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LÚCIO LINCK

THE IMPACT OF COVID-19 ON INPATIENT COSTS IN AN INTENSIVE CARE UNIT:

A Retrospective study with quantitative modeling

Porto Alegre
2021

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Thesis presented as a partial requirement to obtain a Master's Degree in Accounting by the Graduate Program in Accounting of Universidade do Vale do Rio dos Sinos - UNISINOS

Advisor: Prof. Dr. Miguel Afonso Sellitto

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ABSTRACT

Due to its potential severity and rate of dissemination, SARS-CoV-2 has raised the demand for ICU beds, with unknown economic effects on public and private health care. The aim of this study was to estimate the impact of patients with COVID-19 on ICU costs. A retrospective study, with 544 patients admitted to the intensive care unit (ICU), was performed in a private hospital in Southern Brazil. Were analyzed differences in health care costs between patients admitted with COVID-19 or by other causes using Mann-Whitney statistical tests and distribution plots. Ordinary least squares were also applied for estimating ICU costs. Out of 544 hospitalizations, 40 were identified with COVID-19. The median length of stay was seven days (interquartile range [IQR], 3·3–32·5) for patients with COVID-19 and two days (IQR, 1–5) for other patients (p-value < 0·1%). The main cost differences involved medications and medical supplies (p-value < 0·1%). The median of total costs with COVID-19 was R$ 51,752 (IQR, 16,764–149,479), while that for non-COVID-19 causes was R$ (Brazilian Real) 9,935 (IQR, 6,431–19,771). The biggest differences were found in men and in patients over 60 years old (p-value < 0·1%). Hospitalizations by COVID-19 increased direct ICU costs by 36% (95% CI 10–67%). Patients diagnosed with COVID-19 significantly increased ICU costs due to their extended length of stay and severity, particularly considering the use of medications and medical supplies; this illustrates the damage caused by this infection and the lack of knowledge on proper treatment.

Key-words: COVID-19. Health economics. Costs of health care. ICU.

RESUMO

Devido sua potencial gravidade e taxa de disseminação, o SARS-CoV-2 tem aumentado a demanda por leitos de UTI, com efeitos econômicos desconhecidos na saúde pública e privada. O objetivo deste estudo foi estimar o impacto dos pacientes com COVID-19 nos custos de UTI. Um estudo retrospectivo, com 544 pacientes internados em uma Unidade de Terapia Intensiva (UTI), foi realizado em um hospital particular no Sul do Brasil. Foram analisadas diferenças nos custos de cuidados de saúde entre pacientes admitidos com COVID-19 ou por outras causas utilizando testes estatísticos de Mann-Whitney e gráficos de distribuição. Mínimos quadrados ordinários também foram aplicados para estimar os custos de UTI. Das 544 internações, 40 foram identificadas com COVID-19. O tempo médio de permanência foi de sete dias (intervalo interquartil [IQR], 3.3-32.5) para pacientes com COVID-19 e dois dias (IQR, 1-5) para outros pacientes (p-valor < 0.1%). As principais diferenças de custos envolveram medicamentos e suprimentos médicos (p-valor < 0.1%). A mediana dos custos totais com COVID-19 foi de R$ 51.752 (IQR, 16.764-149.479), enquanto que para causas não COVID-19 foi de R$ 9.935 (IQR, 6.431-19.771). As maiores diferenças foram encontradas em homens e em pacientes com mais de 60 anos (p-valor < 0.1%). As internações pela COVID-19 aumentaram os custos diretos de UTI em 36% (IC95% 10-67%). Os pacientes diagnosticados com COVID-19 aumentaram significativamente os custos da UTI devido ao longo tempo de permanência e gravidade, especialmente considerando o uso de medicamentos e suprimentos médicos; isso ilustra os danos causados por essa infecção e a falta de conhecimento sobre o tratamento adequado.

Palavras-chave: COVID-19. Economia da saúde. Custos em Saúde. UTI.

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LIST OF ACRONYMS

COVID-19	Coronavirus Disease - 2019
ICI	Intermediate Care Unit

ICU	Intensive Care Unit
IQR	Interquartile Range
LOS	Length of Stay
NAS	Nursing Activities Score
OLS	Ordinary Least Squares
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
SD	Standard Deviation
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SDG	Sustainable Development Goals
UHS	Unified Health System
VAP	Ventilator-Associated Pneumonia
WHO	Word Health Organization

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1 INTRODUCTION

1.1 Contextualization of the Theme and Research Problem

In early December 2019, cases of pneumonia of unknown origin were reported in Wuhan's Chinese city, with clinical presentations very similar to viral pneumonia (HUANG *et al*, 2020). The pathogen of the disease has been identified as a new version of the severe acute respiratory syndrome (SARS-CoV-2) Guan *et al.* (2020), causing coronavirus disease 2019 (COVID-19). Considering the level of dissemination and severity of COVID-19, the World Health Organization (WHO) characterized it as a pandemic on March 11, 2020 (WHO, 2020). Advanced age, cardiovascular disease, hypertension, diabetes and pulmonary disease are considered risk factors for COVID-19 Mehra *et al.* (2020) and may increase the disease's lethality. In early January 2021, at least 90 million people were infected. Nearly 2 million died of COVID-19 around the world (JOHNS HOPKINS UNIVERSITY & MEDICINE, 2021). Although most countries face a public health problem with a high demand for treatment and effective medicines, governments have budgetary constraints and limited ability to buy or provide treatment (FORSYTHE *et al.*, 2020).

Estimates around the economic impacts caused by COVID-19 project losses of up to 2.7 trillion in low and middle-income countries (CENTER FOR GLOBAL DEVELOPMENT, 2020). However, if it is a new strain of the virus, the costs of hospitalization of this disease are not yet known. A study by the Johns Hopkins Bloomberg School of Public Health inferred from previous hospitalizations for pneumonia and other respiratory diseases that people, health insurers and the government could face high medical costs for hospitalizations by COVID-19 (SCIENCE DAILY, 2020). A simulation model, developed by Bartsch *et al.* (2020), estimates that if 20% of the U.S. population is infected with COVID-19, there may be a median of 2.7 million admissions to intensive care units (ICU) and 163.4 billion dollars spent on direct medical resources.

As the pandemic originated by COVID-19 spread throughout the world, intensive care unit professionals, hospital administrators, governments, legislators, and researchers had to be prepared to increase the number of critically ill patients (PHUA et al., 2020). In a study conducted with 138 patients in the city where the virus originated, the percentage of patients hospitalized for the new coronavirus and infected with pneumonia, requiring ICU care, reached 26% (WANG et al., 2020). Li *et al.* (2020b) show that 49.1% of hospitalizations originated by COVID-19 were identified as severe cases.

Given the severity and prolonged length of stay, ICU patients consume a significant amount of health resources. According to Dasta *et al.* (2005), one of the largest cost generators in the hospital environment is the intensive care unit, responsible for almost 1/3 of the total costs of hospitalization, in which it is estimated that the daily care of these units cost 3 to 5 times more than the care provided in other units. High hospitalization costs are also associated with pneumonia diagnoses, estimated at 4.4 billion dollars for 600,000 discharges of patients over the age of 65 and 3.1 billion dollars for 500,000 discharges from patients under 65 (NIEDERMAN *et al.* 1998). Concerning mechanical ventilation, hospitalizations that use this support represent approximately 33% of all patients in intensive care units and focus on a significant portion of the total cost of these units' treatment (DASTA *et al.*, 2005). These hospitalization costs may be potentiated in the current scenario since mechanical ventilation was necessary for 38.7% of severe cases of COVID-19 Guan *et al.* (2020) and severe pneumonia identified in around 25.5% of patients hospitalized the new coronavirus (YANG *et al.*, 2020).

While it is always desirable to achieve more health and more excellent responsiveness, it is not intrinsically valuable to spend an increasing amount of money on the health system, but rather to distribute the available resources equitably among the population (MURRAY; FRENK, 2000). In the existence of budgetary constraints and limitations of the system, it is necessary to choose decision-making to apply resources. Then comes the health economy, with the function of providing information and elements related to society's capacity and willingness to pay for new intervention strategies necessary for the improvement of health outcomes (WEISS; SULLIVAN, 2001). The authors define health economics as addressing these issues through quantitative methods to assist in allocating resources. Forms used in economic assessments in health, according to Husereau *et al.* (2013), are cost-benefit analysis, cost-effectiveness analysis and cost-utility analysis.

Another form used in economic health assessments is micro-costing studies. This method is used when an intervention is new, with costs of hospitalizations unknown and not yet estimated Frick (2010), as is the case of infection caused by SARS-CoV-2, allowing members of the health system to know the economic impacts of medical services. According to the authors, micro-costing studies are guided by economic theory and involve collecting detailed data for the amount and value of resources.

In the case of COVID-19, there is significant uncertainty about the possible price of any treatment or medication (FORSYTHE *et al.*, 2020). According to Phua *et al.* (2020), even if SARS-CoV-2 infects a small proportion of the 7.8 billion people on earth, many thousands are still seriously ill and require ICU care. Taking into account the high propagation rates and the high number of critically patients who require hospitalizations in intensive care units (with high consumption of hospital resources), this research seeks to answer, in an unprecedented way, the following research question: What is the impact of patients hospitalized with COVID-19 on the costs of intensive care units?

1.2 Objectives

1.2.1 General Objectives

This study aimed to evaluate the influence of COVID-19 on the costs of ICU patients in comparison to patients admitted forother causes.

1.2.2 Specific Objectives

1) Assess whether patients hospitalized with COVID-19 add or not extra costs to intensive care units;
2) Identify the ICU costs originated by COVID-19 according to the profile of hospitalized patients;
3) Identify the main factors that influence the costs of ICU patients with COVID-19

1.3 Justification

Given the population's need for medical services, challenges arise for the financing and sustainability of health systems. In this perspective, Stenberg *et al.* (2017) estimate an additional expenditure of US$274 billion per year on health by 2030 to make progress toward the goals of the SDG (sustainable development goals) 3 (healthy lives and well-being) established by the United Nations General Assembly. On an upward trajectory, health spending is growing faster than the rest of the global economy, accounting for 10% of the world's gross domestic product (OPAS, 2019).

