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Direct costs of hospital care according to coinfection in adult COVID-19 patients

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Abstract

Objective: To estimate the direct costs of hospital care according to coinfection in adult COVID-19 patients.
Materials and methods: A retrospective follow-up study of adult patients hospitalized for COVID-19 between March and August 2020 at the San Vicente Foundation Hospitals (Medellín and Rionegro, Colombia). Patients whose diagnosis of SARS-Cov2 pneumonia was confirmed by RT-PCR test were included. Death from any cause and length of stay were considered outcome variables. Costs were estimated in 20 20 US dollars.
Results: 365 patients with an average age of 60 years (IQR: 46-71), 40% female, were analyzed. 60.5% required an Intensive Care Unit (ICU). All-cause mortality was 2.87 per 100 patient-days. Patients admitted to the ICU who developed coinfection had an average length of stay of 27.8 days (SD:17.1) and an average cost of $23,935.7 (SD: $16,808.2); patients admitted to the ICU who did not develop a coinfection had an average length of stay of 14.7 days (SD:8.6) and an average cost of $9,968.5 (SD: $8,054.0).
Conclusion: A high percentage of patients required intensive care, and there was a high mortality due to COVID-19. In addition, a higher cost of care was observed for those patients who developed coinfection and were admitted to ICU.

Keywords: COVID-19; Health Care Costs; Coinfection

Costos directos de la atención hospitalaria según coinfección en pacientes adultos con COVID-19

Resumen

Objetivo: Estimar los costos directos de la atención hospitalaria según coinfección en pacientes adultos con COVID-19.
Materiales y métodos: Estudio de seguimiento retrospectivo de pacientes adultos hospitalizados por COVID-19 entre marzo y agosto de 2020 en los Hospitales Fundación San Vicente (Medellín y Rionegro, Colombia). Se incluyeron pacientes con diagnóstico de neumonía por SARS-Cov2 confirmado por RT-PCR. La muerte por cualquier causa y la duración de la estancia se consideraron variables de resultado. Los costos se estimaron en dólares estadounidenses de 2020.
Resultados: Se analizaron 365 pacientes con una edad promedio de 60 años (RIC: 46-71), 40% mujeres. El 60,5% requirió unidad de cuidado intensivo (UCI). La mortalidad por todas las causas fue de 2,87 por 100 pacientes-día. Los pacientes ingresados a UCI que desarrollaron coinfección tuvieron una estancia media de 27,8 días (DE:17,1) y un costo medio de $23.935,7 (DE: $16.808,2); los pacientes ingresados a UCI que no desarrollaron coinfección tuvieron estancia media de 14,7 días (DE:8,6) y costo medio de $9.968,5 (DE: $8.054,0).
Conclusión: Un alto porcentaje de pacientes requirió cuidados intensivos y hubo alta mortalidad por COVID-19. Además, se observó un mayor costo de atención para aquellos pacientes que desarrollaron coinfección y fueron ingresados a UCI.

Palabras clave: COVID-19; Costos de la Atención en Salud; Coinfección

Introduction

The COVID-19 pandemic has generated a high morbidity burden and economic impact all over the world. The main element within the crisis management strategies has been the trade-offs between economic and health impacts derived from the actions and decisions taken by governments[1]. One of the central aspects of the response to the pandemic has been strengthening the supply and response capacity in-hospital care, particularly in respiratory and critical care[2,3]. Hospital care lies between economics and health in terms of the joint analysis of outcomes and costs of care.

The response of hospitals and healthcare systems to the COVID-19 pandemic has led to high acquisition and investment costs to strengthen and increase the response capacity and

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volume of care. For example, a study in Brazil established that hospitals invested an average of I$6,800 per COVID-19 patient care, dedicated mainly to the cost of ventilators[4]. Therefore, the reimbursement or recovery of these investments and the direct costs of hospital care should be analyzed in detail to establish the impact and economic sustainability on institutions and the healthcare system[5], especially in low-and-middle-income countries.

