Title: Cost of illness in patients with COVID-19 admitted in three Brazilian public hospitals

Running title: COVID-19 cost of illness

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Abstract

Background: The severity and transmissibility of COVID-19 justify the need to identify the factors associated with its cost of illness (CoI). **Objectives:** To identify CoI, cost predictors, and cost drivers in the management of patients with COVID-19 from hospital and Brazil's public health system (SUS) perspectives. **Methods:** This is a multicenter study that evaluated the CoI in patients diagnosed with COVID-19 who reached hospital discharge or died before being discharged between March and September 2020. Sociodemographic, clinical, and hospitalization data were collected to characterize and identify predictors of costs per patients and cost drivers per admission. **Results:** 1,084 patients were included in the study. For hospital perspective, being overweight or obese, being between 65-74 years old, or being male showed an increased cost of 58.4%, 42.9%, and 42.5%, respectively. For SUS perspective, the same predictors of cost per patient increase were identified. The median cost per admission was estimated at US$359.78 and US$1,385.80 for the SUS and hospital perspectives, respectively. In addition, patients who stayed between 1 and 4 days in the intensive care unit (ICU) had 60.9% higher costs than non-ICU patients; these costs significantly increased with the length of stay (LoS). The main cost driver was the ICU-LoS and COVID-19 ICU daily for hospital and SUS perspectives, respectively. **Conclusion:** The predictors of increased cost per patient at admission identified were overweight or obesity, advanced age, and male sex, and the main cost driver identified was the ICU-LoS. Time-Driven Activity-Based Costing studies, considering outpatient, inpatient, and long COVID-19 are needed to optimize our understanding about cost of COVID-19.

Keywords: COVID-19; Cost of illness; Cost Analysis; Hospital Costs; Hospital Care.

Highlights

What is already known about the topic?

COVID-19 has been impacting health systems since 2020 due to the dimensions of its complications, related to both the management of the disease and to the direct use of available resources from the public health system. Some international studies have reported the high CoI of COVID-19; however, COVID-19 has had different repercussions in different countries.

What does the paper add to existing knowledge?

This is the first Brazilian study of the disease with a multicenter design, where only patients with COVID-19 confirmed by serology or real-time reverse transcription polymerase chain reaction (RT-PCR) were included. In addition, the analyzes were carried out both from the hospital perspective and from the perspective of the Brazil's public health system (SUS).

What insights does the paper provide for informing healthcare-related decision making?

This study identified the predictors of increased cost at admission (overweight or obesity, advanced age, and male sex) and the main cost driver (ICU length of stay).

Introduction

COVID-19 (coronavirus disease 2019) remains a pandemic, according to the World Health Organization (WHO). In the week between June 20 to 26, 2022, the cumulative number of cases reached 541 million worldwide, with 6.3 million cases progressing to death. In recent weeks, new cases have, on average, increased again; this increase reached 47% in the Eastern Mediterranean Region [1]. These numbers demonstrate that caution is still needed when dealing with COVID-19 and there is a potential for us to live with the disease for the unforeseeable future. Therefore, knowing the implications and costs of this disease remains important.

During the first pandemic wave, the Brazilian Society of Infectious Diseases estimated that 80 to 85% of the cases of the disease were mild and did not require hospitalization. On the other hand, among the 15 to 20% of cases that required hospitalization, almost a third of inpatients needed Intensive Care Unit (ICU) [2], as the infection can progress to acute respiratory distress syndrome, severe pneumonia, acute respiratory failure, multiple organ failure, and death [3]. Because of this, it is believed that patients with COVID-19 present a high cost to the Health System. Therefore, determining the costs involved in managing the disease, in addition to identifying the different cost components, provides very useful information and valuable data for the elaboration of complete economic evaluation [4].

To date, only one Brazilian study has reported the costs associated with patients with COVID-19. However, these data were reported only from a single hospital perspective, and not multiple centers [5].The objective of this study was to carry out a cost of illness analysis of patients with confirmed COVID-19 from two perspectives, hospital, and the Brazil's public health system (SUS, for its acronym in Portuguese), as well as to create a predictor model for the costs related to the SARS-CoV-2 through the correlation of clinical and sociodemographic factors.

Methods

Study design

This was a multicenter, retrospective, non-comparative, and analytical observational study with data collection from medical records and hospitalization reports of individuals hospitalized with COVID-19 in three Brazilian public hospitals.

Costs were considered from the hospital perspective, as well as from the SUS perspective. The checklists The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [6] and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [7] were used to report the study.

This study was approved by the Research Ethics Committee of the Clinics Hospital Complex of the Federal University of Paraná (CHC-UFPR) (CAAE 32022720.7.1001.0102).

Settings

The data collected came from individuals hospitalized in three Brazilian public hospitals: the Clinics Hospital Complex of the Federal University of Paraná (CHC-UFPR), a federal hospital, with a capacity of 440 beds, being considered a large size hospital; the Americo Brasiliense State Hospital of the University of São Paulo (HEAB-USP), a state hospital, with a total of 104 beds; and the University Hospital of the Western of Paraná (HUOP), a state hospital, with 279 beds, being considered a large size hospital.

Medical records of patients diagnosed with COVID-19 who were admitted to the study hospitals between March 1 and September 30, 2020, were evaluated.

Participants

All patients admitted to one of the study hospitals diagnosed with COVID-19 were included.

The following patients were excluded from the study: i) patients with suspected, but not confirmed, COVID-19; ii) patients whose medical records were not available; iii) patients who did not reach the outcome (hospital discharge or death) during the study period; iv) patients who were transferred to another hospital before reaching the primary outcome. Additionally, patients without Hospital Admission Authorization were excluded from analyzes from the SUS perspective.

Variables

Hospital discharge or death before discharge were considered the primary outcomes, as they defined the end of hospital care. Cost of hospitalization, medications, procedures, and other health resources were considered secondary outcomes, and were used as indicators of patient care costs.

Clinical, imaging, serology and/or real-time reverse transcription polymerase chain reaction (RT-PCR) were considered for the diagnosis of COVID-19, as recommended by the Brazilian Ministry of Health [8].

Data sources / measurement

Data from each patient were collected from their respective medical records, from the admission in COVID-19 care units to the hospital discharge or death before discharge; they included: i) sociodemographic data (i.e., age, sex, self-declared color); ii) comorbidities (i.e., diabetes mellitus (DM), chronic kidney disease, hypertension, asthma, chronic obstructive pulmonary disease, dyslipidemia, overweight or obesity, smoking, immunodeficiency, hypothyroidism); iii) resources (i.e., medication, materials, laboratory tests, mechanical ventilation [MV] and/or non-invasive ventilation, tracheostomy, hemodialysis, enteral nutrition and imaging tests); and iv) clinical outcome (i.e., hospital discharge or death before discharge).

Clinical data were identified through the patient's history present in the medical report. In addition to medical reports, body mass index (BMI) and/or weight and height were collected, whenever available. BMI was calculated (for all patients with available data and the variable "overweight or obesity" was adjusted for patients whose BMI did not match what had been reported, considering the World Health Organization's definition of overweight and obesity (BMI≥ 25Kg/m² and ≥ 30 Kg/m², respectively) [9]. However, for data collection and analysis purposes, patients were grouped into a single group (overweight or obesity).

Length of stay (LoS) in the emergency room, ward, or ICU was extracted from each patient's hospital admission reports.

Medications and materials were extracted from the medication/materials reports, while the laboratory tests performed were extracted from the billing reports by patient.

