RESEARCH ARTICLE

Total costs of inpatient treatment for COVID-19 in a tertiary hospital in Serbia

Sazdanovic PS[1,2], Milisavljevic S[1,2], Milovanovic DR[1,2], Jankovic SM[1,2], Baskic D[1,3], Ignjatovic Ristic D[1,2], Ruzic Zecevic D[1,2], Tomic Lucic A[1,2], Djordjevic N[1], Jovanovic D[1,2], Stojkovic A[1,2], Lazarevic T[1,2], Begovic Cvetkovic M[2], Kostic MJ[1]

[1]Faculty of Medical Sciences, University of Kragujevac
[2]University Clinical Centre Kragujevac
[3]Public Health Institute
Kragujevac, Serbia

Abstract

Background: Our study aimed to identify the total costs of inpatient treatment for coronavirus disease 2019 (COVID-19) in a tertiary institution in Serbia, an upper-middle-income country in Southeast Europe.

Methods: An observational, retrospective, cost-of-illness study was performed from the perspective of the National Health Insurance Fund and included a cohort of 78 females and 118 males admitted to the COVID-19 ward units of a tertiary center during the first wave of the pandemic.

Results: The median of the total costs in the non-survivors subgroup (n =43) was 3,279.16 Euros [interquartile range (IQR): 4,023.34; range: 355.20-9,909.61) which is higher than in the survivors (n =153) subgroup 747.10 Euros (IQR: 1,088.21; 46.71-3,265.91). The cut-off value of 156.46 Euros regarding the total costs per day was estimated to have 95.3 % sensitivity and 91.5 % specificity for predicting patients' dismal prognosis, with the area under the curve (AUC) of 0.968 (95 % confidence interval: 0.940-0.996, p <0.001).

Conclusions: Direct medical inpatient treatment costs for COVID-19 represent a significant economic burden. The link between increased costs and an ultimate unfavorable outcome should be further explored.HIPPOKRATIA 2022, 26 (2):62-69.

Keywords: Coronavirus, COVID-19, pandemic, Serbia, inpatients, direct costs, cost of illness

Corresponding author: Prof. Dragan R. Milovanovic, M.D., Ph.D., University Clinical Centre Kragujevac, Department of Clinical Pharmacology, 30 Zmaj Jovina str., 3400 Kragujevac; Department of Pharmacology and Toxicology, Faculty of Medical Sciences, University of Kragujevac, Serbia, 69 Svetozara Markovica str., 34000 Kragujevac, Serbia, tel:+38134306800, fax: +38134306800, e-mail: piki@medf.kg.ac.rs

Introduction

The ongoing pandemic of coronavirus disease 2019 (COVID-19) has unprecedented socio-economic implications worldwide. The evaluators projected billions of direct and indirect financial spending and losses for individual countries, the global workforce, and the economy[1,2]. Healthcare systems are among many sectors which experienced losses of revenues and incomes caused by disturbances in managing their regular operations. Hospitals are especially vulnerable to the economic constraints of the current pandemic, particularly the tertiary academic centers[3]. In addition to their already intense clinical and academic workload, they are obliged to implement new measures which set economic constraints due to the need for resource reallocation, perform various additional diagnostic procedures and provide a range of therapeutic approaches within a rapidly changing and complicating institutional and societal environment[4]. Unsurprisingly, investigators from some developed countries reported that the spreading of the disease correlated with negative trends such as a decline in elective hospital services, a decrease in overall hospitalization rate, a reduction of claimed hospital charges, and a lowering of their financial gains[5,6].

The considerable impact of COVID-19 pandemic on the economic performance of healthcare systems needs to be more comprehensively analyzed and studied. The knowledge regarding the exact health economic data assists decision-makers in more appropriate planning and allocating available resources. This is of great importance for a pandemic as its consequences go beyond the health sector itself and spread to all components of society. However, a few only published studies are based on or modeled for hospital data. Examples are the reports from Saudi Arabia and South Africa that estimated the direct medical expenses related to hospital treatment of COVID-19 patients, demonstrating that costs per patient almost doubled compared to the period preceding the pandemic[7,8]. Further, data derived from United States hospitals confirmed that intensive management of critically ill COVID-19 patients (e.g., admission in the critical or intensive care unit, mechanical ventilation) provoked a high financial burden, also showing a sizeable financial gap between charges and cost claims per treated individual[9]. The current status in most other countries needs to be further documented for the time being.

Healthcare planners, analysts, and managers could reasonably presume that the COVID-19 pandemic seriously undermined the economic sustainability of modern hospitals. However, obtaining additional evidence about the main cost drivers and their mitigating factors is necessary because of some difficulties extrapolating health economic data from different cultural, societal, and economic environments. For instance, considering the values of specific economic and health indicators for Serbia and for the countries of origin of the cost studies mentioned earlier (South Africa, Saudi Arabia, United States), one could notice considerable discrepancies: approximately a 10-times ratio of gross national income (GNI) per capita, a near two-times ratio of the annual inflation rate, a 15-year difference of life expectancy at birth and about four-times ratio of crude mortality rate per a thousand people[10]. Such issues may induce variability in the values of the economic and health inputs and outputs among the studies conducted in distinct geographical regions. International extrapolation of their results is still possible, but it should be perpetrated with methodological adaptation, using either simple adjustments or more advanced modeling studies[11].