However, information on the outcomes and costs of care for COVID-19 patients is limited, particularly in Latin American countries. Therefore, to provide evidence for decision making related to the provision of hospital care for COVID-19, we decided to estimate the direct costs of hospital care according to coinfection and admission to the intensive care unit (ICU) in adult COVID-19 patients admitted between March and August 2020 in the hospitals of San Vicente Foundation (Medellín and Rionegro), referral centers for COVID-19 patients in Antioquia, Colombia.

Material and methods

Study design and settings. A retrospective follow-up of a cohort of adult patients hospitalized for COVID-19 between March and August 2020 at the San Vicente Foundation Hospitals in Medellín and Rionegro (Antioquia, Colombia). This study was approved by the San Vicente Foundation Hospital's Ethics Committee.

As of March 1, 2020, these hospitals had 588 adult beds, 98 intermediate care beds, and 75 intensive care (ICU) beds. At the end of the period, the bed supply was 581, 97, and 136, respectively; the increase in ICU beds was 81%. At the beginning of the observation period, the average occupancy rate was 85.03%, and by the end of the period: 82.6%. Regarding the behavior of the pandemic in Antioquia, Colombia, the first confirmed infection was recorded on March 9. According to official figures from the Colombian Government (April 26, 2021; source: datos.gov.co), Antioquia's cumulative total cases and deaths as of August 2020 were 79,779 and 1,785, respectively.

Participants. Adults over 18 years old, hospitalized for, or referred from other institutions with a positive COVID-19 RT-PCR test and diagnosed with SARS Cov2 pneumonia were included. No exclusion criteria were considered.

Clinical data. Death from any cause, intensive care and oxygen support requirement, confirmation of ARDS, and coinfection were considered health outcome variables. The following were considered as personal history variables: hypertension, diabetes mellitus, COPD/asthma, heart disease, chronic kidney disease, cerebrovascular disease, human immunodeficiency virus (HIV), inflammatory bowel disease (IBD), cancer, rheumatologic disease, immunosuppression, obesity (BMI > 30), smoking, transplants, liver disease, and cirrhosis. Additionally, information on age and sex was obtained. These data were obtained from the Hospital's electronic medical records and added to the principal investigator (LGTR) database.

Costs data. The primary cost outcome was the cost of hospitalization per day per patient, and the secondary outcome was the total cost of hospitalization per patient, taking the duration of a patient episode of care as our time horizon. A micro-costing methodology was implemented to calculate costs by multiplying resource utilization by a reference manual fee. Resource utilization was obtained from hospital billing records and classified into procedure-related, laboratory exams, medical supplies, imaging, and medication costs. All resources used by each patient during their entire inpatient stay were included. The fees of procedures, laboratory exams, medical supplies, and medical images were preferably obtained from the 2020 SOAT (Compulsory Insurance for Traffic Accidents) fee manual, second source was the 2001 ISS+30% (Social Security Institute) fee manual, and third source was the healthcare provider fee. Average medication prices were obtained from the Medication Price Information System (SISMED). All costs were expressed in US dollars (source: Central Bank of Colombia -exchange rate: 3591.84 COP December 1, 2020).

Analysis perspective and time horizon. The perspective for this analysis was the healthcare provider perspective for 2020. The time horizon corresponds to the length of stay of hospitalization. Discount rates were not used since hospitalizations lasted less than one year.

Statistical analysis. Item-level resource utilization, cost, and participation on the overall cost of care are presented for resources accounting for at least 0.5% of the total cost. The frequency of utilization of the top-20 most used antibiotics among patients with bacterial coinfection is also presented. Data about utilization of other resources is available upon reasonable request to the correspondence author.