Costs from the perspective of the SUS were collected using a bottom-up micro-costing approach [10,11], being extracted individually from the reports of Hospital Admission Authorization of each patient. Costs from the hospital perspective were collected using bottom-up and top-down (aggregated cost technique) micro-cost approaches [10,11]. The bottom-up micro-costing technique [10,11] was used to measure the costs of drugs and imaging exams. For Hospital 2 and Hospital 3, hemodialysis cost per patient was also available, whereas for Hospital 1, the costs of laboratory tests per patient were available. The top-down micro-costing technique [10,11] was used to identify personnel costs, apportionment of costs from other administrative and auxiliary/support cost centers (i.e., distribution of various overhead items, in proportion to the department, such as hygiene and cleaning service, MV, concierge, security, laundry, sterilization, infection, nutrition, and dietetics, in addition to hemodialysis for the Hospital 1), general costs (water, energy, telephone, building maintenance and contracts for non-medical outsourced services, such as security, in addition to services provided by the foundation for the Hospital 1) and materials (hospital medical supplies, cleaning and hygiene, and gas for hospital use).

The top-down costs [10,11] were calculated considering the ratio of the total monthly cost, related to the type of accommodation (ward or ICU) by the number of patient-days, being then multiplied by the number of days that each patient was hospitalized in the respective accommodation and in the respective month.

For the Hospital 2, the estimated costs using the top-down micro-costing technique [10,11] were calculated using the monthly average of the Hospital 3 costs for the ward and ICU and multiplied by the number of days of hospitalization for each patient. This imputation was necessary because these data were missing for this hospital.

Study size

All individuals hospitalized for COVID-19 and who met the eligibility criteria were included, with no sampling technique being used.

Data analysis

The analysis of the cost of illness for both perspectives, SUS and hospital, was performed using only direct medical costs, defined as all resources that are consumed during treatment or intervention, generated by the use of health services [10].

The analysis was performed to identify and measure aggregated, and disaggregated costs related to COVID-19, cost drivers (most influential cost components per admission), as well as cost predictors (sociodemographic and clinical variables) per patients.

Top-down costs (aggregated by accommodation and month) were apportioned by patients considering the ratio of the total monthly cost of a given type of accommodation (ward or ICU) to the number of patient-days; result that was multiplied by the number of days that each patient was hospitalized in the respective accommodation, as well as varying according to the month. To identify the total cost for each patient, the costs obtained by top-down were added to the costs obtained by bottom-up.

All costs were converted into US dollars (US$) according to the study period (March-September), in which US$ 1 corresponded, on average, to R$ 5.31 [12].

Statistical analysis

For the descriptive analyzes, the continuous variables were described according to the frequency of distribution, measured through the central tendency. Thus, variables with parametric distribution were reported as mean and standard deviation, while those with nonparametric distribution were reported as median and interquartile range 25%-75% (IQR), defined using Shapiro-Wilk normality tests. Binary or categorical variables were expressed as number of cases and percentage.

Nonparametric tests were performed to compare costs between subgroups: Mann-Whitney U test was used for binary variables (sex, comorbidities, outcome, resources used) and Kruskal-Wallis test was used for variables with three or more categories (hospital of study, age group, self-declared color, overweight or obesity, pregnant, and LoS).

Since data collection was performed from medical records, the report of comorbidities was collected as “yes” or “not reported”; not reported was used as the absence of comorbidities was not a reliable information. Additionally, missing data were treated as “not reported”.

Univariate and multivariate analyzes were performed using a gamma-type generalized linear regression model (GLM) with log-link function. Univariate analyzes were used to verify the variables of significance to be included in the multiple models, and the level of significance for the variable to be included in the multivariate model was 10%, in addition to the event having occurred in at least 10% of the total population. Collinearity between the different variables was defined using clinical criteria, as well as the Variance Inflation Factor (VIF); variables with VIF >4 showed collinearity and were included in the multivariate model together as interaction variables.

Two multivariate regressions were performed. The first regression included only baseline characteristics and aimed to identify the predictors cost increase at the time of patient admission. The second model included resources use in addition to the baseline characteristics; it aimed to identify the cost drivers of COVID-19.

All statistical analyzes were performed using IBM SPSS Statistics v.26 (SPSS Inc., Chicago, Illinois, USA). The default significance level considered in the analyzes for statistical significance was two-tailed p-values $\alpha \leq 0.05$.

Data availability

The individual data collected as well as the statistical analysis report are available in the public repository The Open Science Framework – OSF [13].

Results

Considering the period between March 1 and September 30, 2020, 1,084 patients met the inclusion criteria and were included in this study, which corresponds to a total of 1,114 admissions in the hospital perspective; of these, 1,067 patients (1,090 admissions) were included in the SUS perspective (Figure 1). All patients tested positive for SARS-CoV-2 by RT-PCR or serology, in addition to clinical evaluation and/or imaging exams suggestive of COVID-19.

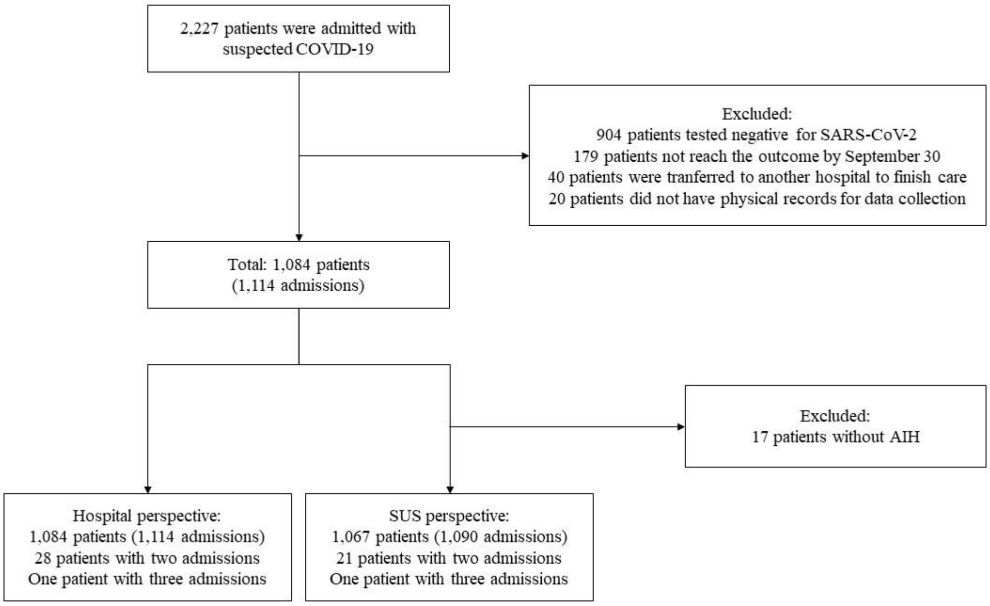

Figure 1. Flowchart of COVID-19 patients included in the study. AIH: Hospital Admission Authorization; SUS: Brazil's public health system

Missing data occurred only for the sex of three patients (0.3%) and self-declared color of 28 patients (2.6%).

Average age was 56 (±17.2) years (n=1,084), the proportion of males was statistically higher (55.4%; n=1,084). Hypertension was the most prevalent comorbidity, followed by overweight or obesity, and DM (Table 1).

TABLE 1 - Sociodemographic and clinical characteristics and comparison of direct medical costs per individual hospitalized for COVID-19, from March to September 2020.