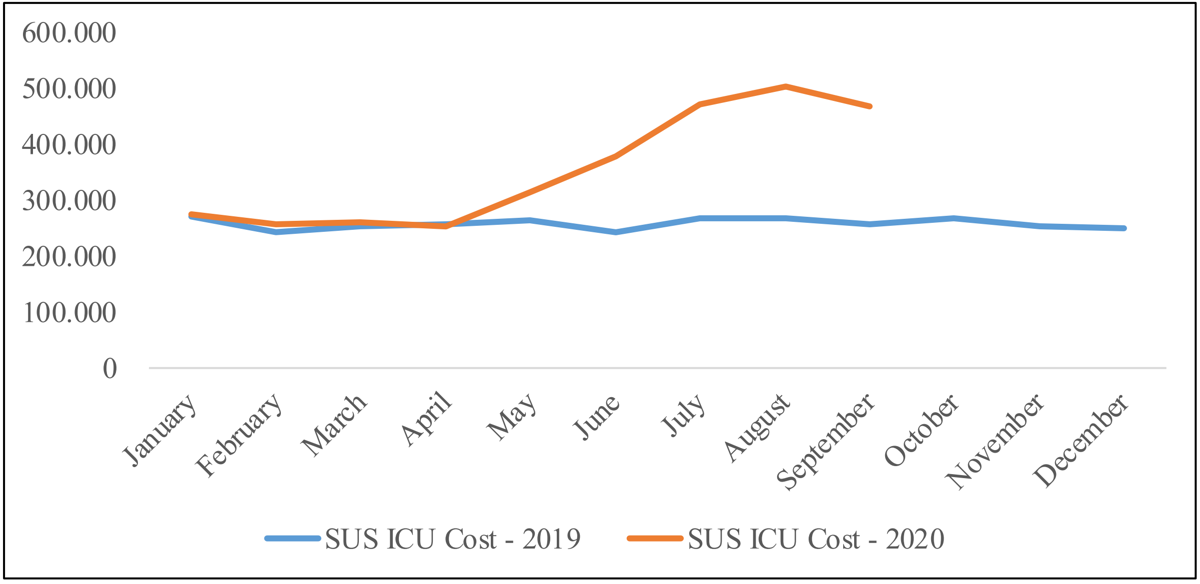
Within the context of the United States, Porter; Teisberg (2006) describe that unless there is a drastic change, the ageing population will cause costs in health to rise even more, resulting in more pressures for cost transfers, price control, rationing and reductions in services for an even more significant number of Americans. However, the resources allocated to health services are endable, restricted. Participants in a health system, such as state, insurance and population, have limited capacity to finance medical services. In this sense, the costs and efficacy of new health treatments, or the emergence of new diseases, need to be known.

Concerning COVID-19, we need to generate initial knowledge about costs to carry out analyses and relationships with treatment effectiveness.

In 2019, as shown in Graph 1 (based on the latest available update), intensive care units cost more than 3 billion for the Unified Health System (SUS) of Brazil. The median monthly ICU cost for the system in 2019 was 258 million. In 2020, using as reference the period from January to September, the monthly median was 313 million, totalling in this period growth of 37% concerning the same period of the previous year, that is, clear evidence of the pressure of the new coronavirus in the national health system.

Source: DATASUS (2020)

Graph 1 - Monthly ICU costs for the SUS: in thousands of reais (R$)



There was a significant increase in ICUs' financial resources from May 2020, a period in which the number of cases and hospitalizations for COVID-19 increased significantly in Brazil. However, we do not yet have scientific publications that elucidate and analyze the impact of hospitalizations by COVID-19 on intensive care units' costs. According to (DATASUS, 2020), the total number of ICU daily grew 12% from January to September 2020 compared to the same period of 2019. As we are still relatively far from an immunization process that reduces the spread and number of hospitalizations caused by this new virus, the combination of the time of hospitalization and the use of resources of patients with COVID-19 should continue to consume a significant share of the financial resources allocated to health. Therefore, the health system participants must be prepared for the economic challenges in the face of the high consumption of resources in the ICU.

The scientific community, mostly medical, makes efforts to reveal therapies to treat patients infected with the new coronavirus. Governments, hospitals and the medical community also step up their efforts to support critical patients with COVID-19. It is also essential to clarify the real economic impact that these patients can have on the health system. This pandemic will inevitably cause a large expenditure of financial resources to public coffers, health plans and hospitals. Therefore, it is emphasized that these participants of the system need to know the financial impacts, especially those originated from severe patients, to plan to allocate available resources in health.

Given the dimensions of Covid-19, especially with regard to lost lives and economic impacts, this study aims to discuss the economic implications for health systems related to the allocation of financial resources for the treatment of severely hospitalized patients with the Sars-Cov-2 virus. In the absence of previous studies on the costs of hospitalizations with Covid-19, the evidence of this research can help health managers to understand the relationship between the characteristics of these patients and ICU costs. The findings of this study can serve as a reference for strategies of health system members, in particular those that are mostly financed by governments and which aims to ensure the financial sustainability of the system.

1.4 Study Delimitation

This study's scope is limited to researching intensive care units' costs, more precisely on the additional costs generated by severe patients infected with the SARS-CoV-2 virus. Therefore, the costs of other inpatient units were not estimated.

The costs of hospitalizations generated by COVID-19 were compared with other diseases' costs to estimate the additional costs generated by the new coronavirus's disease. However, this study's objective was not to characterize, detail and discuss the other diseases (comparison group).

This research also aimed to analyze only the economic aspects of ICU patients with COVID-19. Therefore, the data and clinical characteristics of hospitalized patients were not included in this study.

1.5 Study Structure

The study is presented as follows: Chapter 2 addresses a review of the literature on health economics, bringing concepts about the evaluation models in health economics, followed by empirical evidence on ICU costs and characteristics of hospitalizations due to COVID-19.

Chapter 3 presents the research method used, describing the process used concerning the collection of cost and hospitalization data and the statistical and econometric model applied. Chapter 4 presents the research results through the statistical analysis of data on ICU admission patients' costs with COVID-19. Chapter 5 discusses the results of the research findings with empirical evidence on the subject. Finally, chapter 6 makes a conclusion on the study, recapping the research objectives and relating them with the results.

2. THEORETICAL BACKGROUND

This section presents a literature review to support this study's development and build the research hypotheses. Initially, a brief review on health economics is carried out. Subsequently, models of evaluations in health economics are presented, mainly on micro-costing. In order to construct research hypotheses, empirical evidence on ICU admission costs is presented. Finally, empirical evidence around hospitalizations of patients with COVID-19 in ICUs is reported.

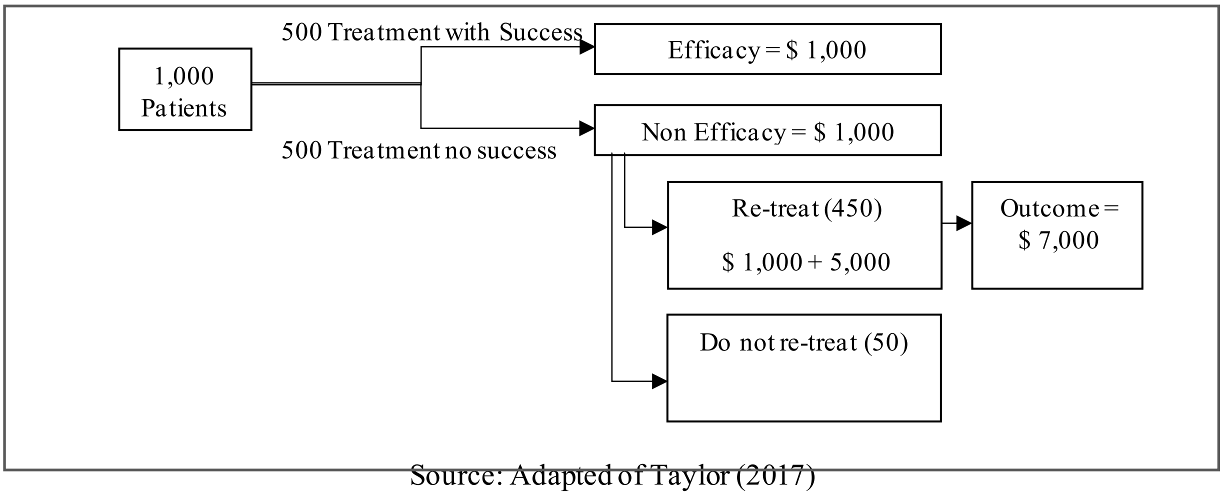
2.1 Health Economics Assessments

While the language of medicine and the clinic has to do with individuals, as the value of a statistical life, state-funded health has to do with populations (DANG; LIKHAR; ALOK, 2016). The state is part of an organism called the health system. The functions of a health system involve, among others, revenue collection, the combination of funds and purchase (MURRAY; FRENK, 2000). Revenue collection involves mobilizing money from primary sources (families and businesses) and secondary sources (governments and donor agencies). These revenues are allocated and managed by funds to the common benefit of the participants. Finally, the funds' resources are earmarked for medical intervention services, where the strategic design includes decisions on what is purchased, in the process of including or excluding interventions.

In health care, to prioritize and allocate scarce resources efficiently, to maximize the result obtained, an analytical tool is needed to consider the costs and benefits of implementing one project to the detriment of the other, thus creating a basis for decision making. Economic evaluation is an analytical tool for this decision-making that, on the one hand, involves cost, and on the other the gain (DANG; LIKHAR; ALOK, 2016). In this context, the economy is included, describing itself with the science of choice under scarcity, providing tools and models to solve prioritisation problems in health care (FRANKEN *et al.*, 2016).

Health economy models are a simplified version of reality and used to try to predict the long-term outcomes associated with a treated patient for a specific condition (TAYLOR, 2017). Let us look at an intervention decision model, as shown in Figure 1, discussed by (TAYLOR, 2017).

Figure 1 – Example of Decision Tree



Source: Adapted of Taylor (2017)

In the example referenced, assuming that 1,000 patients underwent treatment, efficacy was achieved by 50%. Assuming that the cost of the procedure is estimated at $1,000, and the additional cost for the patient who has not succeeded is $5,000, 450 patients will each have a total cost of $7,000 ($1,000 for the 1st and second treatment, plus $5,000 of additional costs). Models such as this, successful and unsuccessful treatment, help in the decision-making process (TAYLOR, 2017).

Health economics assessments have had a limited impact on restricting access to high-cost drugs in some European countries; however, the economic assessment may have helped some countries negotiate price reductions for medicines, where discussions on clinical efficacy have also extended on costs (FRANKEN *et al.*, 2016). Cost-benefit limits in health savings may vary according to the decision-makers budget. The higher the limit, the higher the budget to accommodate all health technologies (GARRISON JR *et al.*, 2018). The authors argue that consumers who make decisions about buying private health insurance or direct spending may vary in their goals and preferences, so they will choose between different health plans that, in turn, will have different limits of willingness to pay for effectiveness and cost.

2.2 Models of Evaluations in Health Economics

Specific forms of analysis in health economics, with a view to decision-making, are used to evaluate the relationships between costs and interventions in health services. These forms are divided into three types of evaluation, as synthesized by (PALMER; BYFORD; RAFTERY, 1999):

a) Cost-benefit analysis: Comparison, in currency units, between cost allocation and treatment benefit. Any net excess of monetary benefits on costs represents the gain of society's well-being. Different alternatives of therapies can be evaluated from the perspective of cost-benefit decision-making. The increased use of interventions with more significant net gain will increase efficiency;

b) Cost-effectiveness analysis: Measure health benefits in natural units, such as saved years of life or improvements in functional status (E.g. blood pressure or cholesterol). Since costs and benefits are measured in non-comparable units, their ratio provides a parameter for assessing efficiency;

c) Cost-utility analysis: Measures the effect of an intervention on quantitative and qualitative aspects of health (morbidity and mortality) using a utility-based measure, such as quality-adjusted years of life (a measure that assesses health status concerning years of life). An intervention is considered productively efficient compared to an alternative, resulting in more significant (or equal) benefits at a lower cost. In that case, cost-utility analysis can address productive efficiency and allocative efficiency.