The cost estimates were obtained through probabilistic analysis, using the best-fit probability functions according to the Akaike information criterion. For this analysis, each estimate was based on 10,000 Monte Carlo simulation iterations for each cost category: procedures (including medical interventions and stay), laboratory exams, medical supplies, medical imaging, and medication costs; the total cost corresponds to the sum of each of these categories. The descriptive statistics of the distribution are presented based on admission to the ICU and confirmation of coinfection, the two variables with the most significant impact on costs and survival. The analyzed subgroups were: (1) ICU: Yes, Coinfection: Yes; (2) ICU: Yes, Coinfection: No; (3) ICU: No, Coinfection: Yes; (4) ICU: No, Coinfection: No. Additionally, to calculate the average cost per day per patient, the cost breakdown was estimated in procedures, laboratory exams, medical supplies, medical imaging, and medication costs. These results were presented using tornado graphs, which allowed us to observe the cost categories with the most significant variability.

Probability functions are presented along with 90% intervals. For health variables, descriptive statistics are shown, and in-hospital mortality and mortality rate per 100 patient-days of hospitalization were estimated. The analyses were run through Excel with the @Risk package and in Stata update 17.

Results

Between March and August 2020, 365 patients who met inclusion criteria were admitted. Their average age was 60 years old (IQR: 46 - 71), 40% were women, 77.4% had a relevant medical history, most frequently hypertension (51.9%), and one out of four patients presented obesity. The most frequently recorded manifestations of COVID-19 symptoms during hospitalization were: dyspnea (87.5%), cough (70.6%), fever over 38 degrees Celsius (66.8%), and fatigue (40.0%) (Table 1).

Regarding treatment, 60.5% of the patients required intensive care and 7.8% intermediate care, 86% required oxygen support, out of the total number of hospitalized patients, 44.4% required invasive ventilatory support, 7.8% non-invasive mechanical ventilation, 4.2% high-flow cannula, and 29.6% required oxygen support by nasal cannula or mask. All-cause mortality was 2.87 cases per 100 days/patient. Coinfections were confirmed in 18.4% of patients; 17.4% had a bacterial, 3.1% a fungal, and 0.5% a viral coinfection. Furthermore, ARDS was observed in 67.5%, while 52.7% presented severe hypoxemia (Table 2).

The patients who developed co-infection admitted to the ICU had an average stay of 27.8 days (sd:17.1) and the total cost was an average of $23,935.7 (sd: $16,808.2, min: $1,079.2, max: $74,092.6); ICU patients without co-infection had an average stay of 14.7 days (sd:8.6) and the average cost was $9,968.5 (sd: $8,054.0, min: $828.5, max: $54,042.9) (Table 3).

The probabilistic distribution of costs showed that patients with coinfection and ICU admission had higher costs than patients who did not have coinfection and were not admitted to an intensive care unit (Figure 1). Moreover, when determining the cost categories with the most significant impact on the total cost, it was observed that procedures and laboratory exams were the categories with the highest care costs for these patients (Figure 2).

Table 4 present the resources with the highest participation in the total cost of care. The use of the ICU accounted for 48.2%of costs, followed using the intermediate care unit (4.6%) and hospitalization beds (4.2%). The top six most used laboratories accounted for 6.8% of the total care costs. On the other hand, drug costs accounted for 6.5% of the total cost, with antibiotics 0.14% due to antibiotics. Among patients with bacterial coinfection (17.4%), the top five most used antibiotics were Piperacillin 4g+Tazobactam 0.5g (28.9 per patient), Ceftriaxone 1g (22.0 per patient), Vancomycin 500mg (18.9 per patient), Ciprofloxacin 100mg (18.9 per patient), and Meropenem 1g (18.3 per patient) (Table 5).

Table 1. Medical history and COVID-19 symptoms during hospitalization.

	n	%
Age, average (Q1 Q3)	60	(46 - 71)
Female	154	40.0
Medical history		
Any	298	77.4
Arterial hypertension	200	51.9
Diabetes mellitus	93	24.2
Chronic obstructive pulmonary disease (COPD)/asthma	57	14.8
Heart disease	53	13.8
Chronic kidney disease	41	10.6
Cerebrovascular disease	10	2.6
Human Immunodeficiency Virus (HIV)	3	0.8
Inflammatory Bowel Disease (IBD)	0	0
Cancer	29	7.5
Rheumatologic disease	11	2.9
Immunosuppressed	19	4.9
BMI>30	95	24.7
Smoking		
Never	121	31.4
Past	77	20.0
Active	28	7.3
No information	159	41.3
Transplanted	6	1.6
Hepatic history	10	2.6
Cirrhotic	5	1.3
COVID-19 symptoms during hospitalization		
Fever >38	257	66.8
Cough	272	70.6
Dyspnea	337	87.5
Fatigue	154	40.0
Odynophagia	67	17.4
Headache	62	16.1
Rhinorrhea	34	8.8
Nausea Vomiting	25	6.5
Diarrhea	55	14.3
Myalgias Arthralgias	80	20.8
Anosmia	26	6.8
Ageusia	35	9.1

