence cost differences. Our findings align with previous studies^{32, 35}, in demonstrating a direct relationship between length of hospital stay and treatment costs. This association is well-established, as length of hospital stay serves as a reliable proxy for resource utilization in patient care³⁸. In our setting, although discharge criteria changed simultaneously with the growth of our knowledge of the disease as well as the load of hospitalized patients at each time period, COVID-19 patients were discharged according to clinical criteria when clinical symptoms improved and the patient remained without fever for 72 hours or on 10 days after the onset of clinical symptoms. It appears that length of stay, shaped by discharge policies, is one of the most critical factors underlying differences in direct

medical costs across studies. According to a systematic review, the average length of hospital stay for COVID-19 patients was 14 days in China compared to 5 days outside China²⁸. It also estimated to be 5.5 days in a study by Jang et al. in Korea³².

In addition to the differences in management and discharge strategies in the various settings, the patient profile and disease severity in each study setting are important influencing factors. Findings of the previous studies showed that disease severity and clinical characteristics of the patients such as comorbidities and age composition are important factors that affect the length of stay³⁸ and treatment outcomes³⁹. It seems that different composition of our cases compared with that of other studies, for example the study by Jang et al, can explain the differences in direct medical costs and length of stay. In our study, over 50% of cases had at least one comorbidity, while in the study by Jang et al. in Korea, this figure was under 30%. Likewise, 80% of our patients were older than 40 years, compared to 60% in Jang et al.'s sample³². This difference in age distribution and comorbidity may partly explain the variation in direct medical costs between our study and that of Jang et al. (US\$ 1193.7).

Our quantile regression analysis demonstrated that patients who need to be intubated had higher costs of hospitalization in $\geq 25^{\text{th}}$ quantile points, and association between costs and this factor was stronger in the higher levels of costs. However, these associations were not seen at the 10th quantile points. These findings are largely consistent with the other studies indicating that disease severity, which was measured by different indicators, is an important predictor of patients' treatment costs. In the study by Yan et al., patients' disease severity was categorized as mild, moderate, severe, and critical, along with the recommendations established by the National Health Commission of the People's Republic of China, and hospitalization costs was increased with increasing the level of disease severity²⁷. Other studies also emphasized that patients who were either hospitalized in the ICU or were at high risk of mortality had higher levels of treatment costs^{32, 35, 40, 41} due to events such as acute respiratory distress syndrome (ARDS) and sepsis, both of which increase direct medical costs. However, if the patients died, they had different profile of treatment costs³⁵, because they were less likely to receive more complicated treatment measures or care in the ICU³⁰. Similarly, in our study, it appears that a subset of patients who died shortly after admission- likely due to critical illness- fell into the lower (e.g., 10th) cost quantiles, while severely ill patients who survived required more intensive interventions and contributed to higher cost quantiles.

Among the comorbidities studied, including diabetes, cardiovascular diseases and other comorbidities, which were related to the hospitalization costs in the univariate analysis, only cardiovascular diseases were associated with the costs in the multivariate analysis. These findings were in line with other studies which indicated that existence of the comorbidities increase disease severity^{33, 34} and risk of mortality^{42, 43}. In our study, diabetes and other comorbidities did not have an independent effect on the costs. The positive associations observed in the univariate analysis were likely due to their influence on disease severity indicators, e.g., patient intubation. Moreover, diabetes as one of the major risk factors for cardiovascular disease, if associated with heart disease, can



cause more severe cases of the disease⁴⁴, which in turn will cost more for COVID-19 patients. According to our findings, presence of cardiovascular disease among patients with the costs levels of 25th and 50th quantile points had an independent effect on increasing their costs. This finding may be because of the reason that in less than 25th quantile points, immediate death of a group of the patients with cardiovascular disease after admission stopped increasing their treatment costs, while their survived counterparts were placed in 25th and 50th quantile points and had higher levels of hospitalization costs than the other patients. The presence of cardiovascular disease in the worst case would increase costs at its median level, but at higher levels of cost (75th quantile points) it did not play an independent effect on increasing the costs, possibly due to selective mortality of the most severe cases before they could accrue prolonged treatment cost.

Age as a significant predictor of the patients' costs in other studies^{32, 41}, had a positive association with the patients' costs in the univariate analysis. However, quantile regression analysis showed that age had no independent effect on the patients' costs. The reason for these findings could be that in our study, patients were more homogenous in terms of their age than the other studies. The majority of our cases were more than 40-years-old and they probably experience more severe disease and had more treatment costs than their younger counterparts, which was reflected in the observed associations between the costs and disease severity indicators in the multivariate analysis.

Male gender was significantly associated with the high hospitalization costs; direct medical costs for males was 9.9% more than females in $\geq 75^{\text{th}}$ quantile points. As the results of studies show, the severity of COVID-19 disease^{45, 46} and consequently hospital costs^{32, 41}, are higher in males than females. However, in our study, a significant relationship was found between male gender and costs only among patients with high costs. These findings show that among patients whose illness was more severe and therefore, had higher costs due to the use of more complicated treatments, female patients recovered better than the males and their costs increased less. Other studies have shown that the presence of the X chromosome and female sex hormones enhances women's immune response to severe illnesses^{47, 48}.

Our study has some limitations; first, our results used local data for analysis, which may be less generalizable nationwide. For better comparison and to evaluate estimated medical costs of Iranian inpatients, further research in other parts of Iran and conducting a national study with different settings are required. Second, private sector data is not included in this study, so the findings cannot be generalized to the non-governmental sector. A methodological limitation was the failure to estimate constrained quantile regression models with non-negative coefficients, as they did not converge or produced unstable results. To overcome this and avoid negative lower bounds in cost confidence intervals, we applied a log-transformation to the cost variable, which stabilized the skewed distribution and ensured strictly positive predicted costs. Despite these limitations, to the best of our knowledge, this is the first study to investigate predictors of direct medical costs of COVID-19 among hospitalized patients in Northeast Iran. Our findings can be used as a local study along with other studies to estimate

direct medical costs and their determinants among COVID-19 patients. Furthermore, using the quantile regression technique, this study provides more detailed information on the relationships between patients' costs and their predictors across different levels of hospitalization costs.

The results of the present study showed that clinical management of COVID-19 patients incurs a significant financial burden on the healthcare system. Bed and hoteling services, along with medications and medical supplies, were the main contributors to the direct medical costs. Disease severity was identified as the only modifiable factor that consistently increased hospitalization costs across different cost levels.

These findings have important practical implications. Targeted interventions to reduce disease severity, such as improving chronic disease management, promoting timely diagnosis, expanding vaccination coverage, and strengthening adherence to health protocols, can significantly reduce hospital costs. Moreover, policymakers and hospital administrators can use these insights to better allocate healthcare resources, optimize treatment strategies, and plan for future public health emergencies.

Ethical Considerations

The ethical code of this study is IR.SHMU.REC.1398.160 from Shahroud University of Medical Sciences. Written informed consent was obtained from all study participants.

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Conflict of Interest

The authors declare no competing interests.

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