Palmer; Byford; Raftery (1999) argue about the practical difficulties of health benefits measurements, which limited the use of the cost-benefit technique. Meanwhile, Guimarães; Barbosa; Laranjeira (2007) cost-effectiveness analyses as being preferred by health professionals. Chart 1 provides a simplified example of a cost-effectiveness application in economic analyses.

Chart 1 - Simplified cost-effectiveness ratio of two treatment options for hypertension

Analysis item	Antihypertensive A	Antihypertensive B
Cost treatment Efficacy (absolute bp reduction)	$ 2.00/day 10 mmHg	$ 1.00/day 4 mmHg
Cost-effectiveness	R$ 0.20/mmHg reduced	R$ 0.25/mmHg reduced

Source: Guimarães; Barbosa; Laranjeira (2007)

This example shows that antihypertensive A has a more advantageous cost-effectiveness ratio because it has less cost per unit of reduced blood pressure and should be a preferential option over antihypertensive B.

For calculating cost-effectiveness ratios, the accounting of costs composes the ratio's numerator, and its estimation is essential. Micro-costing studies can perform evaluations or analyses of health costs. Evaluations based on micro-costing can be presented as self-contained studies or used as entries in cost-effectiveness or cost-benefit analyses (FRICK, 2010). Micro-costing is a cost method that allows accurate estimation of economic costs for health interventions (XU; NARDINI; RUGER, 2014). According to Frick (2010), this type of study should be considered when the intervention or treatment is new and was no opportunity to calculate the average cost.

Cost estimates are fundamental in the definition of public and private health budgets, assisting in establishing reimbursement rates (LIPSCOMB *et al.*, 2009). Economic assessments are increasingly used for decisions to reimburse and provide hospital services. However, decision-making is often hampered by the enormous cost variations observed between economic assessments that consider the same hospital service (TAN, 2009b). These variations occur, among other reasons, by different methodological and cost assessment approaches. A significant cause for methodological differences concerns the level of accuracy that is addressed. The stratification of the identification and evaluation of cost components by the accuracy level results in four costing methodologies for cost evaluation (TAN, 2009b).

Figure 2 - Level of accuracy at the identification and valuation of cost

Identification of resources

\- Accuracy +

Valuation of resources

\- Accuracy +

Top-down Gross-costing	Top-down Micro-costing
Bottom-up Gross-costing	Bottom-up Micro-costing

Source: Tan (2009b)

In gross costing, cost components are defined at a highly aggregated level. In micro-costing, all relevant cost components are defined at the most detailed level. In the top-down approach, cost components are evaluated by separating the relevant costs from comprehensive sources (e.g., annual accounts or national tariffs), resulting in average unit costs per patient. In the bottom-up approach, cost components are evaluated by identifying the use of resources applied directly for a patient, resulting in specific unit costs (TAN, 2009b). From the author's perspective, the micro-costing bottom-up is the gold standard in economic assessments. It identifies all relevant cost components, evaluating each of these components for all individual patients, allowing statistical analyses to be made to detect cost differences between patients of each component. Microcosting studies are often conducted in a single or small number of centres due to the substantial efforts and coordination required to collect detailed resource utilization data (FRICK, 2010).

Health costs can be deployed into four categories, as Tan (2009a) proposed in chart 2. In a cost study, the objective is directly related to the evaluation perspective (society as a whole, patient, public or supplementary health system, or health service provider). Both will indicate which costs should be measured (DA SILVA ETGES *et al*, 2019). From society's perspective, all economic, direct and indirect costs are evaluated and included. Research that uses a social perspective should include a more comprehensive list of features in costing. Research using more limited perspectives is likely to include only a subset of costs (FRICK, 2010).

Chart 2 - Distinction of cost categories within economic assessments

Costs	Medical costs	Non-medical costs
Direct	Health service costs related to the treatment option under consideration.	Patient expenses, such as travel expenses, patient or family time, and home adequacy.
Indirect	Health service costs that do not relate to the treatment option under consideration.	Loss of productivity and reduced efficiency due to the absence of paid work.

Source: Tan (2009a)

The analysis unit is the object of interest for identifying costs, having a close relationship with the decision-making that cost information will support, considering the study's perspective (DA SILVA ETGES *et al*, 2019). In this sense, the study of Shi *et al.* (2012), based on society's perspective, used as a unit of analysis the costs associated with the treatment, dignóstic and treatment of cervical cancer.

Drawings of experimental and non-experimental (observational) studies are more frequent in the medical literature, whose difference lies in the possibility that the researcher has control over a factor's exposure (OLIVEIRA; VELLARDE; SA, 2015). Micro-costing research uses drawings of observational studies, described by Jepsen; Johnsen; Gillman (2004) in three different forms: cohort, case-control and cross-sectional. In cohort studies, patients with different exposure levels are followed up to determine the outcome's incidence in each group (exposed and non-exposed). Case-control studies determine the groups based on the result (case group and control group), in order to identify the incidence in exposed and non-exposed individuals. Cross-sectional studies, also called prevalence studies, include exposure and outcome simultaneously, without establishing a temporal relationship.

Cohort studies can be classified as prospective or retrospective. In retrospective studies, all information on exposure and outcome has already occurred before the beginning of the study. However, in prospective studies, exposure may (or may not) have already occurred, but the outcome has not yet occurred (DE OLIVEIRA; PARENTE, 2010).

2.3 Costs in Intensive Care Units

ICU costs account for much of a hospital's spendings. Medicines account for more than half the cost, and antibiotics account for most of them (KARABATSOU et al., 2016). According to Halpern; Pastores (2010), which analyzed the evolution of costs in ICUs, intensive care beds increased 6.5% (from 88,252 to 93,955), days by 10.6% (from 21 to 23 million), occupancy rates by 4.5% (from 65% to 68%) and patient-day costs at 30.4% (from US$2,698 to US$3,518). Patients admitted to intensive care units accounted for 69.4% and 45.7% of the total cost of hospitalization for medical and surgical patients, respectively (NIEDERMAN *et al.* 1998). The authors suggest that the disease's severity is an important determinant of daily resource consumption and length of stay.

With the increasing demand and cost of intensive care worldwide, it is essential to understand the organizational characteristics and variables of the care process associated with optimal outcomes and costs (CHECKLEY *et al.*, 2015). Severe disease, increased hospital stay, mechanical ventilation, and dialysis are the factors associated with escalating ICU costs (KARABATSOU *et al.*, 2016).

Dasta *et al.* (2005) determined and identified the main factors associated with ICU patients' costs who used mechanical ventilation. The average cost and length of hospital stay were US$ 31,574 and 14.4 days for patients who required mechanical ventilation and US$ 12,931 and 8.5 days for patients who did not use mechanical ventilation. The costs were higher in the first days of hospitalization, in which patients hospitalized with mechanical ventilation consumed more than 10,000 dollars per day, a value higher than the consumption of resources of patients who did not use this intervention (US$ 6,667).

Erbay *et al.* (2004) evaluated the costs and risk factors for ventilator-associated pneumonia (VAP) in adult ICUs. The average length of ICU stay in patients with and without VAP (mechanical ventilation only) was 8.0 and 2.5 days, respectively. Mortality rates were higher in patients with VAP (70.3%) about the control group (35.5%). The costs of patients with ventilator-associated pneumonia were three times higher than the control group. Higher cost differences were observed in antibiotic consumption, followed by laboratory costs.

Nanao *et al.* (2020) examined the economic and clinical effects of ventilator-associated pneumonia in Japan. Patients with VAP add 16.1 days and US$ 24,038, compared to patients who used only mechanical ventilation in the total costs of ICU stay. No differences were observed in patient-day costs between the groups evaluated. Higher severity scores were observed in the group of patients diagnosed with VAP.

In the study by Warren *et al.* (2003), patients diagnosed with VAP were, on average, 26 days hospitalized in intensive care units. Its average costs were $70,568. Multiple linear regression results estimated the cost attributable to VAP at US$ 11,897. Tracheostomy procedure was reported as the variable with the most significant association with costs.

Sosa-Hernández *et al.* (2019) used the micro-costing method to calculate the costs generated by patients diagnosed with ventilator-associated pneumonia. All cases were caused by multiresistant bacteria. The costs of their treatment exceeded the average costs for the use of antimicrobials. More than 70% of the patients diagnosed with this disease belonged to the group of men. The authors found that VAP caused by multiresistant bacteria confers the risk of increasing treatment costs.

Su *et al.* (2020) analyzed patients' costs with hospital care infections due to multidrug-resistant bacteria. Compared to the group of infections not related to multidrug-resistant bacteria, the first group presented significant differences in the hospital's overall costs, medical and nursing services, medications, and length of stay in the ICU.

Moerer *et al.* (2002) analyzed the direct costs of severe sepsis in patients admitted to Germany's intensive care units. The mean hospital mortality of severe septic patients was 42.6%. Non-survivors had higher costs than surviving patients in direct cost items (25,446 vs 21,984) due to increased medication costs and more significant efforts to keep patients alive. The authors conclude that patients with severe sepsis have a high mortality rate and prolonged ICU stay, being substantially expensive to treat.

Brun-Buisson et al. (2003) documented the costs and results of various septic syndrome forms, particularly those associated with infection acquired in intensive care units. Total hospital costs were €26,256, €35,185 and €27,083 for sepsis, severe sepsis and septic shock, respectively. Patients with sepsis associated with ICU-acquired infection incurred total costs about three times higher than patients who had infection and sepsis on ICU admission. Most patients with severe sepsis and septic shock, around 70%, were male. Most patients were over 55 years of age.

According to Adrie *et al.* (2005), severe sepsis is one of the leading causes of death in critically ill patients. In this study, the average cost of hospitalization related to severe sepsis was € 22,800. Advanced age, emergency surgery, septic shock, severity, and severe sepsis acquired in a hospital or ICU were the independent variables associated with higher intensive care units costs.

Bertolini *et al.* (2005) evaluated whether intermediate care units (ICI) are economical alternatives to ICUs for chronic obstructive pulmonary disease exacerbation patients. The total cost per patient was lower in intermediate units than in ICUs. In all items, except medications and nutrition, significantly lower costs were found in the intermediate units.

Gumus *et al. (*2019) investigated the factors that affect patients' costs hospitalized in the ICU with severe pneumonia acquired in the community. Almost half of the patients had chronic obstructive pulmonary disease, and 42% had hypertension. A statistically significant relationship was found between ICU severity scores and health costs. The authors conclude that the presence of certain comorbidities and severity of the disease increases the costs of treatment. The need for mechanical ventilation during treatment and the presence of sepsis are additional factors that increase costs.

Rosenthal *et al.* (2005) calculated the costs of nosocomial pneumonia in patients admitted to intensive care units. The authors concluded that this disease results in significant patient morbidity and considerable resource consumption. Patients with nosocomial pneumonia had significant prolongation of hospitalization, cost and high extra mortality.

Table 1 summarizes the empirical evidence presented. The results of the research show the differences in financial results between certain diseases or interventions. This synthesis also presents the main methodological paths used by the studies.