It is reasonable to assume that each healthcare system should exploit the economic evidence derived from domestic and international research. The importance of country-specific cost data has already been acclaimed for inpatient and outpatient healthcare services[12]. Regarding the COVID-19 pandemic and its dynamic course, the national data could be used for prompt assessment of the disease's economic burden and the cost estimation of various preventive and treatment strategies at an institutional, regional, and entire population level. Dealing with the different available scenarios, the decision makers can choose the ones that best suit the currently available financial resources. Therefore, our study aimed to conduct a detailed analysis regarding the total costs of inpatient treatment for COVID-19 in a tertiary institution in Serbia, an upper-middle-income country in Southeast Europe. We hypothesized that the costs were significantly higher for treating the patients who succumbed to the disease than the survivors.

Patients and Methods

We designed and conducted a cost-of-illness study with an additional nested case-control approach. The sample was based on the observational method. It included a cohort of 196 adult patients (18 years and older, male and female) admitted to the COVID-19 ward units of the University Clinical Center "Kragujevac", Kragujevac, Serbia, between 14th of March and 26th of April 2020, during the first wave of the pandemic. The sample represented approximately three-quarters of all patients admitted to the hospital COVID-19 units during that period. The study group was divided into the case (the non-survivors) and the control patients (the survivors). Data were retrospectively extracted from the patients' electronic medical records. Our trial's general design was established according to previously published clinical studies with similar observational designs, which included COVID-19 inpatients[13,14]. The Institutional Ethics Committee approved the study (decision No 01/20-407, date: 03/04/2020), and it was conducted according to the principles of the Declaration of Helsinki.

During the hospital treatment period, we transformed patients' demographic and clinical data to study variables, selected from recommendations for building case report forms for patients with COVID-19 enrolled in clinical trials[15]. We assessed COVID-19 severity and clinical improvement according to the recommendations of the World Health Organization[16,17]. We used the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems for classifying comorbid disorders[18]. Charlson Comorbidity Index (CCI) total score shows the patient's pre-existing illness burden on admission together with his or her 10-year probability of survival[19].

In the cost analysis, we included the direct medical costs for patient treatment during their hospital stay and used the perspective of the National Health Insurance Fund with the official price tariffs for the hospital health care services, reimbursed prescription drugs, and licensed medical devices (so-called "hospital electronic bill"), which were established for the fiscal year 2020 and can be accessed through the Republic Fund of Health Insurance website at www.rfzo.rs/index.php/davaocizdrusluga/efaktura. The original prices in Serbian Dinars (RSD) were converted to Euros (EUR) with the first exchange rate of the National Bank of Serbia for 2020, released on the 3rd of January 2021 (1 EUR =117.5967 RSD). We compared the calculated costs with average wages in Serbia, according to the official data from the National Statistical Office at www.stat.gov.rs/sr-Latn/oblasti/trziste-rada/zarade.

Regarding medical treatment in our hospital, there are two cost drivers: admission units and hospital wards. In general, the patient's stay in admission units was very short; it did not go beyond one day, so only total costs are shown for these units. The costs for ward management of the patients included medical services (e.g., physician examinations, nurse care, radiological examinations, clinical biochemistry, and pathology analyses), drugs and medical devices (excluding biochemical reagents or various laboratory consumables as they are billed cumulatively, every month, on hospital level).

The sample size calculation followed recommendations for similar cost-of-illness studies[20]. We assumed the wide dispersion of individual treatment costs, and consequently, the coefficient of variation (Cv: ratio of standard deviation to the mean) was set at one. We aimed to estimate the mean of the total treatment costs with a desired precision (V) of 20 % [V: a desired width (± W) of 95% confidence intervals (CI), where W is expressed as % of mean cost]. If our hypothesis is true, the mean total treatment costs for the non-survivors group would be outside the interval towards the higher values (e.g., above the upper limit). Using an appropriate formula, we calculated that a minimum sample size of 97 patients would verify the abovementioned assumptions. However, we decided to double the number to mitigate the influence of possible skewed (non-parametric) data distribution and provide much more precise estimations.

The collected data analysis included descriptive statistics (central tendency measures and variations) and between the study groups comparison, depending on type and data distribution (t-test or Mann-Whitney test, c^2-test or Fisher's exact test, Pearson's or Spearman's correlation). Binary logistic regression included a multivariable approach; however, we imputed a very limited set of study variables, considering methodological and sample-size limitations to avoid flawed outputs (e.g., overfitting). Receiver-operating characteristic curve (ROC) estimation was a tool for analyzing the predictive performance of total costs for final patient outcomes. For all calculations, the probability of the null hypothesis ≤0.05 was considered statistically significant.