Characteristic	n (%)	SUS cost (US$) Median (IQR)	p-value	n (%)	Hospital cost (US$) Median [IQR]	p-value
Total	1,067 (100%)	389.53 [308.17-2,135.84]		1,084 (100%)	1,423.38 [688.30-3,469.12]	
Hospital						
Hospital 1	158 (14.8%)	388.10 [310.57-916.10]	0.000*	158 (14.6%)	3,903.97 [1,607.76-7,509.96]	0.000*
Hospital 2	253 (23.7%)	727.53 [315.69-2,504.87]		256 (23.6%)	1,777.22 [1,012.97-4,095.55]	
Hospital 3	656 (61.5%)	334.54 [289.66-2,414.58]		670 (61.8%)	1,033.46 [506.51-2,325.74]	
Age						
0-34	121 (11.3%)	315.10 [286.07-1,814.76]	0.000*	121 (11.2%)	1,038.34 [459.77-2,379,85]	0.000*
35-44	140 (13.1%)	327.24 [296.33-1,206.18]		143 (13.2%)	1,376.66 [585.30-2,989.42]	
45-54	221 (20.7%)	320.13 [303.98-1,235.66]		224 (20.7%)	1,137.55 [573.47-2,546.00]	
55-64	243 (22.8%)	352.40 [299.32-2,363.68]		248 (22.9%)	1,418.52 [811.45-3,443.04]	
65-74	188 (17.6%)	754.56 [311.76-2,731.83]		192 (17.7%)	1,811.05 [738.09-5,086.72]	
75-84	115 (10.8%)	938.73 [319.52-2,762.50]		117 (10.8%)	2,204.95 [963.76-4,459.23]	
≥85	39 (3.7%)	1,266.93 [451.91-2,438.36]		39 (3.6%)	1,687.56 [932,79-3,484.95]	
Sex**						
Female	474 (44.5%)	333.36 [297.18-1,560.08]	0.004*	480 (44.3%)	1,366.09 [584.27-2,815.22]	0.003*
Male	590 (55.5%)	521.01 [309.37-2,432.38]		601 (55.4%)	1,530.15 [783.95-3,992.07]	
NR	3 (0.3%)	308.17 [284.62-4,937.52]		3 (0.3%)	732.43 [316.58-7,031.48]	
Self-declared color**						
White	834 (78.2%)	387.35 [300.83-2,155.56]	0.774	848 (78.2%)	1,368.99 [669.86-3,419.95]	0.008*
Yellow	7 (0.7%)	402.62 [284.88-3,988.41]		8 (0.7%)	876.73 [483.20-3,692.72]	
Brown	69 (6.5%)	549.91 [314.15-1,266.93]		69 (6.4%)	2,086.79 [1,181.97-6,463.02]	
Black	130 (12.2%)	332.47 [294.44-2,125.65]		131 (12.1%)	1,515.40 [693.40-2,836.80]	
NR	27 (2.5%)	328.50 [310.25-2,174.08]		28 (2.6%)	1,677.56 [707.96-2,449.09]	
Clinical factors						
Active smoking	66 (6.2%)	679.29 [315.35-3,364.20]	0.147	66 (6.1%)	2,131.75 [860.24-7,475.69]	0.015*
Asthma	33 (3.1%)	325.04 [308.17-1,892.85]	0.543	34 (3.1%)	1,435.23 [790.56-2,881.82]	0.936
CKD	37 (3.5%)	624.47 [336.41-2,320.43]	0.077	39 (3.6%)	2,494.14 [1,029.42-6,441.29]	0.015*
COPD	67 (6.3%)	886.32 [316.55-3,210.71]	0.014*	68 (6.3%)	1,934.67 [1,013.88-5,792.94]	0.012*
DM	309 (29.0%)	561.19 [311.11-2,162.71]	0.026*	313 (28.9%)	1,631.57 [932.79-4,275.82]	0.001*
DSLP	101 (9.5%)	451.91 [294.44-2,174.08]	0.887	102 (9.4%)	1,446.45 [692.76-3,594.11]	0.994
Hypertension	542 (50.8%)	626.41 [310.81-2,566.67]	0.000*	551 (50.8%)	1,690.25 [834.19-4,252.25]	0,000*
Hypothyroidism	110 (10.3%)	989.85 [312.96-2,710.97]	0.004*	113 (10.4%)	1,782.16 [838.40-4,459.23]	0.055
Immunodeficiency[1]	72 (6.7%)	963.09 [312.96-3,412.41]	0.040*	74 (6.8%)	2,106.18 [964.56-3,992.07]	0.030*
Overweight/Obesity	365 (34.2%)	698.53 [312.96-2,428.21]	0.000*	368 (33.9%)	2,136.69 [1,081.13-5,376.21]	0.000*
Pregnancy	19 (1.8%)	423.19 [286.07-879.13]	0.465	19 (1.8%)	542.09 [371.76-2,046,73]	0.001*
Other comorbidities	410 (38.4%)	458.69 [309.37-2,480.78]	0.041*	420 (38.7%)	1,661.23 [796.07-3,938.79]	0.000*

*Statistical significance: p<0.05; ** Variables analyzed with and without the NR category; [1]HIV, cancer, transplant; **AMI:** acute myocardial infarction; **DM**: diabetes mellitus; **COPD**: chronic obstructive pulmonary disease; **CKD**: chronic kidney disease; **DSLP**: dyslipidemia; **IQR**: interquartile range; **n**: number; **NR**: not reported; **SUS**: Public Health System.

When considering cost per patient admitted during the study period, a median cost of US$ 389.53 was observed for the SUS perspective compared to a median of US$ 1,423.38 for the hospital perspective. When evaluating the costs between different hospitals from the SUS and hospital perspective, Hospital 2 and Hospital 1 have the highest median costs per patient, respectively (Table 1).

In both perspectives, age groups, sex (male), and comorbidities (hypothyroidism, immunodeficiency, chronic obstructive pulmonary disease, overweight/obesity, hypertension, and DM) had significantly different mean costs per patient (Table 1). From the hospital perspective, being pregnant was associated with a lower median cost when compared to pregnancy not reported in female (US$ 542.09 vs US$ 1,368.84, p=0.001), whereas self-declaring brown was associated with a higher median cost (Table 1).

Considering the hospital perspective, the median cost per admission (n=1,114) was estimated at US$ 1,385.80 (US$ 1,188 for admissions in ward only and US$ 3,213.94 for admissions comprising ICU). The cost significantly increases as the LoS in the ward or ICU increases. It is important to highlight high cost were identified for patients with '0 day in ward' because most of these patients received intensive care during the entire admission. In addition, resource utilization was associated with an increase in the cost of hospitalizations for patients using enteral therapy, hemodialysis, MV. NIV, and tracheostomy. Additionally, death before discharge was the outcome of 250 (23.1%) admissions and was associated with higher costs (Table 2).

TABLE 2 - Use of resources and comparison of direct medical costs per admission for Covid-19, from March to September 2020, from hospital perspective.

Characteristic	n (%)	Hospital cost (US$) -Median [IQR]	p-value
Total	1,114 (100%)	1,385.80 [670.35-3,282.51]	
Hospitalization unit			
Emergency	152 (13.6%)	1,208.37 [749.55-2,303.03]	0.219
Ward	903 (81.1%)	1,188.80 [582.95-2,595.86]	0.000*
ICU	520 (46.7%)	3,213.94 [1,566.06-6,653.45]	0.000*
Length of stay in the ward			
0 day	211 (18.9%)	3,009.75 [1,116.15-6,660.96]	0.000*
1-4 days	457 (41.0%)	684.48 [351.15-1,416.73]	
5-9 days	290 (26.0%)	1,446.45 [882.10-2,476.90]	
10-19 days	136 (12.2%)	3,100.85 [1,831.57-6,419.83]	
20-29 days	13 (1.2%)	4,960.15 [3,527.58-13,218.80]	
30-39 days	4 (0.4%)	9,662.42 [6,514.44-15,641.50]	
40-49 days	2 (0.2%)	17,964.55 [14,591.53-21,337.57]	
50-59 days	1 (0.1%)	27,768.20 [27,768.20-27,768.20]	
Length of stay in the ICU			
0 day	594 (53.3%)	768.68 [399.32-1,329.15]	0.000*
1-4 days	167 (15.0%)	1,444.91 [885.79-2,142.74]	
5-9 days	135 (12.1%)	2,542.53 [1,636.44-3,946.09]	
10-19 days	148 (13.3%)	5,534.06 [3,646.42-7,926.74]	
20-29 days	50 (4.5%)	9,700.34 [6,949.10-13,773.42]	
30-39 days	13 (1.2%)	12,126.19 [10,647.93-16,974.66]	
40-49 days	6 (0.5%)	15,773.16 [11,514.48-20,724.59]	
50-59 days	0	-	
60-69 days	1 (0.1%)	36,430.00 [36,430.00-36,430.00]	
Resources use			
Enteral therapy	345 (31.0%)	5,088.75 [2,659.45-8,509.57]	0.000*
Hemodialysis	105 (9.4%)	6,996.29 [3,882.22-10,424.07]	0.000*
MV	354 (31.8%)	4,598.51 [2,284.47-8,292.15]	0.000*
NIV	764 (68.6%)	1,502.89 [786.36-3,533.83]	0.000*
Tracheostomy	71 (6.4%)	9,698.89 [5,410.10-16,460.13]	0.000*
Outcomes			
Hospital discharge	864 (77,6%)	1,092 [542.49-2,300.84]	0.000*
Death before discharge	250 (22,4%)	3,420.33 [1,545.04-6,949.10]	

*Statistical significance: $p<0.05$. **IQR**: interquartile range; **MV**: mechanical ventilation; **n**: number; **NIV**: Non-invasive ventilation; **SUS**: Public Health System.