Table 1 - Synthesis of empirical evidence of costs in UTI

Study	Collection period	N - Qt of patients	Observational method	Classification of the study	Exposed Group/Case	Non-Exposed Group/Control	Exposed Average	Control Average	Exposed Median	Control Median
(DASTA *et al.*, 2005)	3 months	51,009	Cohort	Retrospective	Mechanical ventilation	Non-mechanical ventilation	$31,574	$12,931	$18,954	$8,317
(ERBAY *et al.*, 2004)	3 years	97	Case-control	Retrospective	VAP	Mechanical ventilation	$2,832	$869	$2,839	$653
(NANAO *et al.*, 2020)	7 years	44	Case-control	Retrospective	VAP	Mechanical ventilation	$41,080	$17,042	0	0
(WARREN *et al.*, 2003)	2 years	819	Cohort	Prospective	VAP	Mechanical ventilation	$70,568	$21,620	$0	$0
(SOSA-HERNÁNDEZ *et al.*, 2019)	1 year	48	Transverse	Retrospective	VAP	Unverified	$10,796	0	0	0
(SU *et al.*, 2020)	8 years	558	Case-control	Retrospective	Multi-resistant bacteria infections	Non-multi-resistant bacteria infections	NT$532	NT$474	$0	$0
(MOERER *et al.*, 2002)	4 years	385	Cohort	Retrospective	Sepsis: Surgical patient	Sepsis: Non-surgical patient	€ 25,412	€ 13,995	€ 20,295	€ 9,372
(BRUN-BUISSON *et al.*, 2003)	1 year	424	Cohort	Prospective	Sepsis	Non-sepsis	$26,256	$12,719	$0	$0
(ADRIE *et al.*, 2005)	3,75 years	1,698	Cohort	Prospective	Severe sepsis acquired in hospital	Severe sepsis acquired in the community	€ 17,400	€ 12,600	€ 14,100	€ 8,900
(BERTOLINI *et al.*, 2005)	5 months	125	Cohort	Prospective	ICU	ICI	$1,507	$754	$0	$0
(GÜMÜŞ *et al.*, 2019)	4 years	291	Cohort	Retrospective	Community pneumonia	Unverified	€ 2,722	0	0	0
(ROSENTHAL *et al.*, 2005)	4 years	614	Cohort	Prospective	Nosocomial pneumonia	Non-nosocomial pneumonia	$4,946	$2,693	$4,010	$2,257

Source: The author

2.4 COVID-19 in Intensive Care Units

The SARS-COV-2 virus is characterized by the high propagation rates and high demand for intensive care unit beds. In the study by Zhao et al. (2020), which selected and analyzed 641 hospitalizations of cases confirmed with COVID-19, 38% were admitted to the ICU. Turcotte *et al.* (2020) identified that 30.8% of the cases of COVID-19 were admitted to the ICU. The mean length of stay in the ICU of these patients was 14.86 days, against 9.26 days of non-ICU patients. They are units that receive severe COVID-19 patients with a significant risk of death.

In the study of Li *et al.* (2020b), with 548 hospitalizations originated by COVID-19, almost half of the patients (49.1%) were identified as severe cases. The mortality rate of critically ill patients was 32.5%. Analyzing 1,715 critical hospitalizations in Italy, on May 30, 2020, Grasselli *et al.* (2020) identified 836 (48.7%) patients that died in intensive care units.

Men, advanced age, patients with hypertension, diabetes and patients located in America were variables considered as risk factors and associated with death among patients with COVID-19 (ALBITAR *et al.*, 2020). As reported by Fang; Karakiulakis; Roth (2020), based on previous studies, patients who developed the severe form of COVID-19 had comorbidities, diabetes and hypertension. Analyzing the results of 3,988 patients with COVID-19 hospitalized in ICU in the region of Lombardy, Italy, Grasselli *et al.* (2020) found 3,355 hospitalizations that needed some respiratory support, mainly invasive mechanical ventilation with 2,929 records (73% of the total). Twenty-five per cent of the patients were hospitalized for more than 21 days in the ICU. Men accounted for 80% of patients. The median age was 63 years.

Analyzing 117 hospitalizations of patients with COVID-19, Turcotte *et al.* (2020) identified 34 patients who required mechanical ventilation. Chang *et al.* (2020) analyzed twenty-eight studies involving 12,437 ICU admissions by COVID-19. Of the total number of ICU admissions, 69% of the cases required invasive mechanical ventilation. The authors conclude that the significant association of mechanical ventilation and severe acute respiratory discomfort syndrome with mortality has implications for planning ICU resources. In the analysis of results with 24 confirmed cases of COVID-19, Bhatraju *et al.* (2020) identified that all patients were admitted for respiratory failure and 75% required mechanical ventilation. According to François *et al.* (2020), patients with COVID-19 often require prolonged mechanical ventilation, representing a high risk of secondary acquisition in hospital, especially pneumonia associated with mechanical ventilation. This type of pneumonia occurred in 31% of patients who required mechanical ventilation (ZHOU *et al.*, 2020) .

Guan *et al.* (2020) showed that, during hospitalization, most patients with COVID-19 were diagnosed with pneumonia by the doctor (91.1%). In this study, patients with severe disease had a higher incidence of pneumonia than those with non-severe disease. Du *et al.* (2020) analyzed 179 patients (97 men and 82 women) with COVID-19 pneumonia, of whom 21 died. Logistic regression analysis revealed that age greater than 65 and pre-existing diseases were associated with an increased risk of mortality from COVID-19 pneumonia. Analyzing 15 studies, which included a total of 2,473 patients confirmed with COVID1-9, Alqahtani *et al.* (2020) describe that patients with chronic obstructive pulmonary disease are more likely to develop the most severe form of COVID-19.

Li *et al.* (2020a) observed that many patients severely or critically ill with COVID-19 developed typical septic shock clinical manifestations. The authors formulate the hispóthesis that a process called viral sepsis is crucial for the COVID-19 mechanism. Sepsis was the most frequent complication (59% of 191 cases), observed in the study by Zhou *et al.* (2020), about adult patients hospitalized with COVID-19 in the Chinese city of Wuhan. The authors argue that sepsis was a common complication, which can be directly caused by SARS-CoV-2 infection. In this study, most patients were men, 62%, and the median age was 56 years. The median length of stay in the ICU was eight days.

Emanuel *et al.* (2020) show that the pandemic caused by coronavirus is a new infection with severe clinical manifestations, including death, being enough to overload health care and infrastructure. The authors discuss the growing imbalance between supply and demand for medical resources to treat patients with COVID-19. The pandemic resulting from COVID-19 has put unprecedented pressure on health systems, with a growing demand for health care in hospitals and intensive care units worldwide (REES *et al.*, 2020). The authors identified 52 studies on hospitalizations on COVID-19. The median length of stay ranged from 4 to 53 days in China and from 4 to 21 days outside China. According to Lee *et al.* (2020), the coronavirus outbreak presents a threat that can overwhelm health resources. Chart 3 synthesizes the main findings of empirical evidence on hospitalizations around COVID-19 in intensive care units.

Chart 3 - Synthesis of empirical evidence

(continue)

Study	Type of Study	Classification of the study	N – Qtd of patients	Synthesis of findings
(ZHAO *et al.*, 2020)	Observational	Retrospective	641	Considering the total number of patients hospitalized with COVID-19, 38% were admitted to the ICU. History of smoking and chronic obstructive pulmonary disease were some of the predictor variables of ICU admission and mortality.
(TURCOTTE *et al.*, 2020)	Observational	Retrospective	117	Of the total number of patients with COVID-19, 30.8% were admitted to the ICU and 29.1%, of total ICU stay, required mechanical ventilation. The average ICU was 14.86 days.
(LI *et al.*, 2020b)	Observational	Retrospective	548	Severe patients were identified in 49.1% of the cases. The mortality rate in severe cases was 32.5%. Advanced age and hypertension were factors associated with severe cases of COVID-19.
(GRASSELLI *et al.*, 2020)	Observational	Retrospective	3,988	A total of 1,715 critical cases were identified. Deaths occurred in 836 cases in the ICU. At ICU admission, 87.3% required mechanical ventilation. Twenty-five per cent of the patients spent more than 21 days in the ICU. Men accounted for 80% of hospitalizations. The median age was 63 years.
(ALBITAR *et al.*, 2020)	Observational	Retrospective	828	Men, advanced age, hypertension and diabetes were factors associated with death.
(BHATRAJU *et al.*, 2020)	Observational	Retrospective	24	All patients were identified with respiratory problems and 75% required mechanical ventilation. Half of the patients died between day 1 and day 18 in the ICU.
(ZHOU *et al.*, 2020)	Observational	Retrospective	191	Ventilator-associated pneumonia occurred in 31% of patients who required ventilation. Sepsis was present in 59% of cases. Most of the hospitalized patients were men. The median ICU stay was 8 days.

Study	Type of Study	Classification of the study	N – Qt of patients	Synthesis of findings
(GUAN *et al.*, 2020)	Observational	Retrospective	1,099	Severe cases were described in 17% of patients. The median hospital stay of

				severe cases was 13 days. Most patients (91%) identified with pneumonia.
(DU *et al.*, 2020)	Observational	Prospective	179	Of 179 patients with pneumonia, 21 died. Age over 65 years and pre-existing diseases were associated with a higher risk of death.
Chang *et al.* (2020)	Meta-analysis	Not available	12,437	Of the total number of cases in the ICU, 69% used mechanical ventilation. The main correlations with ICU death were invasive mechanical ventilation and severe acute respiratory syndrome.
Alqahtani *et al.* (2020)	Meta-analysis	Not available	2,473	Patients with chronic obstructive pulmonary disease are more likely to develop a severe form of COVID-19.
(REES *et al.*, 2020).	Systematic Review	Not available	Not available	The median hospital LOS ranged from 4 to 53 days in China and 4 to 21 days outside China. Regarding ICU admissions, the median of LOS inside and outside China was 6 to 12 and 4 to 19 days, respectively.

(conclusion)

Source: The author

2.5 Research Hypothesis

Due to the potential severity of the disease and risk of death, a considerable proportion of patients hospitalized with COVID-19 are admitted to intensive care units. Pneumonia may be associated with severe patients hospitalized with COVID-19 who are often submitted to mechanical ventilation. Severe sepsis can also affect patients with the new coronavirus. Advanced age and men present a risk factor for hospitalizations of COVID-19. All these factors may explain the high use of resources and increased length of stay of patients hospitalized in ICU with COVID-19, with consequent overload in the system.

Intensive care units are expensive and consume a large portion of the resources allocated to health. Empirical evidence on ICU costs shows that mechanical ventilation, pneumonia, sepsis, as well as severity and advanced age are factors that add extra costs and additional days of hospitalization in patients admitted to intensive care units.

The combination of these questions and premises form the basis for building the following set research hypothesis (H1):

H1: Patients hospitalized with COVID-19 severely add costs to intensive care units;
H1a: Men hospitalized with COVID-19 have higher costs than men hospitalized for other causes in ICU;

H1b: Age positively influences the costs of patients with COVID-19 hospitalized in the ICU;
H1c: LOS positively influences the costs of patients with COVID-19 hospitalized in the ICU;
H1d: Severity positively influences the costs of patients with COVID-19 hospitalized in the ICU.

All the factors that support these hypotheses are elements present in the empirical evidence on ICU admissions of patients with COVID-19 (section 2.4). These same elements appear in the literature as causes of additional costs in intensive care units (section 2.3).

3. METHODS

This chapter presents the research methodology used to reach the proposed objects. In this way, this chapter describes the study's classification, presents and defines the hospital in which the patients objects of this study were admitted and, finally, synthesizes the process of collecting and statistical processing of data.