Results

Clinical characteristics of study patients

Most of the study's population were men in the mid-sixth decade of life. There were 150 (76.5 %) subjects with a positive test of polymerase chain reaction (PCR) for SARS-CoV-2, and the others were hospitalized based on sound clinical and/or epidemiological features strongly suggestive of COVID-19 disease. The main demographic and clinical characteristics of the study subjects are presented in Table 1. Other co-morbid conditions at hospital admission were moderate-to-severe chronic kidney disease in six patients and connective tissue disease in one within the fatal outcome group, and leukemia in one patient who survived; no formal diagnoses of peripheral vascular disease, dementia, liver disease, hemiplegia, lymphoma, and acquired immunodeficiency syndrome had been documented in the patients' medical records. Information regarding symptom onset was available for 158 (80.6 %) patients, and for that subgroup, COVID-19 medical treatment lasted about three weeks. The case fatality rate was 21.9 %, as 43 study subjects died during hospital treatment.

The distribution of COVID-19 disease severity in the study cohort was as follows: five (2.6 %) asymptomatic patients, 31 (15.8 %) subjects with mild disease, 64 (32.7 %) patients with moderate disease (pneumonia), 32 (16.3 %) patients with severe disease (severe pneumonia), and 64 (32.7 %) critically ill patients. All patients in the non-survivor group succumbed after developing a critical illness. Distribution of the clinical improvement score among the patients who survived was as follows: score three in 85 patients (55.6 %), four in 47 (30.7 %), five in 12 (7.8%), six in seven (4.6 %) and seven in two patients (1.3 %). The clinical improvement score of eight was finally assigned to all patients who succumbed to the disease. Besides COVID-19 complications noted within the Table, acute respiratory distress syndrome was documented in seven patients (16.3 %) who died but not among the survivors; delirium was diagnosed formally in five (3.3 %) patients, all of whom recovered. A very short hospital stay (<5 days) was recorded for eight patients (4.1 %), but since costs for their treatment were still substantial, they were included in the final analysis set.

Treatment costs and patient outcomes

The direct medical cost of hospital care per patient in COVID-19 units was substantial (Table 2). The median total cost for the entire study cohort, compared to the national average monthly salary expressed as the total earnings (brutto) and wages without taxes and obligatory insurance expenses (netto), was higher by 39.6 % and 92.9 %, respectively. In addition, the costs were significantly higher for the subjects of the non-survivor group compared to the patients who survived (p <0.001), except for the cost at hospital admission units.

The median of patients' costs for ward health-care services, ward drugs, ward medical devices, and total costs were approximately 2.7, 2.2, 10, and 4.4 times higher, respectively, for the fatal outcome group than for the group of patients who recovered the diseases, the difference being highly statistically significant (p<0.001, for all cost types). Logarithmic base-10 transformed total cost data (performed to provide data with normal distribution) positively correlated with the patient's age (Pearson's r =0.381, p <0.001), total CCI score (Spearman's rho =0.465, p <0.001), and duration of treatment within the hospital (Pearson's r =0.585, p <0.001).

In addition, every one-point increase in a patient's total CCI score and every 100-Euros increase in a patient's total hospital treatment costs significantly elevated the odds for fatal outcome by 80.4 % [odds ratio (OR): 1.804, 95 % CI of OR: 1.408-2.311, p <0.001) and 5 % (OR: 1.050, 95 % CI of OR: 1.029-1.072, p <0.001), respectively (the model with two variables). ROC curve for the prediction of a fatal outcome based on the total cost had an area under the curve (AUC) of 0.825 (95 % CI of AUC: 0.752-0.897, p <0.001) (Figure 1). The cut-off value (calculated by Youden's rule) of 1,930.61 Euros for the total costs had 74.4 % sensitivity and 81.7 % specificity for the prediction of patients dying from COVID-19 disease during hospital treatment.

The standardized cost analysis

The additional cost analysis included standardized values - costs per patient per day of hospital treatment. Taking into account these data, the median of patients' costs for ward health-care services, ward drugs, ward medical devices, and total costs were almost 3, 9.1, 10.9, and 4.6 times higher, respectively, for the group with a fatal outcome than for the group of patient who recovered the disease, the difference being highly statistically significant (Table 3). Logarithmic base-10 transformed total cost per day was positively correlated with the patient's

Table 1: Demographic and main clinical characteristics of the 196 adult patients admitted to the COVID-19 ward units of a tertiary center during the first wave of the pandemic who were included in this observational, retrospective, cost-of-illness study.