The main component identified for the composition of the cost from the hospital perspective was cost with professionals (39.0%), followed by apportionment cost (33.7%), costs with materials and medicines (17.8%), hemodialysis (6.3%), imaging exams (2.1%), and costs with laboratory test (1.0%) (Figure S1 – appendix). The main component in the composition of the SUS perspective cost was ICU daily (78.1%), followed by COVID-19 treatment package (15.0%), other costs (2.6%), tomography (1.3%), hemodialysis (1.2%), enteral therapy (0.8%), physiotherapeutic treatment (0.8%), and ultrasonography (0.2%) (Figure S2 – appendix). The COVID-19 treatment package corresponds to the amount reimbursed for each patient with a minimum stay of five days, comprising the necessary actions for the clinical treatment of the hospitalized patient diagnosed with COVID-19 [14].

After performing multivariate analyzes (Table 3), the main predictor of increased cost at admission for the hospital perspective was the patient being overweight or obese (58.4% higher cost), followed by being between 65 and 74 years old (42.9%), and being male (42.5%). Patients with BMI ≤ 25kg/m^2 demonstrated a 67% higher cost, however it is not possible to confirm this due to the small number of hospitalizations in this category (7.7%).

Table 3 – Multivariable regression using a generalized linear model of gamma distribution to adjust variables to create a cost prediction for patients with COVID-19 from a hospital perspective (n=1,084).

	Beta	SE	p-value	OR	OR 95% CI	
Intercept	7.082	0.1019	0.000	1,190.80	975.21	1,454.05
Hospital (versus Hospital 3)						
Hospital 1	0.762	0.0978	0.000*	2.142	1.768	2.595
Hospital 2	0.234	0.0855	0.006*	1.264	1.069	1.495
Age (versus ≤34 years)						
35-44 years	-0.095	0.1228	0.441	0.910	0.715	1.157
45-54 years	-0.004	0.1134	0.969	0.996	0.797	1.243
55-64 years	0.225	0.1147	0.050*	1.252	1.000	1.567
65-74 years	0.357	0.1198	0.003*	1.429	1.130	1.808
75-84 years	0.272	0.1348	0.043*	1.313	1.008	1.710
≥85 years	0.084	0.1847	0.651	1.087	0.757	1.562
Self-declared color (versus white)						
Yellow	-0.494	0.3495	0.157	0.610	0.307	1.210
Brown	0.171	0.1303	0.189	1.187	0.919	1.532
Black	0.048	0.0933	0.609	1.049	0.874	1.259
Not reported	-0.221	0.2051	0.281	0.802	0.536	1.198
Sex (versus female)						
Male	0.354	0.0608	0.000*	1.425	1.265	1.606
Not reported	0.998	0.6021	0.097	2.714	0.834	8.832
Comorbidities (versus 'not reported')						
DM	0.102	0.0735	0.166	1.107	0.959	1.279
Hypertension	0.095	0.0702	0.177	1.099	0.958	1.261
Overweight/obesity (yes)	0.460	0.0732	0.000*	1.584	1.372	1.829
Overweight/obesity (no)	0.513	0.1257	0.000*	1.670	1.306	2.137

*Statistical significance: p<0.05; **CI**: confidence interval; **DM**: diabetes mellitus; **OR**: odds ratio; **SE**: standard error.

For the SUS perspective, in the multivariate analysis, the following categories of variables were associated with a significantly increase in costs: being male (37.6% higher cost), being between 65 and 74 years old or 75 and 84 years old (46.5% and 38.7% higher costs, respectively) and being overweight or obese (69.0% increase in costs) (Table S1 – appendix). For the multivariate analyzes, the hospital was included only to adjust for a likely confounding factor in both perspectives.

In the multivariate analysis for hospital perspective, when both baseline and admission variables were included, the main observed cost driver was ICU admission, with patients who stayed between 1 and 4 days in the ICU having 60.9% higher costs than patients who were not admitted to the ICU. The cost increases with the increase in LoS, reaching a prediction of 15 times higher costs for patients who were hospitalized in the ICU between 40 and 49 days when compared to individuals who were not in the ICU. Additionally, men, DM, overweight/obesity, death, non-invasive ventilation, MV with enteral therapy, and Hospital 2 predicted a cost increase from 1.1 to 1.7 times (Table 4).

Table 4 - Multivariable regression using a generalized linear model of gamma distribution to adjust the variables to identify the drivers of increased cost for patients with COVID-19 from the hospital perspective (n=1,114).

	Beta	SE	p-value	OR	OR 95% CI	
Intercept	5.916	0.0894	0.000	370.843	312.230	441.875
Hospital (versus Hospital 3)						
Hospital 1	0.989	0.0482	0.000*	2.689	2.447	2.956
Hospital 2	0.464	0.0406	0.000*	1.590	1.469	1.722
Age (versus ≤34 years)						
35-44 years	0.102	0.0583	0.078	1.108	0.988	1.242
45-54 years	0.026	0.0548	0.639	1.026	0.922	1.142
55-64 years	0.083	0.0549	0.132	1.086	0.975	1.209
65-74 years	-0.068	0.0589	0.247	0.934	0.832	1.048
75-84 years	0.014	0.0660	0.837	1.026	0.891	1.154
≥85 years	-0.010	0.0921	0.912	0.990	0.826	1.186
Self-declared color (versus white)						
Yellow	-0.045	0.1680	0.790	0.956	0.688	1.329
Brown	-0.003	0.0621	0.959	0.997	0.883	1.099
Black	0.007	0.0447	0.877	1.007	0.922	1.126
Not reported	0.042	0.0954	0.661	1.043	0.865	1.257
Sex (versus female)						
Male	0.103	0.0289	0.000*	1.108	1.047	1.173
Not reported	0.338	0.2845	0.235	1.402	0.803	2.449
Comorbidities (versus not reported)						
DM	0.105	0.0348	0.002*	1.111	1.038	1.189
Hypertension	-0.013	0.0335	0.691	0.987	0.924	1.054
Overweight/obesity (yes)	0.171	0.0587	0.003*	1.187	1.058	1.332
Overweight/obesity (no)	0.106	0.0594	0.074	1.112	0.990	1.249
Outcome (versus hospital discharge)						
Death before discharge	0.328	0.0605	0.000*	1.388	1.233	1.563
Length of stay in the ward (versus 0 days)						
1-4 days	-0.167	0.0574	0.004*	0.846	0.756	0.947
5-9 days	0.501	0.0636	0.000*	1.650	1.456	1.869
10-19 days	0.969	0.0696	0.000*	2.636	2.299	3.021
20-29 days	1.266	0.1494	0.000*	3.545	2.645	4.751
30-39 days	1.682	0.2503	0.000*	5.377	3.292	8.782
40-49 days	2.566	0.3463	0.000*	13.014	6.601	25.658
50-59 days	2.002	0.4778	0.000*	7.403	2.902	18.885
Length of stay in the ICU (versus 0 days)						
1-4 days	0.475	0.0448	0.000*	1.609	1.473	1.756
5-9 days	0.880	0.0601	0.000*	2.412	2.144	2.713
10-19 days	1.618	0.0714	0.000*	5.041	4.383	5.798
20-29 days	2.024	0.0916	0.000*	7.568	6.324	9.056
30-39 days	2.388	0.1452	0.000*	10.896	8.198	14.483
40-49 days	2.723	0.2050	0.000*	15.222	10.185	22.750
50-59 days**	-	-	-	-	-	-
60-69 days	2.479	0.4973	0.000*	4.503	4.503	31.622
NIV (versus not)						
NIV	0.217	0.0356	0.000*	1.243	1.159	1.333
Interaction MV and enteral therapy (versus not)***						
MV with ET	0.169	0.0667	0.011*	1.185	1.039	1.350
MV without ET	-0.190	0.0945	0.044*	0.827	0.687	0.995
ET without MV	0.031	0.1021	0.759	1.032	0.845	1.260

* Statistical significance: p<0.05 **no patients with ICU stay between 50-59 days; ***variables showed collinearity through the VIF test. **ET**: enteral therapy; **MV**: mechanical ventilation; **NIV**: non-invasive ventilation.