Table 2. In-hospital management and complications

	n	%
Required intensive management		
No	122	31.7
Special care unit	30	7.8
Intensive care unit	233	60.5
Oxygen support requirement		
No	54	14.0
Mask	44	11.4
Orotracheal intubation	171	44.4
Nasal cannula	70	18.2
High flow cannula	16	4.2
NIV	30	7.8
SDRA Confirmed	260	67.5
Severity of Hypoxemia		
No	115	29.9
Slight	16	4.2
Moderate	51	13.3
Severe	203	52.7
Confirmed coinfection	71	18.4
Mortality rate	385	2.87 *

Per 100 patient-days. NIV: Non-invasive Mechanical Ventilation; ARDS: Acute Respiratory Distress Syndrome.

Discussion

This study estimated the direct costs of hospital care according to coinfection in adult COVID-19 patients in two referral hospitals in Antioquia, Colombia. The analysis included patients hospitalized in a period of high ICU bed occupancy during the first peak of the COVID-19 pandemic in the country. Moreover, as a result, high mortality in ICU and high costs of care were observed, mainly due to hospitalization in ICU and the development of coinfections. In addition, the clinical procedures and laboratory exams performed as part of patient care had the most significant impact on the cost of hospitalization.

Ghaffari Darab et al. (2020) estimated the average direct cost of care for COVID-19 patients in Fars province, Iran[6]. The average cost was $3,755 per patient (sd: 4,684), a lower estimate than our study's average total cost of care, yet similar to the average cost of care for patients who did not require intensive management and did not present coinfection. Additionally, only 7% of their patients were admitted to the ICU, versus 60.5% in our study. Also, Ghaffari Darab et al. identified that ICU and inpatient bed stays, medications, and medical supplies were the most critical components in the cost of

Table 3. Statistics of stay, total direct cost, and direct cost per day (probabilistic estimation)

	min	max	mean	SD	median	IQR
	Length of stay					
ICU: Yes Coinfection Yes	2	83	27.8	17.1	25	19.5
ICU: Yes Coinfection No	1	54	14.7	8.6	14	9
ICU: no Coinfection: Yes	2	12	7.4	3.8	8	8
ICU: no Coinfection: No	1	36	7.4	5.2	6	5
Total	1	83	14.0	11.8	11	12
	Total cost					
ICU: Yes Coinfection Yes	$1,079.2	$74,092.6	$23,935.7	$16,808.2	$19,840.2	$18,023.8
ICU: Yes Coinfection No	$828.5	$54,042.9	$9,968.5	$8,054.0	$8,420.1	$6,601.9
ICU: no Coinfection: Yes	$607.5	$5,798.6	$3,502.1	$1,863.7	$3,951.2	$3,636.7
ICU: no Coinfection: No	$97.9	$49,776.8	$3,046.8	$5,647.8	$1,652.7	$1,547.0
Total	$97.9	$74,092.6	$9,582.9	$11,752.3	$5,787.5	$9,623.4
	Cost per day					
ICU: Yes Coinfection Yes	$17.7	$8,201.9	$1,000.4	$1,024.2	$777.7	$335.9
ICU: Yes Coinfection No	$243.1	$2,376.6	$683.8	$314.1	$653.1	$323.0
ICU: no Coinfection: Yes	$202.5	$1,975.6	$605.1	$616.1	$483.2	$250.4
ICU: no Coinfection: No	$33.7	$9,955.4	$421.1	$868.8	$273.5	$182.7
Total	$17.7	$9,955.4	$636.6	$737.7	$509.2	$443.3