Variable	All patients (n =196)	Survivors (n =153)	Non-survivors (n =43)	Statistical test; p
Age (years)	58.4 ± 15.3 (60, 21, 19-88)	55.6 ± 14.9 (58, 22, 19-88)	68.3 ± 12.4 (70, 20, 45-88)	T =5.1; p <0.001
Gender (male)	118 (60.2)	92 (60.1)	26 (60.5)	χ^2 <0.1; p =0.968
Hypertension	87 (44.4)	65 (42.5)	22 (51.2)	χ^2 =1.0; p =0.312
Myocardial infarction history	12 (6.1)	9 (5.9)	3 (7.0)	χ^2 <0.1; p =0.728
Chronic heart failure	8 (4.1)	3 (2.0)	5 (11.6)	χ^2 =8.1; p =0.014
Cerebrovascular accident or TIA history	3 (1.5)	1 (0.7)	2 (4.7)	χ^2 =3.6; p =0.122
Chronic obstructive pulmonary disease	28 (14.3)	13 (8.5)	15 (34.9)	χ^2 =19.1; p <0.001
Peptic ulcer disease	5 (2.6)	3 (2.0)	2 (4.7)	χ^2 =1.0; p =0.302
Diabetes mellitus, uncomplicated	16 (8.2)	12 (7.8)	4 (9.3)	χ^2 =0.1; p =0.756
Diabetes mellitus, complicated	19 (9.7)	12 (7.8)	7 (16.3)	χ^2 =0.1; p =0.756
Solid tumor	3 (1.5)	2 (1.3)	1 (2.3)	χ^2 =2.7; p =0.140
CCI, score	2.3 ± 1.9 (2, 3, 0-8)	1.8 ± 1.7 (2, 3, 0-8)	3.8 ± 1.8 (4, 3, 1-8)	z =-5.9; p <0.001
CCI, survival	75.9 ± 29.2 (90, 43, 0-98)	82.6 ± 23.6 (90, 21, 0-98)	51.9 ± 34.3 (53, 69, 0-96)	
COVID-19 disease duration / hospital treatment (days)**	23.4 ± 8.1 (23, 9, 4-53; 158)	23.8 ± 8.1 (23, 10, 4-53; 128)	21.5 ± 8.1 (21, 13, 7-38; 30)	t =1.4; p =0.161
Hospital stay (days)**	15.2 ± 7.0 (15, 7, 1-39)	15.8 ± 6.6 (15, 7, 1-39)	13.4 ± 8.1 (12, 11, 1-30)	z =-2.3; p <0.024
Pneumonia	160 (81.6)	117 (76.5)	43 (100)	χ^2 =12.4; p <0.001
Sepsis	64 (32.7)	21 (13.7)	43 (100)	χ^2 =113.6; p <0.001
Septic shock	26 (13.3)	2 (1.3)	24 (55.8)	χ^2 =86.7; p <0.001
Acute coronary syndrome	8 (4.1)	3 (2.0)	5 (11.6)	χ^2 =8.1; p =0.014
High-flow oxygen	15 (7.7)	11 (7.2)	4 (9.3)	χ^2 =14.5; p =0.001
Non-invasive ventilation	2 (1.0)	1 (0.7)	1 (2.3)	
Mechanical ventilation	45 (23.0)	9 (5.9)	36 (83.7)	
Duration of mechanical ventilation (h)	247.4 ± 161.8 (209, 246, 18-735; 40)	242.6 ± 136.6 (202, 231, 72-500; 13)	249.7 ± 175.1 (216, 269, 18-735; 27)	t =0.1; p =0.899

Values are presented as number of patients and percent in brackets, or means ± standard deviation and in brackets median, interquartile range, minimal, maximal; and number of patients, as appropriate. z: Mann-Whitney test, t: Student's t-test, χ^2: Fisher's exact or χ^2 test, p: probability for difference between the groups, CCI: Charlson Comorbidity Index, estimated 10-year survival, **: data for prehospital symptoms and treatments were missing for 39 patients and hospital stay was identified for 158 subjects.

age (Pearson's r =0.330, p <0.001) and total CCI score (Spearman's rho =0.420, p <0.001).

In addition, every one-point increase in a patient's total CCI score and every 10-Euros increase in a patient's total costs per day of hospital treatment significantly elevated the odds for fatal outcome by 2.5 times (odds ratio 2.517, 95 % CI: 1.575-4.022, p <0.001) and 36 % (odds ratio 1.360, 95 % CI: 1.226-4.509, p <0.001), respectively. ROC for the prediction of a fatal outcome based on the total cost per day had an AUC of 0.968 (95 % CI: 0.940-0.996, p <0.001) (Figure 2). The cut-off value (according to Youden's rule) of 156.46 Euros for the total costs per day had 95.3 % sensitivity and 91.5 % specificity for the prediction of patients dying from COVID-19 disease during hospital treatment.