VIF test showed that MV and enteral nutrition presented collinearity, and these two variables were included in the multivariate model as interaction factors; from Table 4, it is possible to observe that the cost driver is MV, since patients who required enteral nutrition without MV showed no significant cost difference. Patients who required MV without enteral nutrition

(34/1,114) presented a 20% decrease in cost, possibly because these patients, in most cases, died more quickly (26/34) or used MV for short period [2 (IQR 1-3) days].

For the SUS perspective, the variables included in the multivariate analysis were different, as only those identified in the Hospital Admission Authorizations were included. The estimated median cost per admission was US$ 359.78 (US$ 428.72 for admissions that included the COVID-19 treatment package). COVID-19 ICU stay was associated with the highest costs, reaching a median of US$ 14,026.81 for patients with a stay between 40 and 49 days (Table S2 – appendix). In the multivariate analysis for the SUS perspective, the main cost driver was the COVID-19 ICU stay (Table S3 – appendix).

Discussion

COVID-19 has become a public health problem, being a matter of great concern to managers and health professionals. The first months of the pandemic were the most critical, given the lack of knowledge about the disease, the lack of a treatment options with proven efficacy and the beginning of vaccine development.

To our knowledge, there is no published cost of illness study with the objective of predicting the cost increase based on available data at patient admission (i.e., baseline data). This information may be of great value, since it may help optimizing hospitals budget management. Our study showed that being aged between 55-64, 65-74 and 75-84 years, being male and being overweight or obese are related to an increase of 25.2%, 42.9%, 31.3%, 42.5% and 58.4%, respectively, in patient cost.

Being overweight or obese was associated with increased patient cost at admission. The worsening of obese patients was shown in a systematic review with meta-analysis where obese patients had a 2.32-fold greater probability of ICU admission and a 2.63-fold greater probability of needing MV, and 49% greater risk of death in the adjusted analysis; all these factors were related to increased patient cost [15].

A median cost per admission identified was US$ 1,385.80 for the hospital perspective, while the median cost of reimbursement made by the SUS (federal portion) was US$ 360.52, which means that SUS provided a transfer of 26% of the cost spent by the hospital through the Hospital Admission Authorization. Currently, it is known that this cost difference is due to the tripartite distribution of reimbursement in Brazil (i.e., reimbursement is shared between the municipal, the state and the federal governments). The Institute for Applied Economic Research identified that, between 2015 and 2019, federal, state, and municipal governments were responsible for financing 40%, 47%, and 13% of general admissions costs, respectively [16]. Within this proportion, there was a gap in the reimbursement that should be investigated in detail.

Difference in costs was observed between the hospitals in the study, which may be related to possible differences in the standard of care, as well as in data collection. There was a remarkable difference in the mean cost of the aggregated cost categories from hospital perspective, mainly related to the cost of professionals. From the SUS perspective the main difference was related to the cost of the ICU daily, which for hospital 1 was not reimbursed how specific COVID-19 UCI daily, but the general ICU daily, which corresponds to 37.5% of the cost of the specific COVID-19 ICU daily. In this context, studies point to the need to develop new methodologies to improve care delivery and avoid wasting already scarce resources. The Time-Driven Activity-Based Costing (TDABC) method allows for measuring costs with high precision, as well as for identification of processes that can direct actions to improve the quality of care [17].

The cost of illness study carried out at Clinic Hospital of the Faculty of Medicine of the University of São Paulo (HCFMUSP), identified an average cost of US$ 12,637.42 per admission, almost 10 times higher than the median cost identified in this study (US$ 1,385.80). However, HCFMUSP was designated for COVID-19 patients in critical conditions, while the hospitals included in our study had patients with disease severity ranging from mild to critical. Another discrepancy between the studies was that all our patients had diagnostic confirmation, in disagreement with the 17.9% of patients with negative RT-PCR or serology included in the HCFMUSP study. Additionally, 8.5% of patients did not complete care at the study hospital, with 0.6% of patients still hospitalized in the HCFMUSP study. Finally, although it was not possible to assess the correlation of hemodialysis in the patients in our study because only 9.4% of hospitalizations used this resource, 19% of patients in the HCFMUSP study used this resource, which was associated with an increase in the cost of hospitalizations [5].

Unlike the study conducted at HCFMUSP, which identified a 24% decrease in cost for patients who died [5], our study identified an increase in cost (38.7%) related to this outcome. This is due to the median LoS in ICU (10 [5-17] days) for our patients who died, corroborated by the fact that LoS was the main driver of high cost.

On the other hand, a study carried out in Colombia identified a median cost of $1,688.00 per patient, in addition to a median cost of $4,118.00 for patients hospitalized in the ICU [18]. These values are very close to those identified in our analyzes.

Finally, it is important to highlight that many patients were discharged with recommendations for rehabilitation or treatment for COVID-19-related conditions acquired during the course of the disease, but cost data were only collected from hospital admission to hospital discharge, as the treatment for any COVID-19-related condition was performed in other health units. Thus, long-term outcomes have not been assessed; future research could potentially include costs related to these outcomes, including the ones covered by a scoping review, in which 52 potential long-term outcomes related to COVID-19 were described [19]. The inclusion of these costs may increase the cost of the patient, especially those with greater severity of the disease.

This study has some limitations. Firstly, data were collected from medical records, which may cause reliability issues with regards to completeness and accuracy of the data collected.

Secondly, some categories of variables presented (age ≥85 years old, being pregnant, admission to ward, ICU for more than 20 days, and hemodialysis) showed significant results, but relied on a small number of patients, which may introduce uncertainty issues due to sample size and therefore, must be interpreted with caution. Thirdly, new SARS-CoV-2 variants and the development of vaccines, which has modified the profile of COVID-19 patients and the severity of the disease [20–22]. This study is valuable in characterizing the first wave of COVID-19 and allowing comparison with future studies that show costs of subsequent waves.

Conclusions

This multicenter study, including 1,084 patients (1,114 admissions), showed that predictors of rising cost of admission were being overweight or obese (58.4% higher cost), followed by being between 65 and 74 years old (42.9%) and male (42.5%). In addition, ICU admission was identified as the main cost driver, forecasting costs 15 times higher for patients who were hospitalized between 40 and 49 days when compared to individuals who were not in the ICU. Furthermore, patients who died also showed a 38.8% higher cost than patients who were discharged with an outcome.

Time-Driven Activity-Based Costing studies, considering outpatient, inpatient, and long COVID-19 are needed to optimize our understanding on cost of COVID-19.