3.1 Study Design

The research method is quantitative modelling. Between the main quantitative techniques employed are linear regression, logistic regression, structural equations and time series. Creswell (2007) describes this technique as the reasoning of cause and effect, reducing specific variables and hypotheses, using measurement and observation, and testing theories. It employs investigation strategies, such as experiments, surveys and data collection and predetermined instruments that generate statistical data. In this study, statistical and econometric techniques were used to analyze the observed data and verify the research hypotheses on the economic impacts in ICU of patients hospitalized with COVID-19. The use of statistical and econometric models makes the research method of this study a quantitative modelling, capable of answering a research problem applied in the health area. According to Dresch; Lacerda; Antunes (2015), modelling is a research method that supports researchers to understand problems better.

As far as the approach is concerned, this is explanative research. This study goes beyond a descriptive approach that, according to Gil (2008), has as its primary objective the description of the characteristics of a given population or phenomenon or the establishment of relationships between variables. Thus, this study describes the impacts economics and characteristics of patients with COVID-19 in the ICU but state the cause-effect relationship, which brings an explanative research approach, considering that it advances to explaining and understanding the factors affecting ICU patients' costs with COVID-19. According to Gil (2008), explanative research has as its central concern to identify the factors that determine or contribute to the occurrence of phenomena. According to the author, this is the kind of research that deepens the knowledge of reality because it explains the reason, the why of things.

3.2 Analized Case

This is a retrospective study of micro-costing. Two groups (cohort), performed with patients admitted to an ICU with a 76-bed capacity at a private hospital located in Southern Brazil. The hospital is a private non-profit institution with 474 beds and is a reference center for high-complexity and critical cases. The institution has been accredited since 2002 by the Joint Commission International and affiliated with Johns Hopkins Medicine since 2013.

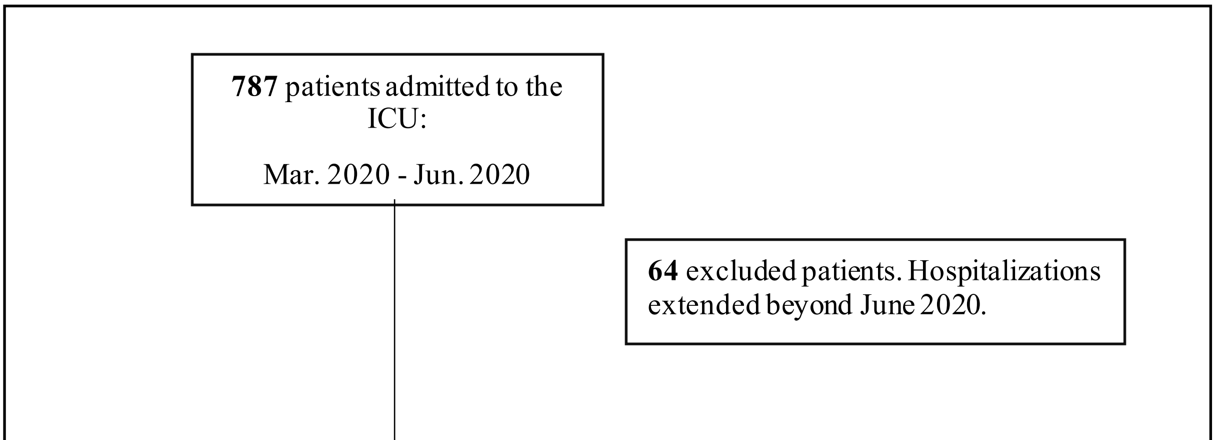
We did not have access to patient identification data nor to their medical records, thus the need for an Ethics Committee approval and patient consent was waived by the hospital.

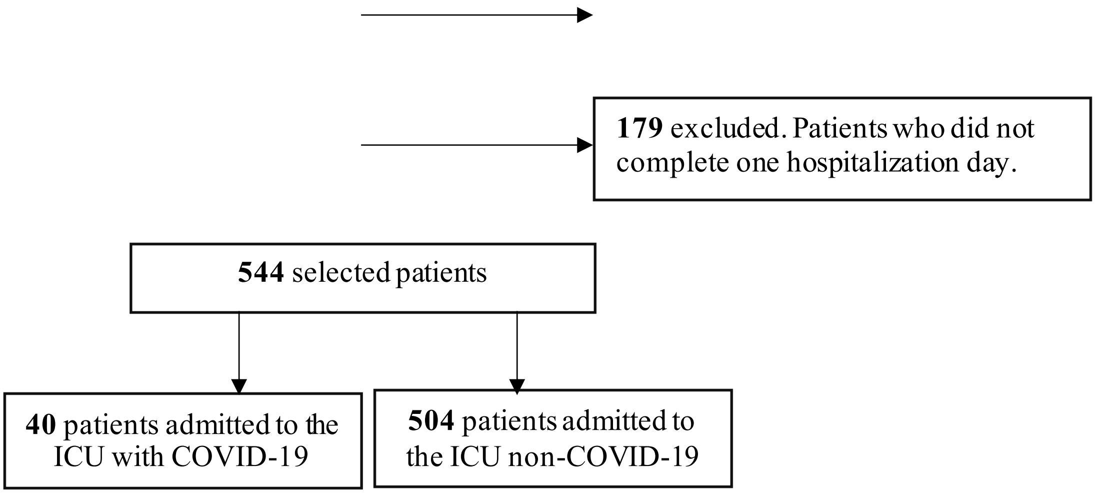
3.3 Data Collect

3.3.1 Hospitalization Data

Data collection happened between March and June 2020 and identified patients with COVID-19 and those hospitalized for non-COVID-19 causes. The total population included 787 patients admitted to the ICU. Due to the end of the hospital's accounting period, hospitalizations extended beyond June 2020 were excluded from the database. Additionally, patients who did not complete one hospitalization day were excluded. Our final sample consisted of 544 patients (figure 3).

Figure 3 - ICU selection diagram





Source: The author

A service number was assigned to each patient. The attendance list was extracted from the hospital database and recorded the dates of admission and discharge (LOS), as well as the patients' age and sex. Reverse transcriptase-polymerase chain reaction (RT-PCR) tests confirmed that all patients identified with COVID-19 were correctly reported by the hospital's assistance sector. All other service admissions were classified as non-COVID-19 causes of hospitalization.

As a measure of the severity of patients admitted to the ICU, we calculated the mean daily nursing activities score (NAS), as stated by Miranda et al. (2003), for each patient. High NAS scores in the ICU (>66,4%) are associated with increased mortality, LOS and severity (GRILLO et al., 2008). This score measures the daily nursing workload dedicated to ICU patients. The hospital's assistance sector also recorded these scores. Thus, the following variables were used in the study:

1) Age: Continuous variable of each patient selected in the database;
2) Gender: Nominal variable identifying the sex of each patient;
3) NAS: Continuous variable that represents the severity score of each patient.;
4) LOS: Discrete variable of the length of hospital stay of each patient.

3.3.2 Cost Accounting Method

Costs were classified as direct or indirect. Total costs result from the sum of direct and indirect costs. Direct costs consisted of medications and hospital supplies employed directly with each patient admitted to the ICU and calculated using the mean unit cost of the consumed products. Indirect costs included medical and nursing staff, maintenance, equipment depreciation, electricity, and hospital supplies recorded by the ICU cost center. These costs, in their relationship with the ICU, could be mentioned as direct. However, concerning the final cost object (patient), these costs cannot be directly related to a patient and require an allocation criterion, therefore, treated as indirect costs. Therefore, these costs were connected to patients according to an allocation factor (Equation 1), which is a representative measure of the effort directed at hospitalizations. The ICU occupation levels were within the normal range.

Equation (1)

$$\textbf{Overhead allocation} = \frac{\boldsymbol{\Sigma}\ \textbf{factors of patient i}}{\boldsymbol{\Sigma}\ \textbf{total factors}} * (\textbf{Total indirect costs})$$

Most of these factors correspond to hospital rates, including health insurance reimbursements that cover hospital procedures and infrastructure. For direct costs, a bottom-up approach was used; this approach is the overall preferred methodology as it values each cost component for individual patients. On the other hand, for indirect costs, we used a top-down method because it considered all indirect costs at the aggregate level and prorated for patients, without further details on each activity.

All cost components, per patient, direct and indirect, were extracted from the hospital's management control area's databases. In this way, all cost information for patients was associated with the due hospitalization information (age, sex, LOS and NAS). The costs were collected and analyzed by the total period of hospitalization of each patient. Additionally, for daily costs, hospitalization costs were divided by the total hospitalization length for each patient. All costs were collected and analyzed in the currency R$ (Brazilian Real), without converting between currencies.

3.4 Statistical and Econometric Analyses

Initially, the costs of ICU care were separated into two groups: the costs of patients suffering from COVID-19 and those of non-COVID-19 patients. Data on cost, severity, and length of stay (LOS) were subjected to tests and normality analyses. As data did not present normal distributions, the Mann-Whitney non-parametric test was performed to compare the differences between medians of costs, severity, and LOS of both groups; p-values below 5% were considered statistically significant. In addition to measures of central tendency, differences in interquartile ranges were observed between groups, including in the direct cost component (medications and medical supplies). Differences in costs and LOS were also analyzed according to sex and age groups. Costs are continuous variables expressed in Brazilian Real (R$). Length of stay, age, and severity are also presented as continuous variables.

An econometric model was used to analyze the influence of patients with COVID-19 on ICU costs during the whole hospitalization period, employing a multiple linear regression estimate using ordinary least squares (OLS) in cross-section. For a better estimation of betas, we performed tests and adjustments to the models, which are specified in Appendix D to O. Patients with COVID-19 were considered a dummy variable. Their coefficients were interpreted as differential costs in comparison to the reference category (non-COVID-19). LOS, severity, and age were used as variables independent of the model. Given our sample variability (except for the dummy variable), values were transformed into log, which made the estimators less susceptible to the influence of outliers (WOOLDRIDGE, 2017). The log coefficients of LOS, severity, and age were interpreted as elasticity and sensitivity to costs. The log coefficient of the dummy variable was interpreted as the increment (%) in ICU costs caused by patients with COVID-19. Thus, equation 2 presents the OLS model's estimates, that is, the betas' numerical value. Statistical and econometric tests were performed using the Stata software (version 12) and SPSS software.

Equation (2)

$$\boldsymbol{Ln_{Custos} = B_0 + B_1 D\_COVID - 19_i + B_2 lnLOS_i + B_3 lnage_i + B_4 lnseverity_i + u_i}$$

B_0: model intercept;

B_1: dummy of patients with $\mathrm{COVID} - 19$ (1 when the patient is identified with $\mathrm{COVID} - 19$ and 0 otherwise);

B_2: natural log of LOS;

B_3: natural log of the patient's age;

B_4: natural log of patient severity (NAS)

u: residual error of the regression model

To analyze the association between explanatory variables (NAS, age and LOS) and ICU costs, however, only in the group of patients with COVID-19, a second model of multiple linear regression was performed. Except for the dummy variable COVID-19, the other variables remained in this second model.

Chart 4 presents a research synthesis, relating the statistical hypotheses with the research objectives, research hypothesis and statistical analyses.