Min: minimum; **Max:** maximum; **SD:** standard deviation; **IQR:** interquartile range

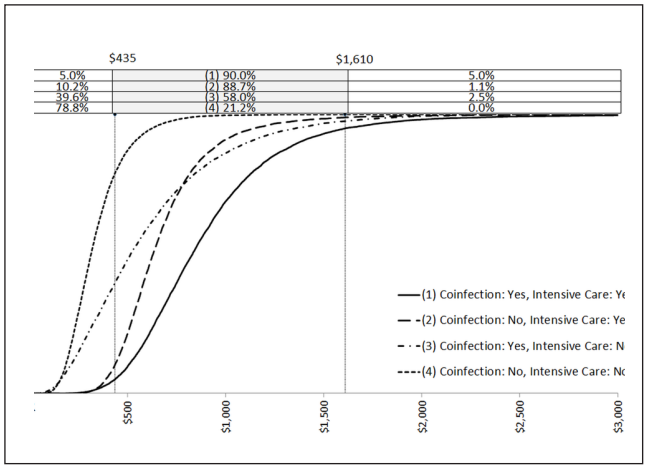

Figure 1. Cumulative probability of direct cost per day by ICU requirement and coinfection

care. Conversely, the most critical components in our study were procedures and laboratory exams, followed by medical supplies in third place.

Another study conducted in the United States by Di Fusco et al. (2020) in patients with a primary or secondary diagnosis of COVID-19 at discharge established an average hospital stay of 5 days and an average cost of $12,046[7]. In our study, the average stay was 11 days, and the average cost was $5,787.5. However, considering that by 2020 the Colombian peso was undervalued by 33.9%[8] at purchasing power parity, the average costs of care in our study were higher. Furthermore, the difference in the patients' admission profile and the heterogeneity in the complexity level of the institutions included made their ICU admission rate (21.9%) and hospital mortality (13.6%) considerably[7] lower than ours, which influenced the estimates of costs of care. Moreover, in our study, all patients had a primary diagnosis of COVID-19 and were symptomatic with pneumonia.

Similarly, a study of the Medicare beneficiary medical records showed that out of the COVID-19 related medical care, 92.6% of the costs corresponded to hospitalizations. The average cost of hospitalization was $21,752, and the average hospital stay was 9.2 days; the cost of hospitalization and length of stay was higher if the patient required a ventilator ($49,441 and 17.1 days) or passed away ($32,015 and 11.3 days)[9]. These findings are consistent with ours in the extent that they reveal the high costs of care associated with ICUs.

Barasa et al. (2021) estimated the average daily direct costs of COVID-19 patients[10]. This study estimated an average of $124.53 per critical hospitalized patient and an average of $599.61 per critical ICU patient. Comparatively, in our study, the costs were higher among hospitalized patients, while the costs reported by Berasa et al. for ICU were similar to those estimated by us for ICU patients without confirmed coinfection. However, they did not report patient characteristics to better contextualize the cost comparison according to the prognostic profile.

A brief report in Greece showed that the cost per hospital day in a general ward was €443.1, while the cost per ICU day was €2,245.5, the cost per non-ICU patient and ICU patient was estimated at €8,852 and €24,167, respectively[11]. Overall, these findings show that general bed and ICU care costs imposed a high economic burden on health systems.

Regarding the results, in our study, in-hospital mortality was 40.3%, with a rate of 2.87 deaths per 100 patient-days, and 60.5% of the patients required ICU management. These percentages were explained by the prognostic profile of the patients treated in these high complexity hospitals, considering 77.4% had some comorbidity or relevant risk factor and an average age of 60. Furthermore, a systematic revision confirmed hypertension as a risk factor for severe disease and mortality due to COVID-19.[12]. In our study, 51.9% of patients had hypertension. In addition, Colombia has had high mortality due to COVID-19, particularly among older adults[13], whose lethality has been estimated to be up to 200 times higher[14].