Discussion

This study showed a substantial direct medical cost

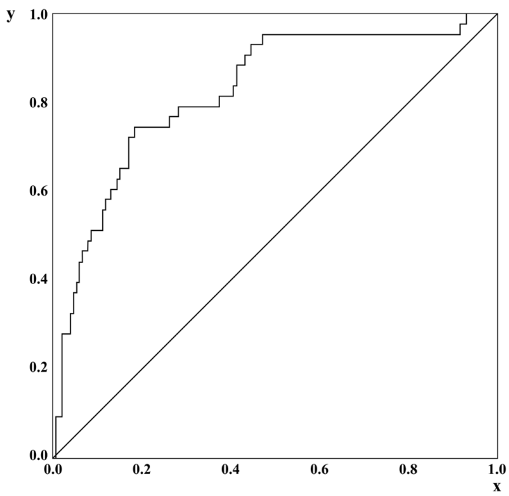

Figure 1: Receiver operating curve (ROC) for the prediction of the fatal outcome based on the total direct medical costs per patient; y axes: sensitivity, x-axes: 1 - specificity.

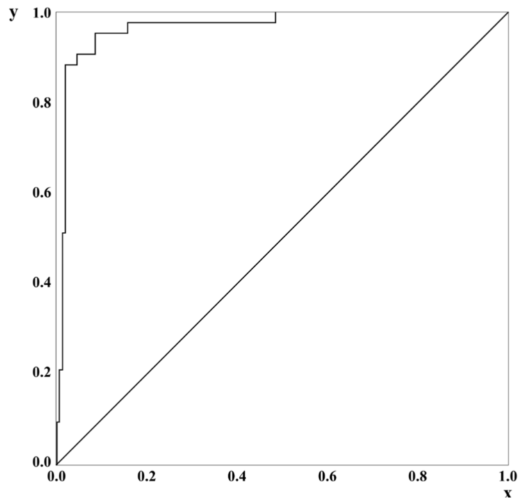

Figure 2: Receiver operating curve (ROC) for the prediction of the fatal outcome based on the direct medical costs per patient per day of hospital treatment; y axes: sensitivity, x-axes: 1 - specificity.

Table 2: Direct medical cost of hospital care (EUR) in COVID-19 units, per a patient, for total duration of hospital stay.

Costs	All patients (n =196)	Survivors (n =153)	Non-survivors (n =43)	Statistics (test; p)
Admission units	4.62 ± 14.64 (2.41, 0, 0-138.85)	4.18 ± 13.41 (2.41, 0, 0-138.85)	6.20 ± 18.45 (2.41, 3.94, 0-105.68)	z =-0.0; p =0.990
Ward unit services	1023 ± 878.34 (665.77, 823.00, 0-5685.00)	827.08 ± 732.29 (569.04, 481.71, 0-5685.00)	1722.68 ± 1000.06 (1514.10, 1457.86, 246.83-3929.43)	z =-5.9; p <0.001*
Ward unit drugs	599.80 ± 920.61 (201.70, 783.22, 0-6227.15)	377.38 ± 685.30 (125.93, 467.24, 0-6227.15)	1391.17 ± 1189.07 (1030.09, 1702.60, 15.73-5466.84)	z=-6.6; p <0.001*
Ward unit medical devices	248.62 ± 432.73 (69.30, 271.04, 0.40-3298.01)	146.19 ± 266.58 (40.28, 124.39, 0.40-1400.30)	613.07 ± 661.80 (400.52, 687.37, 13.86-3298.01)	z=-6.9; p <0.001*
Total	1876.60 ± 2083.00 (983.04, 1818.83, 146.71-13265.91; 15.6)	1354.84 ± 1608.03 (747.10, 1088.21, 146.71-13265.91; 19.0)	3733.11 ± 2503.28 (3279.16, 4023.34, 355.20-9909.61; 20.6)	z=-6.5; p <0.001*

n: number of patients, values are presented as means ± standard deviation and in brackets median, interquartile range, minimal, maximal; width of 95% CI, for total costs only as appropriate, z: Mann–Whitney test; *: significant difference.

of treating COVID-19 inpatients in a tertiary hospital setting. The median total cost per patient was 983.1 Euros, showing wide and skewed distribution, from 146.7 Euros to 13,265.9 Euros. They were significantly higher for patients with fatal outcomes (a median of 3,279.2 Euros) than those who survived (a median of 747.1 Euros). The medical services cost during the ward stay dominated among the other cost types (54.5 % of the mean total cost), which included drug prescription (32 %), medical devices (13.2 %), and ambulatory admission care (0.25 %). The main cost drivers were the comorbidity burden at admission, the patient's age, the duration of hospital treatment, and the organ support measures. Moreover, the patient's comorbidity and total costs were independent predictors of the fatal outcome. We quantified the magnitude and variability of the influence of these factors on total direct medical costs. We proposed the cost to be a marker of poor prognosis (increased risk for mortality 2.5 times per 10-Euro unit rise per day of hospital stay) with an adequate diagnostic performance (95.3 % sensitivity, 91.5 % specificity for the cut-off value of 156.46 Euros per day of hospital stay). Considering the paucity of similar data, we consider the current study a significant and original contribution to this topic.