Chart 4 - Synthesis of the Research Method

Hypothesis	Definition of the statistical hypothesis	Research hypothesis	Specific Objectives	Statistical Analysis
H_o: $\mu = 0$ H_1: $\mu \neq 0$	**Null:** Average costs of patients with COVID-19 is the same concerning other ICU admissions. **Alternative:** Average costs of patients with COVID-19 is higher than other ICU admissions.	H1 H1a H1b	Assess whether patients hospitalized with COVID-19 add or not extra costs to intensive care units. Identify the ICU costs originated by COVID-19 according to the profile of hospitalized patients.	Mann-Whitney non-parametric test. Multiple linear regression estimate using ordinary least squares (OLS).
H_o: $B = 0$ H_1: $B \neq 0$	**Null:** LOS, Age and severity are not related to the costs of patients with COVID-19. **Alternative:** LOS, Age and severity are related to the costs of patients with COVID-19.	H1b H1c H1d	Reveal the main factors that influence the costs of ICU patients with COVID-19.	Multiple linear regression estimate using ordinary least squares (OLS).

Source: The author

Mean tests are applied to evaluate the central hypothesis of cost differences between patients with COVID-19 and other causes in the ICU. The mean tests were also implemented in the secondary hypotheses of evaluating cost differences considering the sample profile (gender and age). Regarding the causes that impact the costs of patients with COVID-19, a multiple regression model was employed.

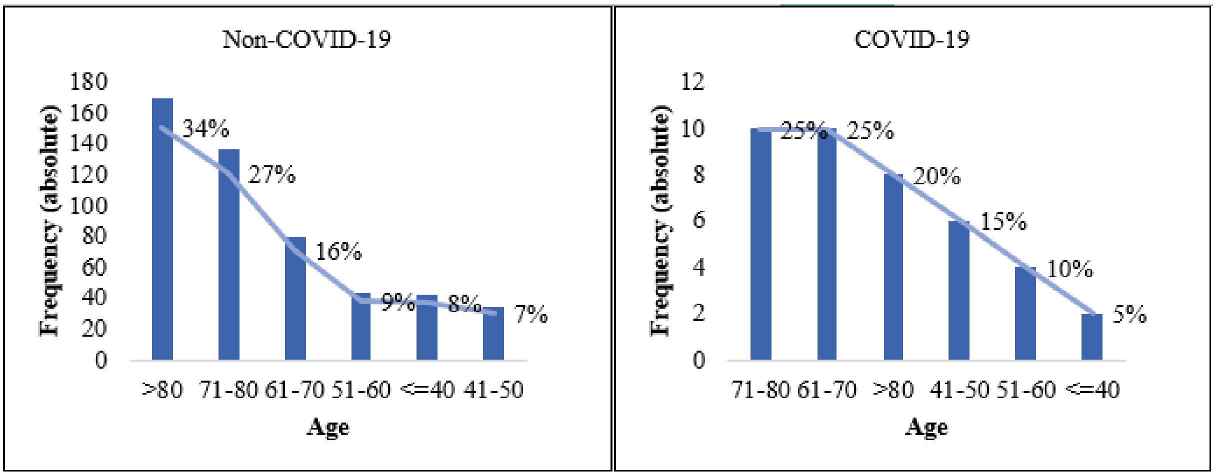
4. RESULTS

This section presents the research results based on the data collected and analyzed of the ICU patients' costs. In the first part, the sample profile, related to age and gender, is presented. Subsequently, the cost differences in the ICU, with the comparison of data between patients with COVID-19 and other causes of hospitalization, are presented. Finally, this section estimates, based on quantitative modeling, which factors influence ICU costs.

4.1 Sample Profile

The study included a final sample of 544 patients, of whom 40 were diagnosed with COVID-19 and 504 had other causes of hospitalization. Figure 4 and Table 2 show the distribution of data by age and gender.

Figure 4 - Age Profile of Patients



Source: The author

Table 2 - Gender Distribution

Sex	Total Cases	%	Non-COVID-19	%	COVID-19	%
Male	282	52%	254	50%	28	70%
Female	262	48%	250	50%	12	30%
Total	544		504		40	

Source: The author

The mean age of all patients was 70·5 years, while that of patients with COVID-19 was 67·3 years (50% between 61 and 80 years old; standard deviation [SD], 15); patients with other hospitalization causes had a mean age of 70·7 years (34% over 80 years old; SD, 18). Most patients hospitalized for COVID-19 were male (70% of the sample); there was a similar distribution between males and females among patients hospitalized for non-COVID-19 causes.

4.2 Costs of Inpatient in ICU

The distributions of cost, severity, age and LOS are provided in Appendix A and B. Asymmetric data distributions were identified in all cases, except for age and NAS in the COVID-19 group. In addition to the lack of normality, confirmed by the tests obtained in table 3, the cost data and the LOS data of non-COVID-19 patients showed a concentration from values on the left in the distribution graph. In the group of patients with COVID-19, this asymmetry on the left was less intense. Thus, this data behaviour is an initial indicator of higher costs in the group of patients admitted with a COVID-19.

Table 3 - Normality Test: The Shapiro-Wilk Test

	Non-COVID-19			***COVID-19***		
Variable	**Obs**	**W**	**Prob > z**	**Obs**	**W**	**Prob > z**
Length of stay	504	0.6051	0.000	40	0.8319	0.000
Age	504	0.9403	0.000	40	0.9717	0.408
NAS	504	0.9773	0.000	40	0.9718	0.409
Daily hospitalization costs						
Direct costs	504	0.5950	0.000	40	0.8953	0.001
Indirect costs	504	0.9413	0.000	40	0.7563	0.000
Total costs	504	0.9481	0.000	40	0.8608	0.000
Total hospitalization costs						
Direct costs	504	0.4659	0.000	40	0.6347	0.000
Indirect costs	504	0.5671	0.000	40	0.8377	0.000
Total costs	504	0.5646	0.000	40	0.7929	0.000

Source: The author

Note: Except for age and NAS within the COVID-19 group (p-value > 5%), none of the other variables showed a normal distribution (p-value < 5%). Considering all 544 patients of the sample, we did not identify a regular pattern of variables.

Table 4 - Descriptive Statistics of the Sample

	Non-COVID-19 (n = 504)					**COVID-19 (n = 40)**				
Hospitalization	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
LOS	5	7	2	1	70	20	21	7	1	84
Age	71	18	75	16	104	67	15	68	37	94

Severity (NAS)	71	11	70	42	138	76	12	76	53	102
Patient daily costs – R$										
Direct costs	655	805	448	26	9,147	1,081	706	973	239	2,951
Indirect costs	4,186	1,356	3,901	650	10,051	4,034	1,494	3,558	2,790	10,016
Total costs	4,842	1,548	4,560	822	12,687	5,116	1,533	4,886	3,186	10,572
Total hospitalization costs – R$										
Direct costs	4,002	8,751	929	26	73,179	28,831	45,608	8,295	556	247,884
Indirect costs	16,333	21,437	8,450	2,342	195,886	67,307	66,270	44,131	5,633	256,464
Total costs	20,335	28,579	9,935	2,441	245,512	96,138	106,631	51,752	6,371	504,438
Direct cost components - mean costs – R$										
Medications	10.3	14.4	6.8	1.0	174.0	17.0	9.9	15	7.0	49.0
Medical supplies	2.6	2.2	2.0	0.0	19.0	4	2	3	1.0	13.0
Direct cost components – quantity										
Medications	223	367	94	3	3,269	1,119	1,314	445	39	4,613
Medical supplies	260	367	131	3	2,990	1,118	1,267	461	55	5,459

Source: The author

Patients suffering from COVID-19 were hospitalized for a median of seven days and stayed in the hospital for 1 to 84 days (interquartile range [IQR], 3.3–32.5). In non-COVID-19 patients, the median LOS was only two days (table 4; p-value < 0.1%), ranging from 1 to 70 days in the hospital (IQR, 1–5), as shown in table 4 and figure 5. The probability of patients with non-COVID-19 hospitalization causes staying in the ICU longer than patients with COVID-19 was only 21.5% (table 6). The median severity score was 76.11 (SD, 11.76) for the COVID-19 and 70.66 (SD, 11.28) for non-COVID-19 (table 4).

Table 5 - Descriptive Statistics: Quartiles

	Non-COVID-19		***COVID-19***	
	Q1	**Q3**	**Q1**	**Q3**
Length of stay	1	5	3	33
Patient daily costs – R$				
Direct costs	207	856	529	1,451
Indirect costs	3,178	5,131	3,032	4,421
Total costs	3,782	5,750	4,088	5,624

Total hospitalization costs – R$				
Direct costs	352	3,108	1,569	40,336
Indirect costs	5,633	16,740	14,019	110,344
Total costs	6,431	19,771	16,764	149,479
Direct cost components - mean costs – R$				
Medications	3	12	10	20
Medical supplies	1	3	3	4
Direct cost components – quantity				
Medications	48	204	99	1,883
Medical supplies	72	269	148	1,893

Source: The author

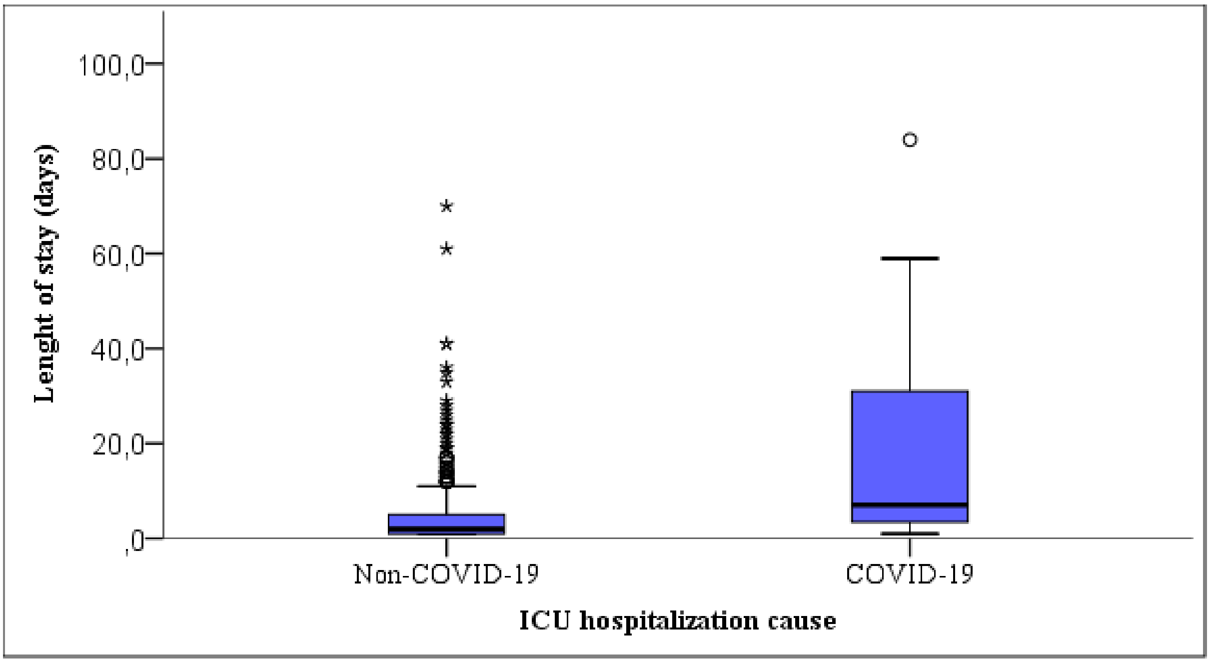
Table 6 - Non-Parametric Test: Mann-Whitney

	Obs		***Ho***		***P Variable: non-COVID-19 > COVID-19***
Variable	**Non-COVID-19**	**COVID-19**	**z**	**Prob> |z|**	**Porder test**
Length of stay	504	40	-6.127	0.0000	0.215
Age	504	40	-1.734	0.0830	0.582
Severity	504	40	-2.878	0.0040	0.363
Daily hospitalization costs – R$					
Direct costs	504	40	-4.876	0.0000	0.269
Indirect costs	504	40	-1.211	0.2261	0.557
Total costs	504	40	-1.037	0.2999	0.451
Total hospitalization costs – R$					
Direct costs	504	40	-6.383	0.0000	0.197
Indirect costs	504	40	-6.521	0.0000	0.191
Total costs	504	40	-6.551	0.0000	0.189

Source: The author

Note: Obs: observations; Ho: null hypothesis; prob: probability. The Mann-Whitney median test was applied as a normal sample distribution was not observed. The results showed statistically significant differences (p-value < 5%) in medians between the non-COVID-19 and COVID-19 groups, except for the variables age and indirect and total daily costs. The Porder test found good indicators of the observed results.