The results reported in this study reflect the direct costs of care in Colombia's first months of the pandemic. It is essential to highlight that although the Colombian Ministry of Health resolutions 914 and 1068 modified the fees hospitals could charge for patients with COVID-19 during the health emergency (ended June 30, 2022), our analyses were performed with fees from reference manuals to obtain comparative estimations of the cost of care. It is vital to continue analyzing the costs of care, recognizing the differences over time in characteristics such as collective lock-down measures or increased vaccination coverage, and changes related to care such as the experience curve of facilities caring for COVID-19 patients and changes in management guidelines, which affect the volume and risk profile of patients and the effectiveness and safety of treatment alternatives, impacting the costs.[15-17]. Moreover, we consider it relevant to complement these studies with cost-of-disease studies and studies of the budgetary impact of investments, expenses, and costs of care from the perspectives of the patient, the provider, and society[18].

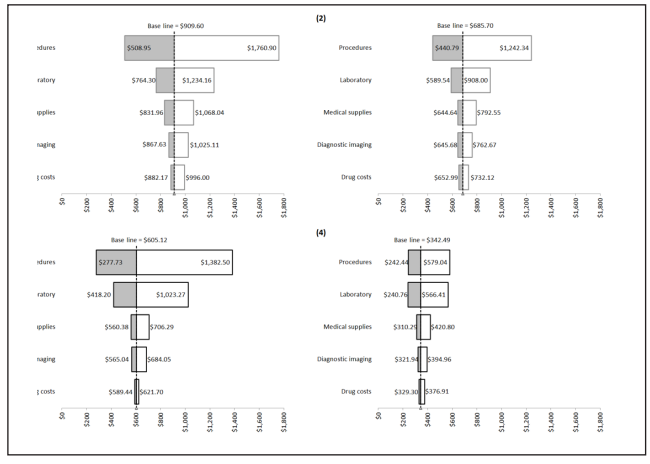

Figure 2. Tornado diagram by ICU requirement and coinfection
(1) ICU: Yes, Co-infection: Yes; (2) ICU: Yes, Co-infection: No; (3) ICU: No, Co-infection: Yes; (4) ICU: No, Co-infection: No.

Table 4. Utilization and average cost per patient of laboratory and procedures accounting for at least 0.5% of average total cost

Group	Item, unit	count	Fee	Average cost	%
Procedures	Intensive Care Unit, day	3,202	$404.9[a]	$3,552.4	48.2
Procedures	Intermediate Care Unit, day	571	$217.8[a]	$340.8	4.6
Procedures	Hospitalization (Internal medicine), day	1,288	$105.0[a]	$309.1	4.2
Laboratory	Arterial gases, test	3,511	$15.1[a]	$145.7	2.0
Laboratory	Enzymatic lactic acid, test	2,878	$11.8[a]	$93.1	1.3
Laboratory	C-Reactive Protein (CRP), Quantitative, test	2,393	$13.9[a]	$91.1	1.2
Laboratory	Ionized calcium, test	2,727	$11.8[b]	$88.4	1.2
Procedures	Leukocyte-poor red blood cells, processed unit	150	$105.6[a]	$43.4	0.6
Laboratory	Identification of virus by molecular tests, test	323	$48.7[c]	$43.1	0.6
Procedures	Continuous venovenous hemodiafiltration, day	33	$473.7[c]	$42.8	0.6
Laboratory	Glucomety, test	14,968	$0.9[b]	$38.1	0.5
Laboratory	Cutaneous oximetry record, Hour	3,472	$3.7[b]	$34.8	0.5

a: SOAT 2020 fee, **b:** ISS+30%, **c:** Provider; %: Percentage of the overall average total cost