To compare reported data with the results of other studies, one has to consider patients' characteristics and socio-economic and cultural differences among countries. Our study's patients appear more frequently to suffer severe forms of chronic diseases on admission and severe type of COVID-19 with more extended hospital stay (~2-3 times), more mechanical ventilation treatments (up to three quarters), and higher case fatality rate (up to two thirds) than those reported from Saudi Arabia and the United States[7,9]. Some discrepancies in patients' age and gender also exist between the three studies. Despite these facts, the median of the total costs in our study was 9-10

Table 3: Direct medical cost of hospital care (EUR) in COVID-19 units, per a patient for standardized cost data (per day of hospital stay).

Costs	All patients (n =196)	Survivors (n =153)	Non-survivors (n =43)	Statistics (test; p)
Admission units	0.33 ± 0.76 (0.16, 0.13, 0-6.61)	0.31 ± 0.73 (0.16, 0.11, 0-6.61)	0.40 ± 0.87 (0.17, 0.36, 0-5.03)	z =-0.2; p =0.817
Ward unit services	71.27 ± 51.85 (57.73, 58.35, 0-360.66)	52.13 ± 34.41 (44.31, 36.10, 0-360.66)	139.36 ± 45.97 (133.91, 30.88, 58.56-304.84)	z =-9.5; p <0.001*
Ward unit drugs	36.12 ± 41.59 (19.90, 50.60, 0-182.23)	20.05 ± 24.28 (9.98, 29.03, 0-159.67)	93.29 ± 40.16 (91.00, 57.18, 2.62-182.23)	z =-8.8; p <0.001*
Ward unit medical devices	16.99 ± 29.54 (5.74, 18.22, 0.04-194.00)	8.36 ± 15.28 (3.21, 9.22, 0.04-144.25)	47.70 ± 44.41 (35.07, 35.14, 2.31-194.00)	z =-8.4; p <0.001*
Total	124.71 ± 106.01 (87.66, 122.94, 23.54-512.93)	80.85 ± 59.18 (60.33, 69.19, 23.54-409.60)	280.75 ± 87.00 (275.90, 96.74, 64.15-512.93)	z =-9.4; p <0.001*

n: number of patients, values are presented as means ± standard deviation and in brackets median, interquartile range, minimal, maximal; width of 95% CI, for total costs only as appropriate, z: Mann–Whitney test; *: significant difference.

times lower than in the other two countries (the median of 38,436.71 Saudi Riyals and 12,046 United States dollars, respectively, which, based on the exchange rates of 0.23 and 0.88, corresponds to 8,841 Euros and 10,239 Euros, respectively). A similar difference (4-6 times lower) remained even when the comparison also included the results of the modeling study from South Africa, in which the cost per admission was 75,127 and 103,030 South African rands for general ward and general ward plus intensive care unit, respectively (corresponding to 8,841 Euros and 10,239 Euros, respectively, based on the exchange rate of 0.058)[8].

We could examine the data of a standardized economic indicator such as gross domestic product at purchasing power parity per capita (GDP PPP) for these countries, trying to mitigate the influence of societal and healthcare system differences on the study data extrapolations[10]. Such an endeavor revealed ~3 times less GDP PPP-to-cost ratio based on our study's data (representing an upper-middle-income society, Serbia) than the respective ratios based on data from the two studies mentioned above from high-income countries, the United States and Saudi Arabia[21]. Our results framed the cost data in the context of the average national workers' monthly earnings. They found that the median total cost was higher than the brutto and the netto national average monthly salary by 39.6 % and 92.9 %, respectively. In addition, one could consider macroeconomic and health data for Serbia as additional tools for appropriate extrapolation between current and future equivalent research in the field worldwide. For example, some key macroeconomic indicators in Serbia for 2019 were: gross domestic product of 46 billion Euros, exports of 23.3 billion Euros, imports of 27.9 billion Euros, average wages of 465.9 Euros, and an unemployment rate of 11.2 %[22]. In the same year, the total estimated population of Serbia was 6,945,235 inhabitants (48.7 % males, 51.3 % females) with an average life expectancy of 75.7 years (73.1 years for men, 78.3 years for women) and a negative trend for the natural increase rate per 1,000 inhabitants (-5.3). The leading mortality causes were cardiovascular diseases (51.6 %), neoplasms (21.7 %), respiratory system diseases (5.4 %), endocrine, nutritional, and metabolic diseases (3.2 %), and digestive system diseases (3.1 %)[23].

Other societal, economic, and cultural differences probably contributed to the observed variation in the findings between studies. The researchers could follow them using general categorizations (e.g., Saudi Arabia and the United States are classified as high-income economies while Serbia and South Africa as upper-middle-income ones) or the plethora of standardized indicators. Besides several ones which have been mentioned already in comparison of country-specific data (e.g., GNI, GDP), one could count additional indices such as the poverty headcount ratio (a socio-economic proxy) and the data regarding exports and imports of cultural goods trade (a monitor of progress towards sustainable development goals). For instance, the percentage of the population living on less than 3.2 United States dollars (USD) per day, in 2014, for the United States, Serbia, and South Africa were 1.5 %, 12.2 %, and 37.3 %, respectively; further, the values of international trade of cultural goods in 2019 for Serbia, Saudi Arabia, and the United States were 179.4 million USD, 1.6 billion USD, and 75.7 billion USD, respectively[24]. Such significant differences must be accounted for when healthcare economists make comparative analyses and extrapolations based on individual country data.