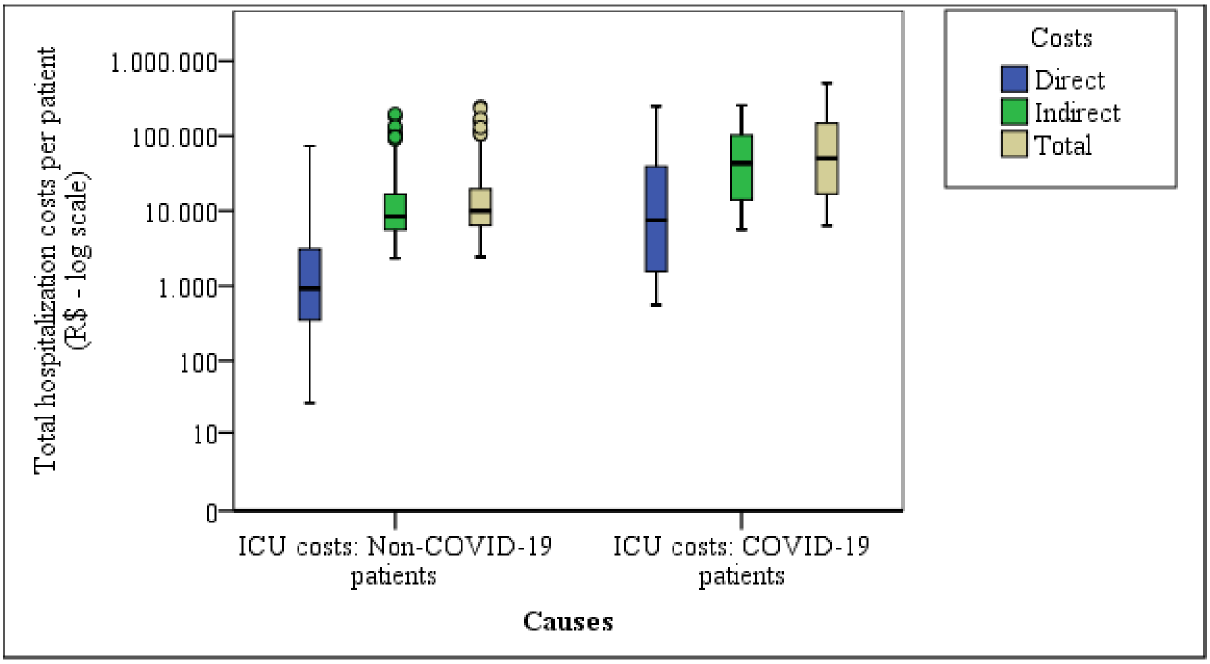
Figure 5 - Distribution of LOS between patients hospitalized for COVID-19 and other causes



Source: The author

No differences in statistics in both indirect and total daily costs per patient were found between groups (table 6; p-value >5%). However, the minimum costs were higher in patients with COVID-19 (table 4). In the analysis of daily costs per patient, hospitalization from COVID-19 added R$ 525 (973 – 448) to direct costs (p-value < 0.1%). Total hospitalization costs of all origins were higher in patients with COVID-19 (Figure 6; p-value < 0.1%). Patients diagnosed with COVID-19 presented a total cost median of R$ 51,752 (IQR, 16,764–149,479), a median of direct costs of R$ 8,295 (IQR, 1,569–40,336), and a median of indirect costs of R$ 44,131 (IQR, 14,019–110,344) (table 4 and 5). On the other hand, the total cost median for non-COVID-19 patients was R$ 9,935 (IQR, 6,431–19,771), the median for direct costs was R$ 929 (IQR, 352–3,108), and that for indirect costs was R$ 8,450 (IQR, 5,633–16,740). One patient with COVID-19 reached R$ 504,438 in costs during the hospitalization period, while in the non-COVID-19 group, the highest outlier reached R$ 245,512.

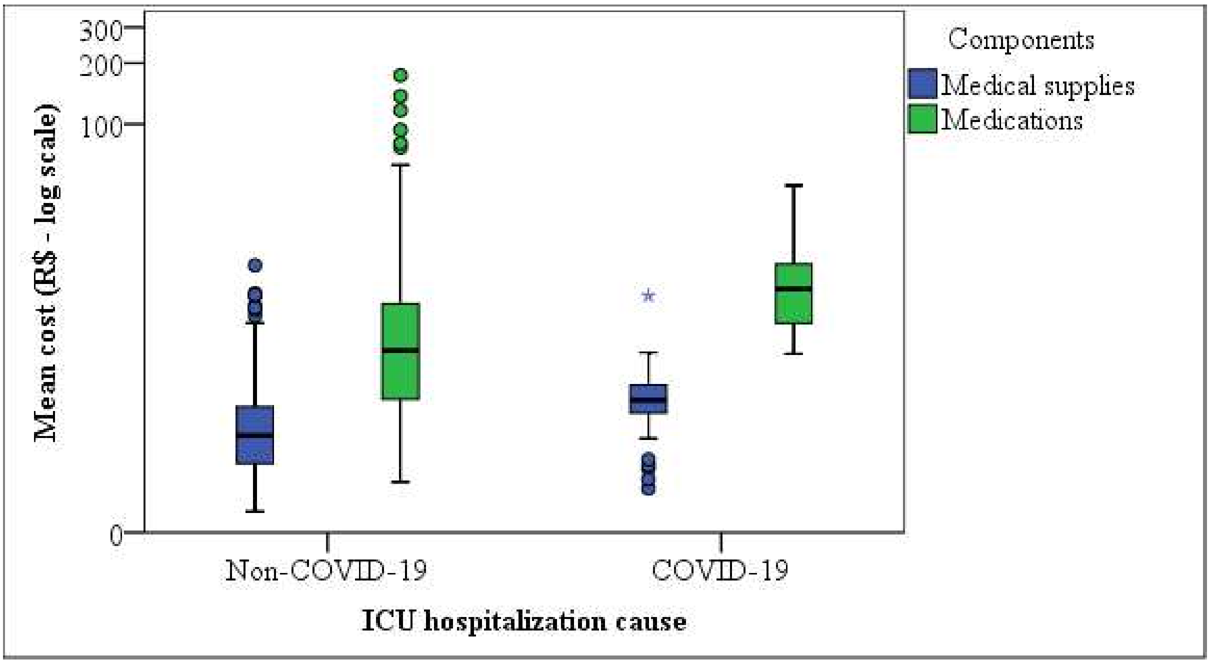
Figure 6 - Distribution of costs between patients hospitalized for COVID-19 and other causes



Source: The author

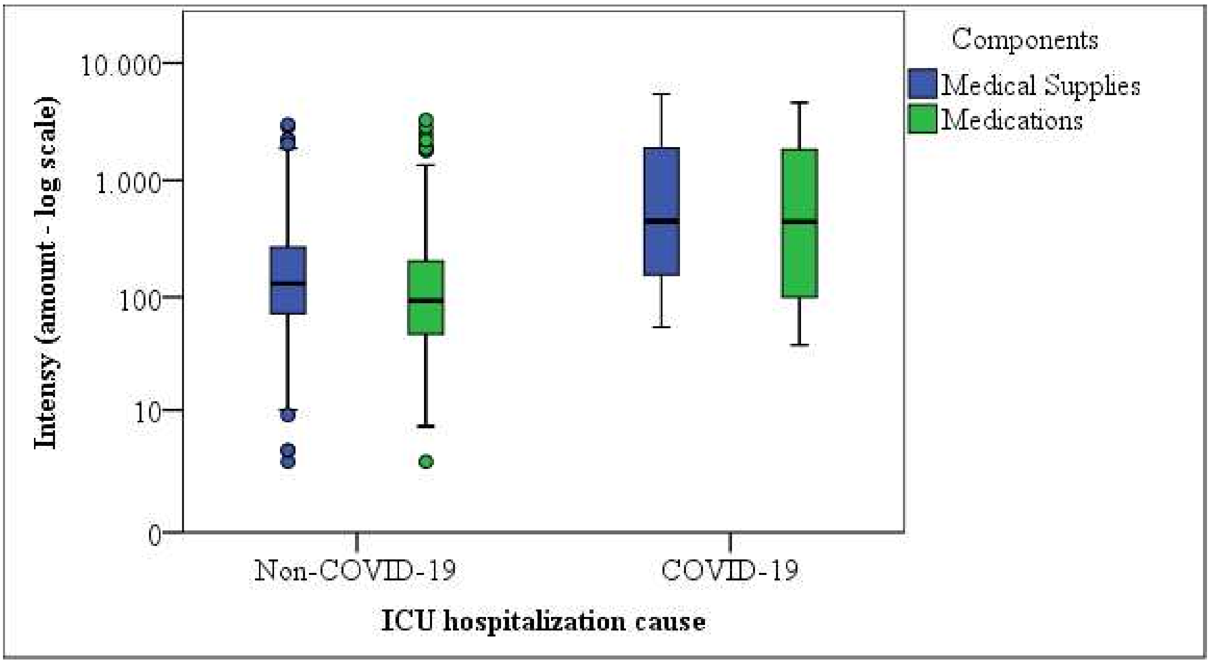
Differences in direct costs (medications and medical supplies) between groups are indicated by both mean costs and intensity (table 4, 5, and figure 7 and 8). The median of mean costs (total item costs/total item quantity) of medications regarding hospitalizations with COVID-19 was R$ 15 (IQR, 10–20), while for non-COVID-19 hospitalizations, it was R$ 7 (IQR, 3–12). Differences in median values for mean medical supply costs were also identified, but to a lesser extent: R$ 3 (IQR, 3–4) for patients with COVID-19 and R$ 2 (IQR, 1–3) for the other group. The median intensity of medications applied to patients with COVID-19 was 445 (IQR, 99–1,883), and similar results were observed in the amount of medical supplies used by this group. For the non-COVID-19 group, the median amount of medications was 94 (IQR, 48–204), and that of medical supplies was 131 (IQR, 72–269).