Finally, our study has limitations to be considered in its interpretation. First, we used secondary billing sources to establish utilization, which may under or overestimate patient utilization due to administrative traceability of some elements of care. However, this is unlikely to occur for items with the most significant impact on the cost; thus, the probabilistic analyses are robust to this situation. In addition, we focused on the direct costs of care and did not consider costs associated with furniture, utilities, and other fixed costs of running the Hospital. However, healthcare systems and institutions usually know these fixed costs, and our results reduce the uncertainty in estimating the direct costs of hospital care for COVID-19 patients. Lastly, our findings come from a single high-complexity center database, limiting its generalizability to other institutions. As this is a single-center study, our results are not easily generalizable. However, they provide relevant evidence to quantify the medical and economic burden of the pandemic. Additionally, the changes in the predominance of SARS-CoV-2 variants and vaccination rates have reduced the disease's medical (complications and mortality) and economic burden. For instance, Bagshaw established in a comparative analysis by vaccination status of patients admitted to the ICU in Alberta, Canada, avoidable costs of up to CAD 61.33 among the unvaccinated, compared to CAD 2.06 million among the partially vaccinated (one dose received)[19]. Nevertheless, our results provide part of the overall picture for the analysis of the economic burden of the pandemic.

Nevertheless, our study also has strengths. We analyzed total and average daily costs according to patient complication profiles, generating more specific information for future analysis and cost modeling exercises. This analysis approach is robust to the differences in mortality costs, which are considerably high in patients hospitalized by COVID-19. In addition, we presented a detailed description of patients accor-

Table 5. Average utilization of the 20 most used antibiotics in patient with bacterial coinfection (n = 67)

	count	Uses/patient	cost*
Piperacillin 4g + tazobactam 0.5g	1,934	28.9	$1,244.3
Ceftriaxone 1g	1,475	22.0	$49.9
Vancomycin 500mg	1,266	18.9	$244.6
Ciprofloxacin 100mg/10ml	1,266	18.9	$170.9
Meropenem 1g	1,224	18.3	$221.5
Cefepime 1g	1,107	16.5	$60.1
Ampicillin 1g + sulbactam 0.5g	1,034	15.4	$117.7
Oxacillin 1g	755	11.3	$47.3
Clindamycin 600mg/4ml	446	6.7	$310.8
Amikacin 500mg/2ml	182	2.7	$4.0
Linezolid 600mg/300ml	153	2.3	$103.0
Ampicillin 1g	152	2.3	$2.8
Clarithromycin 500mg	142	2.1	$105.8
Cefazoline 1g	84	1.3	$8.7
Gentamicin 160mg/2ml	51	0.8	$3.9
Doxycycline 100mg	42	0.6	$7.6
Aztreonam 1g	42	0.6	$4.6
Daptomycin 500mg	38	0.6	$56.7
Trimethoprim 80mg/5ml + Sulfamethoxazole	35	0.5	$0.7
Ciprofloxacin 500mg	33	0.5	$16.8

***:** average price from SISMED.

ding to comorbidities and relevant risk factors, management, and health outcomes, which allows a better contextualization of care costs according to specific needs, providing relevant evidence for decision-making in trade-offs between health and economics.

In conclusion, according to the results of this study, a considerable percentage of patients at the San Vicente Foundation Hospitals in Medellín and Rionegro (Antioquia, Colombia) required intensive care. In addition, there was high mortality due to COVID-19. Moreover, a higher cost of care was observed in patients with coinfection and admitted to the ICU, resulting in a high economic burden for the healthcare system. Furthermore, given the high ICU mortality and cost of care, our findings support the urgent need to implement effective interventions, including safe and effective vaccines.

Ethical considerations

Conflicts of interest and financial disclosure. None.

Ethical board approval. This study was approved by the San Vicente Foundation Hospital's Ethics Committee (Antioquia, Colombia). No identifying information is exposed in this study.

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Conflicts of interest. The authors declare that they did not have a conflict of interest in the execution and writing of this research product.

Data availability. The data required to reproduce these findings is available upon reasonable request to the correspondence author.

Author contribution. LGTR: Conceptualization, Methodology, Investigation, Writing - Review & Editing, Supervision, DFRG: Methodology, Formal analysis, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, FART: Conceptualization, Investigation, Writing - Review & Editing, CAPU: Investigation, Writing - Review & Editing, UPB: Methodology, Formal analysis, Writing - Review & Editing, Visualization

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