Our study has several limitations owned to its single-center and observational design with retrospective data collection and the absence of the study's outcomes adjustment for a few significant factors (e.g., prescription drugs, COVID-19 complications, and care within intensive care units). We solely analyzed the direct costs for patients' medical treatment without considering the effects of indirect factors on the overall cost burden for the hospital's economic performance, such as the implementation of infection control measures or changes in the operational productivity of the hospital personnel due to psychological stress[25,26]. In conducting the current study, logistic reasons (e.g., managerial obstacles, technical constraints of the hospital's database) precluded, in general, a more comprehensive methodological approach.

The absence of cost comparisons with the treatment of other diseases in our hospital (e.g., acute coronary syndrome or intrahospital pneumonia) made the results of our study less generalizable to the health economic environments of other countries, particularly outside the upper-middle income category. In order to diminish such limitations, we discussed several basic, macroeconomic, and healthcare data for Serbia to provide a broader context for the study's result interpretations and transferability to conditions in other countries.

Contrariwise, health economic researchers should consider the study time frame within the dynamics of the epidemic course, a circumstance of particular interest. Accumulating evidence shows that changes in SARS-CoV-2 biology and disease pattern, improvement of preventive measures, and diagnostic and treatment modalities significantly affect many pandemic-related outcomes regarding individual subjects and societies. For instance, the case-fatality rate regarding inpatients with COVID-19 in the United States decreased from 22.1 % at the onset of the pandemic (similar to our results) to 6.5 % after several months[27]. At the same time, treatment guidelines incorporated new evidence, recommending a clear shift from the diversity of empiric and off-label drug use, some with potentially harmful adverse effects, to a limited number of therapeutics with proven efficacy and safety, such as corticosteroids and oxygen administration[28-31]. We expect these changes to result in more favorable economic profiles of the novel, modified healthcare protocols. However, other disturbing trends are developing simultaneously, like the emergence of mutated virus strains with stronger pathogenicity and adverse disease outcomes and exhausting hospital resources with unapproved therapeutic uses[32,33]. Therefore, future economic research in the field could implement more detailed and diverse designs and the historical context of pandemic dynamics.

In conclusion, direct medical inpatient treatment costs for COVID-19 in the units of a tertiary institution in a developing country during the first wave of the pandemic were high, representing a significant economic burden from the perspective of health insurance payers. The link between increased costs and an ultimate unfavorable outcome should be further explored.

Conflict of interest

Authors declare no conflict of interest.

Acknowledgment

The research was partially supported by a grant of The Ministry of Education, Science and Technological Development of the Republic of Serbia No175007. The authors praise the work and dedication of physicians and nurses of COVID-19 hospital units and thank them for contributing to the patient's medical documentation, on which a large part of the study relied.