Author contributions: LAO was responsible for concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; and statistical analysis. RCL was responsible for concept and design; analysis and interpretation of data; critical revision of paper; obtaining funding; and supervision. AEMM was responsible for acquisition of data; analysis and interpretation of data; critical revision of paper; and administrative, technical, and logistic support. AFB was responsible for acquisition of data; critical revision of paper; and provision of study materials. CSX was responsible for acquisition of data; analysis and interpretation of data; and critical revision of paper. ACCS was responsible for acquisition of

data; analysis and interpretation of data; and critical revision of paper. HHLB was responsible for analysis and interpretation of data; drafting of the manuscript and critical revision of paper. AFRO was responsible for acquisition of data; and critical revision of paper. PR was responsible for acquisition of data; critical revision of paper; and provision of study materials. PCM was responsible for critical revision of paper; obtaining funding; and administrative, technical, or logistic support. RV was responsible for drafting of the manuscript; and critical revision of paper. SV was responsible for acquisition of data; analysis and interpretation of data; and critical revision of paper. TRN was responsible for drafting of the manuscript; and critical revision of paper. AW was responsible for concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of paper; provision of study materials and supervision.

Conflict of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Précis: COVID-19 and its complications are associated with different care measurements and with a high cost to the health system.

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APPENDIX

Table S1 – Multivariable regression using a generalized linear model of gamma distribution to adjust variables to create a cost prediction for patients with COVID-19 from the SUS perspective (n=1,067).

	Beta	SE	p-value	OR	OR 95% CI	
Intercept	6.903	0.1214	0.000	995.265	784.464	1,262.713
Hospital (versus Hospital 3)						
Hospital 1	-1.138	0.1100	0.000*	0.320	0.258	0.397
Hospital 2	-0.168	0.0954	0.085	0.849	0.704	1.023
Age (versus ≤34 years old)						
35-44 years old	-0.160	0.1459	0.273	0.852	0.640	1.134
45-54 years old	0.048	0.1331	0.718	1.049	0.808	1.362
55-64 years old	0.167	0.1357	0.219	1.181	0.905	1.541
65-74 years old	0.382	0.1430	0.008*	1.465	1.107	1.939
75-84 years old	0.327	0.1588	0.039*	1.387	1.016	1.893
≥85 years old	0.261	0.2187	0.232	1.299	0.846	1.993
Sex (versus female)						
Male	0.319	0.0728	0.000*	1.376	1.193	1.587
Not reported	0.639	0.6730	0.343	1.894	0.506	7.084
Comorbidities (versus 'not reported')						
Hypertension	0.145	0.0772	0.061	1.156	0.993	1.344
Hypothyroidism	0.109	0.1200	0.362	1.115	0.882	1.411
Overweight/obesity (yes)	0.524	0.0864	0.000*	1.690	1.426	2.001
Overweight/obesity (no)	0.506	0.1474	0.001*	1.658	1.242	2.214

*Statistical significance: $p<0.05$. **CI**: confidence interval; **OR**: odds ratio.

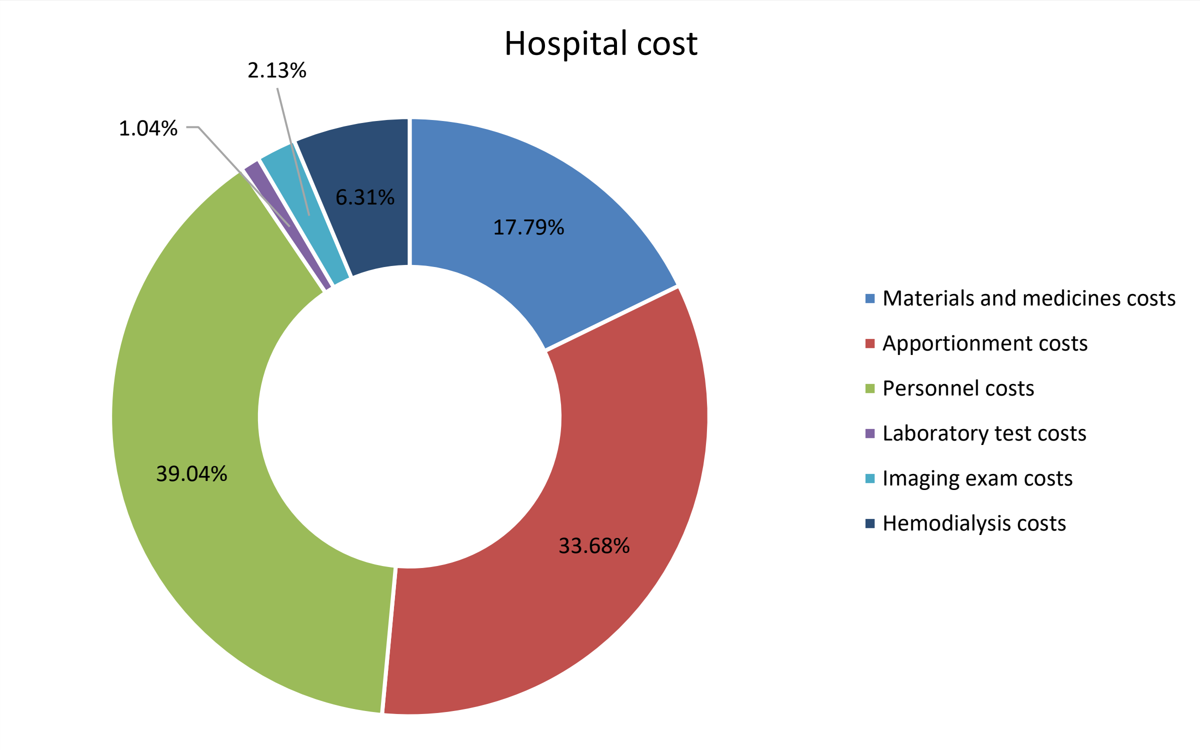

Figure S1A – Composition of the total cost from the hospital perspective.

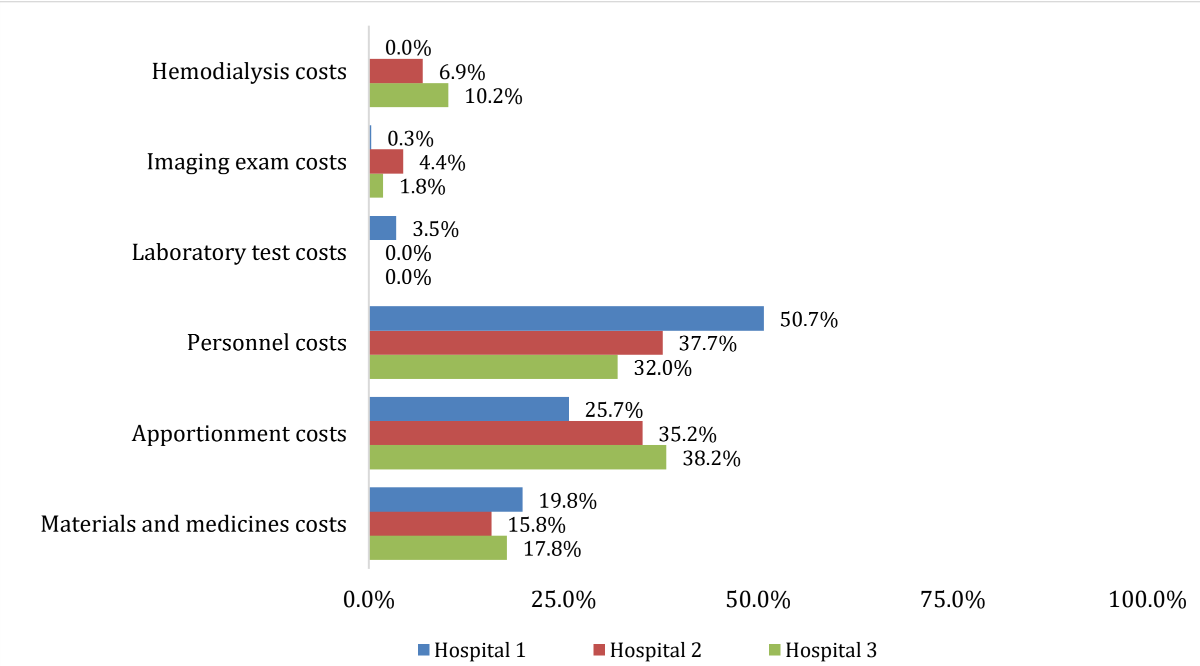

Figure S1B – Composition of the total cost of each hospital from the hospital perspective.

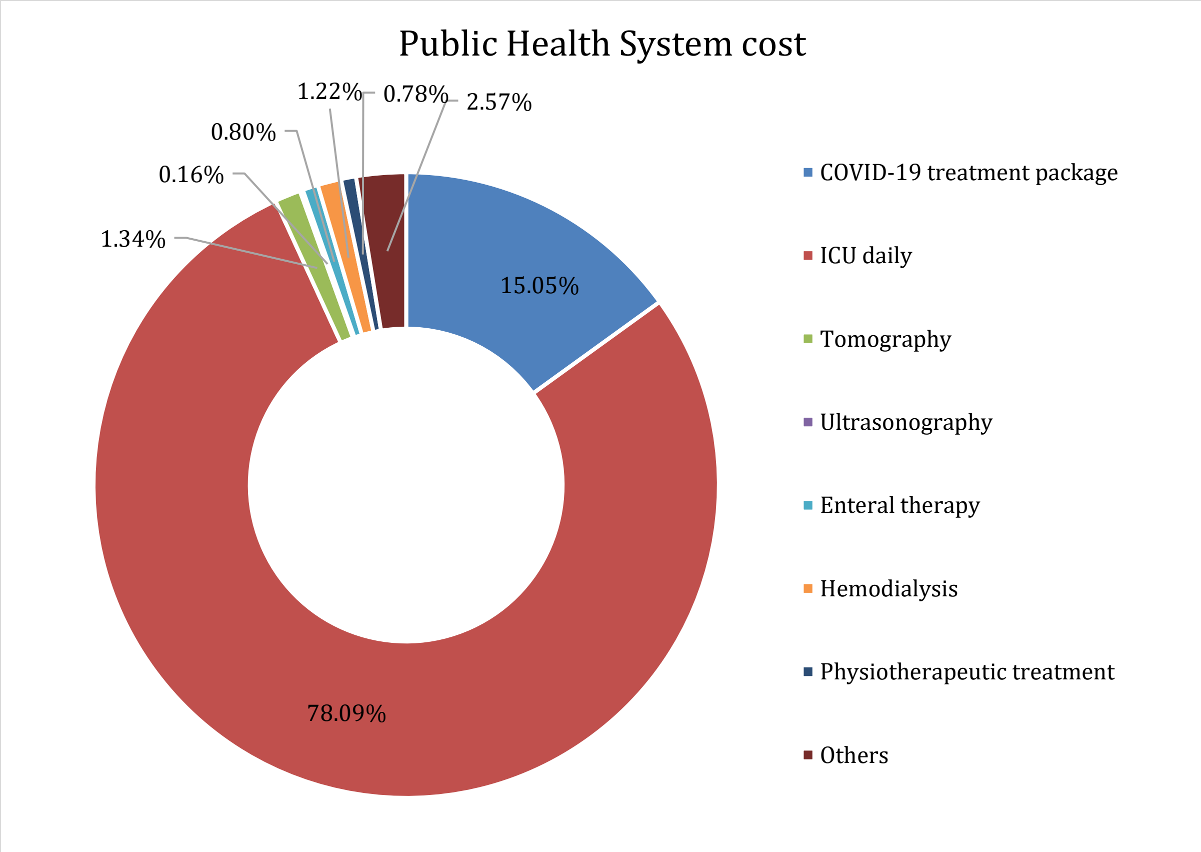

Figure S2A – Composition of the total cost from the SUS perspective

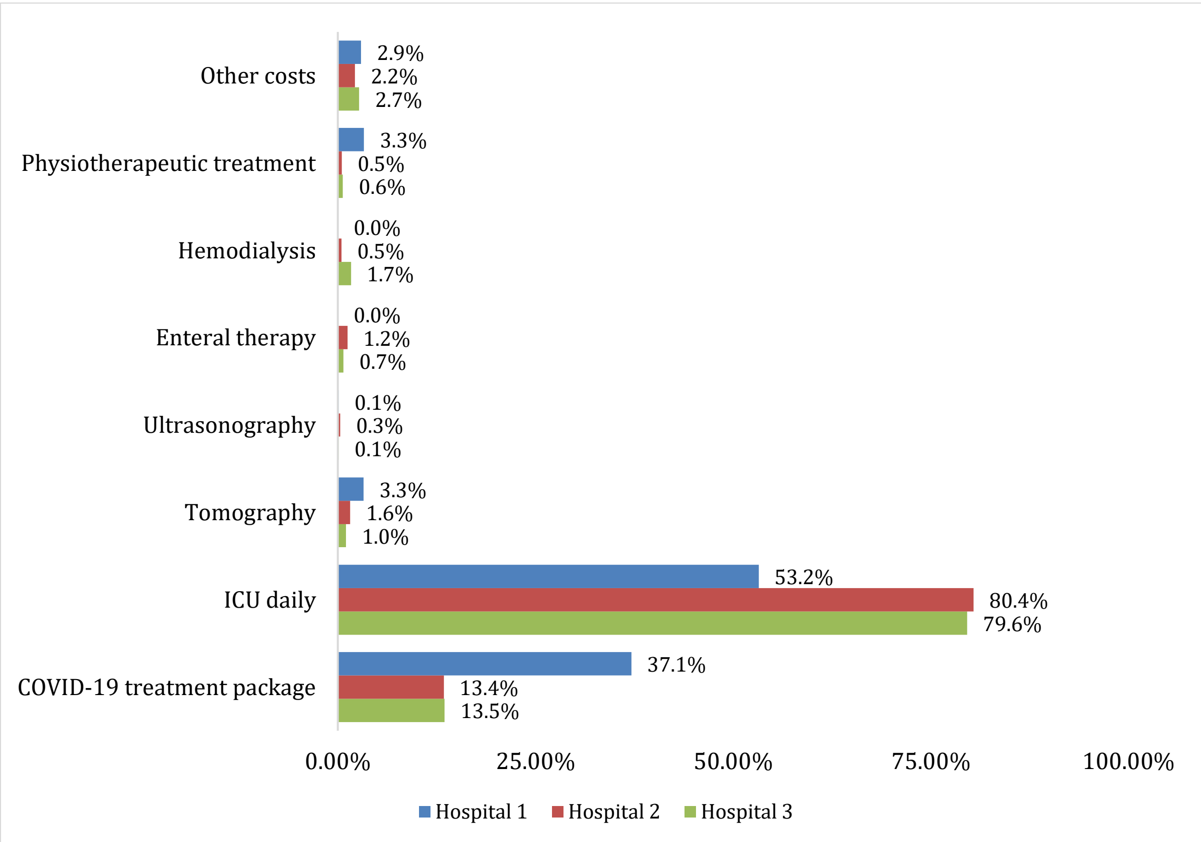

Figure S2B – Composition of the total cost of each hospital from the SUS perspective.

Table S2 – Use of resources and comparison of direct medical costs per hospitalization for Covid-19, from March to September 2020, from the SUS perspective (n=1,090).