References

1. Jin H, Wang H, Li X, Zheng W, Ye S, Zhang S, et al. Economic burden of COVID-19, China, January-March, 2020: a cost-of-illness study. Bull World Health Organ. 2021; 99: 112-124.
2. Nicola M, Alsafi Z, Sohrabi C, Kerwan A, Al-Jabir A, Iosifidis C, et al. The socio-economic implications of the coronavirus pandemic (COVID-19): A review. Int J Surg. 2020; 78: 185-193.
3. Colenda CC, Applegate WB, Reifler BV, Blazer DG 2nd. COVID-19: Financial Stress Test for Academic Medical Centers. Acad Med. 2020; 95: 1143-1145.
4. Härter M, Bremer D, Scherer M, von dem Knesebeck O, Koch-Gromus U. Auswirkungen der COVID-19-Pandemie auf die klinische Versorgung, Arbeitsprozesse und Mitarbeitenden in der Universitätsmedizin: Ergebnisse einer Interviewstudie am UKE [Impact of COVID-19-pandemic on Clinical Care, Work Flows and Staff at a University Hospital: Results of an Interview-study at the UKE]. Gesundheitswesen. 2020; 82: 676-681.
5. Best MJ, Aziz KT, McFarland EG, Anderson GF, Srikumaran U. Economic implications of decreased elective orthopaedic and musculoskeletal surgery volume during the coronavirus disease 2019 pandemic. Int Orthop. 2020; 44: 2221-2228.
6. Shin JH, Takada D, Morishita T, Lin H, Bun S, Teraoka E, et al. Economic impact of the first wave of the COVID-19 pandemic on acute care hospitals in Japan. PLoS One. 2020; 15: e0244852.
7. Khan AA, AlRuthia Y, Balkhi B, Alghadeer SM, Temsah MH, Althunayyan SM, et al. Survival and Estimation of Direct Medical Costs of Hospitalized COVID-19 Patients in the Kingdom of Saudi Arabia. Int J Environ Res Public Health. 2020; 17: 7458.
8. Cleary SM, Wilkinson T, Tamandjou Tchuem CR, Docrat S, Solanki GC. Cost-effectiveness of intensive care for hospitalized COVID-19 patients: experience from South Africa. BMC Health Serv Res. 2021; 21: 82.
9. Di Fusco M, Shea KM, Lin J, Nguyen JL, Angulo FJ, Benigno M, et al. Health outcomes and economic burden of hospitalized COVID-19 patients in the United States. J Med Econ. 2021; 24: 308-317.
10. The World Bank. World Bank Open Data. Indicators. 2022. Available at: https://data.worldbank.org/indicator, date accessed: 08/02/2022.
11. Drummond M, Barbieri M, Cook J, Glick HA, Lis J, Malik F, et al. Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force report. Value Health. 2009; 12: 409-418.
12. Stenberg K, Lauer JA, Gkountouras G, Fitzpatrick C, Stanciole A. Econometric estimation of WHO-CHOICE country-specific costs for inpatient and outpatient health service delivery. Cost Eff Resour Alloc. 2018; 16: 11.
13. Lu QB, Jiang WL, Zhang X, Li HJ, Zhang XA, Zeng HL, et al. Comorbidities for fatal outcome among the COVID-19 patients: a hospital-based case-control study. J Infect. 2021; 82: 159-198.
14. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395: 1054-1062.
15. World Health Organization. Global COVID-19 Clinical Platform. RAPID CORE CASE REPORT FORM (CRF). Available at: https://apps.who.int/iris/rest/bitstreams/1287200/retrieve, date accessed: 02/05/2021.
16. World Health Organization. Clinical management of COVID-19: interim guidance, 27 May 2020. Available at: https://apps.who.int/iris/handle/10665/332196, date accessed: 31/05/2021.
17. World Health Organization. COVID-19 Therapeutic trial synopsis. Available at: https://www.who.int/publications/i/item/covid-19-therapeutic-trial-synopsis, date accessed: 02/05/2021.
18. World Health Organization. ICD-10 Version: 2019. Available at: https://icd.who.int/browse10/2019/en, date accessed: 02/05/2021.
19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40: 373-383.
20. Johnston KM, Lakzadeh P, Donato BMK, Szabo SM. Methods of sample size calculation in descriptive retrospective burden of illness studies. BMC Med Res Methodol. 2019; 19: 9.

21. United Nations. World Economic Situation Prospects. Available at: www.un.org/development/desa/dpad/wp-content/uploads/sites/45/WESP2020_Annex.pdf, date accessed: 02/05/2021.
22. National Bank of Serbia. Data. Key macroeconomic indicators. Available at: https://nbs.rs/en/finansijsko_trziste/informacije-za-investitore-i-analiticare/podaci/index.html, date accessed: 08/02/2022.
23. Institute of public health of Serbia „Dr Milan Jovanovic Batut". Health statistical yearbook of Republic of Serbia 2019. Available at: https://www.batut.org.rs/download/publikacije/pub2019a.pdf, date accessed: 08/02/2022.
24. UNESCO Institute for Statistics. Welcome to UIS.Stat. Available at: http://data.uis.unesco.org/Index.aspx, date accessed: 08/02/2022.
25. Squire MM, Munsamy M, Lin G, Telukdarie A, Igusa T. Modeling hospital energy and economic costs for COVID-19 infection control interventions. Energy Build. 2021; 242: 110948.
26. Ignjatović Ristić D, Hinić D, Banković D, Kočović A, Ristić I, Rosić G, et al. Levels of stress and resilience related to the COVID-19 pandemic among academic medical staff in Serbia. Psychiatry Clin Neurosci. 2020; 74: 604-605.
27. Nguyen NT Chinn J, Nahmias J, Yuen S, Kirby KA, Hohmann S, et al. Outcomes and Mortality Among Adults Hospitalized With COVID-19 at US Medical Centers. JAMA Netw Open. 2021; 4: e210417.
28. Milovanović DR, Janković SM, Ružić Zečević D, Folić M, Rosić N, Jovanović D, et al. Treatment of coronavirus disease (COVID-19). Med Čas. 2020; 54: 23-43.
29. Jankovic SM. Antiviral therapy of COVID-19. Scripta Medica. 2020; 51: 131-133.
30. WHO Solidarity Trial Consortium; Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med. 2021; 384: 497-511.
31. RECOVERY Collaborative Group; Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021; 384: 693-704.
32. Chalmers JD, Crichton ML, Goeminne PC, Cao B, Humbert M, Shteinberg M, et al. Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline. Eur Respir J. 2021; 57: 2100048.
33. Vernaz N, Agoritsas T, Calmy A, Gayet-Ageron A, Gold G, Perrier A, et al. Early experimental COVID-19 therapies: associations with length of hospital stay, mortality and related costs. Swiss Med Wkly. 2020; 150: w20446.