Characteristic	n (%)	Hospital cost (US$) -Median (IQR)	p-value
Total	1,090 (100)	359.78 [299.41-2,121.17]	
COVID-19 treatment package			
Yes	941 (86.3%)	428.72 [310.81-2,293.50]	0.000*
No	149 (13.7%)	99.19 [35.74-402.62]	
COVID-19 ICU 0.000*			
Yes	411 (37.7%)	2,736.69 [1,508.63-5,094.17]	0.000*
No	679 (62.3%)	310.57 [286.00-332.66]	
COVID-19 ICU daily			
0 days	679 (62.3%)	310.57 [286.00-332.66]	0.000*
1-4 days	130 (11.9%)	1,192.42 [887.51-1,458.86]	
5-9 days	105 (9.6%)	2,432.38 [2,124.42-2,762.50]	
10-19 days	121 (11.1%)	4,641.12 [3,973.07-5,562.14]	
20-29 days	35 (3.2%)	7,981.77 [7,341.51-8,560.61]	
30-39 days	13 (1.2%)	10,567.60 [9,870.95-11,098.11]	
40-49 days	6 (0.6%)	14,026.81 [13,109.80-14,677.16]	
50-59 days	0 (0.0%)	-	
60-69 days	1 (0.1%)	21,963.40 [21,963.40-21,963.40]	
Daily			
General ICU	80 (7,3%)	1,028.72 [685.69-2,083.90]	0.000*
Longer stay	130 (11.9%)	608.62 [358.99-2,296.11]	0.000*
Resources use			
Tomography	665 (61.0%)	505.58 [314.15-2,239.66]	0.000*
Ultrasonography	259 (23.8%)	1,665.45 [360.27-4,338.66]	0.000*
Enteral therapy	249 (22.8%)	4,069.24 [2,479.47-6,041.38]	0.000*
Hemodialysis	59 (5.4%)	5,269.63 [2,736.69-7,730.19]	0.000*
Physiotherapeutic treatment	900 (82.6%)	374.33 [309.21-2,120.27]	0.002*
Outcome			
Discharge	843 (77.3%)	315.63 [289.41-892.30]	0.000*
Death before discharge	247 (22.7%)	2,740.41 [1,502.98-4,973.30]	

*Statistical significance: $p<0.05$. **IQR**: interquartile range; **MV**: mechanical ventilation; **n**: number; **NIV**: Non-invasive ventilation; **SUS**: Public Health System.

Table S4 – Multivariable regression using a generalized linear model of gamma distribution to adjust the variables to identify the drivers of increased cost for patients with COVID-19 from the SUS perspective (n=1,090).

	Beta	SE	p-value	OR	OR 95% CI	
Intercept	4.859	0.0578	0.000	128.895	115.096	144.348
Hospital (versus Hospital 3)						
Hospital 1	0.697	0.0518	0.000*	2.007	1.813	2.221
Hospital 2	0.026	0.0375	0.484	1.027	0.954	1.105
Age (versus ≤34 years)						
35-44 years	-0.090	0.0284	0.122	0.914	0.815	1.024
45-54 years	-0.069	0.0542	0.200	0.933	0.839	1.038
55-64 years	-0.031	0.0547	0.566	0.969	0.871	1.079
65-74 years	-0.092	0.0588	0.117	0.912	0.813	1.023
75-84 years	-0.112	0.0662	0.090	0.894	0.785	1.018
≥85 years	-0.135	0.0912	0.139	0.874	0.731	1.045
Sex (versus female)						
Male	0.102	0.0296	0.001*	1.107	1.045	1.173
Not reported	0.185	0.2734	0.499	1.203	0.704	2.056
Comorbidities (versus not reported)						
Hypertension	0.063	0.0317	0.046*	1.065	1.001	1.133
Hypothyroidism	-0.056	0.0481	0.247	0.946	0.861	1.039
Overweight/obesity (yes)	0.083	0.0360	0.021*	1.087	1.013	1.166
Overweight/obesity (no)	0.055	0.0590	0.348	1.057	0.942	1.187
Outcome (versus alive)						
Death	0.391	0.0421	0.000*	1.478	1.361	1.605
COVID-19 treatment package (versus no)						
Yes	0.779	0.0431	0.000*	2.180	2.003	2.371
COVID-19 ICU daily (versus 0 days)						
1-4 days	1.369	0.0479	0.000*	3.933	3.580	4.320
5-9 days	1.968	0.0530	0.000*	7.155	6.449	7.938
10-19 days	2.559	0.0529	0.000*	12.927	11.652	14.340
20-29 days	3.021	0.0855	0.000*	20.508	17.342	24.251
30-39 days	3.373	0.1339	0.000*	29.172	22.437	37.929
40-49 days	3.501	0.1959	0.000*	33.137	22.571	48.651
50-59 days**	-	-	-	-	-	-
60-69 days	3.866	0.4728	0.000*	47.774	18.899	120.616
Longer stay (versus no)						
Yes	0;276	0.0091	0.000*	1.318	1.205	1.443

* Statistical significance: p<0.05 **no patients with ICU stay between 50-59 days. **MV**: mechanical ventilation; **NIV**: non-invasive ventilation.

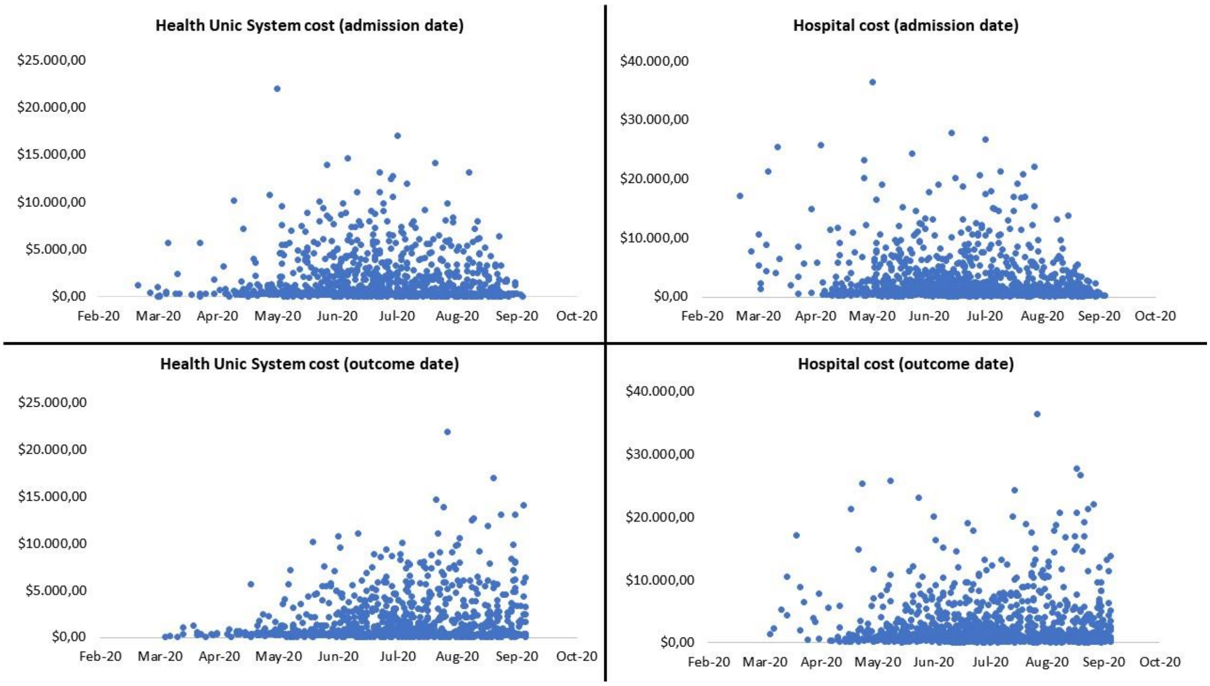

Figure S4 – Distribution of cost per hospitalization over the seven months of analysis (by admission date and by outcome date).

Table S2 – Median time of resource use per admission from hospital perspective.

Resources	**n (%)**	**Median time of use (IQR) – days**
Ward length of stay	903 (81.1%)	4 (2-7)
ICU length of stay	520 (46.7%)	6 (3-14)
MV	354 (31.8%)	8 (4-15)
Tracheostomy *	71 (6.4%)	8 (4-16)
NIV	764 (68.6%)	4 (2-7)
Hemodialysis **	105 (9.4%)	3 (2-6)
Enteral therapy	345 (31.0%)	9 (5-17)

*Data not available for Hospital 1; **session number. **ICU**: intensive care unit; **IQR**: interquartile range; **MV**: mechanical ventilation; **NIV**: non-invasive ventilation; **n**: number.