Figure 7 - Direct Cost Components: Mean Unit Cost



Source: The author

Figure 8 - Direct cost components: Intensity



Source: The author

Differences in costs between the two groups can also be observed within sex and age groups (table 7). Significant differences were found only in the daily direct costs of male patients and patients aged 60 years or older (p-value < 0.1%) and direct costs of female patients (p-value < 1%). Men suffering from COVID-19 resulted in R$ 483 higher direct costs compared to other hospitalization causes. In patients older than 60 years, this difference was R$ 567. Total hospitalization costs of patients over 60 years old and with COVID-19 were 11 times higher than those of other patients, reaching 26 times when considering only direct costs (p-value < 0.1%). In patients under 60 years of age, the difference in total costs was reduced to 2 times (p-value < 5%). Patients with COVID-19 who were older than 60 years had a 12-fold longer LOS than those hospitalized for other causes (p-value< 0.1%). Differences in total hospitalization costs and LOS were also found within the COVID-19 group when comparing patients older or younger than 60 years (p-value < 5%).

Table 7 - Differences in Costs and Length of Stay by Sex and Age Groups

Variables	**Patient daily costs – R$**			**Total hospitalization costs – R$**			**Length of stay**		
	Non-COVID-19	**COVID-19**	**p-value**	**Non-COVID-19**	**COVID-19**	**p-value**	**Non-COVID-19**	**COVID-19**	**p-value**
Male							2.00	23.00	0.000
Total costs	4,630	4,757	0.514	9,440	91,797	0.000			
Direct costs	452	935	0.000	889	18,487	0.000			
Indirect costs	3,956	3,320	0.115	8,370	68,674	0.000			
Female							2.00	5.00	0.004
Total costs	4,534	5,053	0.337	10,394	20,895	0.001			
Direct costs	447	973	0·009	1,015	4,149	0.001			
Indirect costs	3,793	4,155	0.734	8,653	17,334	0.001			
≥ 60 years old							2.00	23.50	0.000
Total costs	4,526	5,025	0.209	10,136	110,640	0.000			
Direct costs	456	1,023	0.000	1,027	26,886	0.000			
Indirect costs	3,901	3,439	0.117	8,450	76,046	0.000			
< 60 years old							2.00	4.50	0.057
Total costs	4,756	4,287	0.865	9,094	17,432	0.020			
Direct costs	432	588	0.090	674	2,245	0.020			
Indirect costs	3,901	3,764	0.783	8,450	14,721	0.017			

Source: The author

Note: Mann-Whitney median test. Differences between men and women in the COVID-19 group were: patient daily costs – equal, with p-value > 5%. Total hospitalization costs – equal, with p-value > 5%. Length of stay – equal, with p-value > 5%. Differences between the COVID-19 age groups were: patient daily costs – equal, with p-value > 5%. Total hospitalization costs – different, with p-value < 5%. Length of stay – different, with p-value < 5%.

Men with COVID-19 added more than R$ 80,000 to total hospitalization costs and 21 days to hospitalization periods (p-value < 0.1%). Among women, this difference was smaller (p-value < 1%). We did not observe significant differences between male and female patients with COVID-19 (p-value > 5%).

4.3 Factors of Influence on ICU Costs

The relationships between age, LOS, severity, and COVID-19 with costs during the hospitalization total period were estimated by log-linear coefficients of elasticity and percentage variation (table 8 and 9).

Table 8 - Log-Linear - Ordinary Least Squares (OLS) Regression for All Patients

	Direct Costs (LN)		**Indirect Costs (LN)**		**Total Costs (LN)**	
	Coef.	**CI (95%)**	**Coef.**	**CI (95%)**	**Coef.**	**CI (95%)**
Covid-19	0.306** (2.91)	0.09;0.51	0.183*** (3.89)	0.09;0.27	0.196*** (4.01)	0.10;0.29
Length of stay (LN)	1.212*** (33.24)	1.14;1.28	0.820*** (69.78)	0.79;0.84	0.874*** (70.22)	0.84;0.89
Age (LN)	-0.111 (-0.87)	-0.36;0.14	0.022 (0.6)	-0.05;0.09	-0.036 (-0.83)	-0.12;0.04
Severity (NAS_LN)	2.327*** (9.9)	1.86;2.78	0.196* (2.28)	0.02;0.36	0.456*** (5.14)	0.28;0.63
Const	-3.599*** (-3.26)	-5.77;-1.43	7.533*** (19.83)	6.78;8.27	6.773*** (17.11)	5.99;7.55
F(4 , 539)	623.06***		1823.3***		1928.01***	
R-square	0.7468		0.9104		0.9141	
N	544		544		544	

Source: The author

Note: Dependent variables: Direct costs, indirect costs, and total costs. Independent variables: Patients with COVID-19, length of stay (LOS), severity, and age. Variables were expressed in logarithms. The coefficient value measured the cost elasticity regarding LOS, severity, and age, that is, the variation in costs when these variables increased in 1%. The coefficient of patients with COVID-19 (dummy variable) represents the cost increment (in %) compared to patients hospitalized for other causes. Results of T-statistic testing are in parentheses. ***p-value < 0.001, **p-value < 0.01 e *p-value < 0.05.

Table 9 - Log-Linear -Ordinary Least Squares (OLS) Regression for Patients with COVID-19

	Direct Costs (LN)		**Indirect Costs (LN)**		**Total Costs (LN)**	
	Coef.	**CI (95%)**	**Coef.**	**CI (95%)**	**Coef.**	**CI (95%)**
Length of stay (LN)	1.1055*** (12.94)	0.93;1.27	0.9000*** (22.6)	0.81;0.98	0.9427*** (21.22)	0.85;1.03

Age (LN)	0.0382 (0.10)	-0.76;0.83	0.216 (1.27)	-0.12;0.56	0.1788 (1.02)	-1.17;0.53
Severity (NAS_LN)	2.0670* (2.43)	0.34;3.79	-0.3917 (-1.13)	-1.09;0.31	0.0892 (0.25)	-0.63;0.81
Const	-2.5525 (-0.70)	-9.94;4.83	9.2695*** (7.39)	6.72;11.81	7.50*** (5.29)	4.62;10.37
F(3 , 36)	94.5***		221.66***		206.64***	
R-square	0.916		0.9521		0.9585	
N	40		40		40	

Source: The author
Note: Dependent variables: Direct costs, indirect costs, and total costs. Independent variables: length of stay (LOS), severity, and age. Variables are expressed in logarithms. The coefficient value measured the cost elasticity regarding LOS, severity and age, that is, the variation in costs when these variables were increased by 1%. Results of T statistic testing are in parentheses. ***p-value < 0.001, **p-value < 0.01, *p-value < 0.05.

Age, LOS, and COVID-19 determined a high explanatory (R-squared) power in ICU cost variations. Using regression coefficients, table 8 shows that costs (especially direct costs) are elastic to the LOS (Coefficient [Coef.] 1.212; 95% CI, 1.14–1.28). Considering only the group with COVID-19 (table 9), this elasticity is 1.1055 (95% CI, 0.93–1.27). It is important to note that LOS exerts a strong influence on R-squared, as the total costs during the hospitalization period are highly correlated with hospitalization length. However, the elasticity results reveal that ICU costs increase in a more significant proportion regarding the increase in the number of days of hospitalization; that is, a LOS variation positive indicates a slight increase in daily hospitalization values (the expected would be elasticity of 1.00).

A negative elasticity of total costs was verified with age in the regression analysis considering all patients (Coef. -0.036; 95% CI, -0.12–0.04). A low elasticity was found in the regression considering patients with COVID-19 (Coef. 0.1788; 95% CI, -0.17–0.53) even though patients with COVID-19 and aged older than 60 years presented higher costs (table 7). In summary, patient age did not influence ICU costs (p-value > 5%).

Both models confirmed a high elasticity of direct costs with severity. In this case, the regression for all patients showed an elasticity coefficient of 2.327 (95% CI, 1.86–2.78), and when considering only COVID-19 patients, the elasticity coefficient was 2.067 (95% CI, 0.34–3.79). That is, higher severity scores mean that costs will be increased by more than 2x.

After we tested median costs between the two groups (table 6), the overall results suggested that the incidence of COVID-19 increased direct costs by 36% (antilog [0.306] -1) during the hospitalization period (95% CI, 10%–67%). In indirect and total costs, these proportions were 20% (95% CI, 10–32%) and 22% (95% CI, 11–34%), respectively. The results indicated that, on average, patients diagnosed with COVID-19 were positively correlated with

ICU costs, especially when analyzing the use of medications and medical supplies (figure 7 and 8).

5. DISCUSSION

The outbreak of the disease caused by the new coronavirus has resulted in hundreds of thousands of deaths worldwide, with severe impacts on the capacity of health care systems and ultimately on the global economy. However, the economic consequences to the health care sector have not yet been clarified and discussed in light of scientific evidence. As the new coronavirus disease spread worldwide, the ICU community had to be prepared for the challenges of this pandemic, and critical care triage was necessary to allow the rationing of scarce resources (PHUA *et al.*, 2020). The study analyzed the impact of patients with COVID-19 on ICU costs by comparing them with patients admitted for other reasons. The results revealed that patients suffering from COVID-19 increased ICU costs, confirming this study's alternative hypothesis, mainly regarding the direct costs of medical supplies and medications.

The observed differences were greater than those found in health care-associated infections due to multidrug resistant bacteria, for example, which increased mean ICU direct costs in 26% (SU *et al.*, 2020). Given the uncertainties and severe clinical manifestations of the disease, optimal resource allocation is necessary. Otherwise, the pandemic can overburden the health care system Emanuel *et al.* (2020) and generate additional costs. We also detected that the direct costs of patients with COVID-19 were susceptible to the severity score (verified by the nursing workload). One of the possible causes for this relationship could include the pre-existing comorbidities found in patients with COVID-19 (FANG; KARAKIULAKIS; ROTH, 2020).

Hospitalizations for COVID-19 considerably exceeded the LOS of those for other causes. The need for mechanical ventilation can explain these additional days in the ICU: Most of the ICU patients, who spent a median of 15 days of hospitalization, needed mechanical ventilation (TURCOTTE *et al.*, 2020). Understanding the length of hospitalization for patients with COVID-19 is required to estimate the limits of hospital capacity and forecast staff and equipment (REES *et al.*, 2020). This difference is more significant among male than female patients, and among those over 60 years old in comparison to younger patients. The median LOS in the ICU for patients over 65 years old with pneumonia is between 9 and 12 days Rozenbaum *et al.* (2015), while that of patients with COVID-19, according to our results, is around 23 days. The direct costs of patients with COVID-19 were found to be more sensitive to the LOS than the indirect and total costs, revealing that additional days of hospitalization increased the use of medications and medical supplies in these patients.

The results also showed that age was not a significant variable regarding ICU costs. Particularly in patients over the age of 60, COVID-19 had a strong influence on costs. Ages over 65 are associated with risk factors for death Mehra *et al.* (2020), which may be related to the high costs identified in this age group. Male patients diagnosed with COVID-19 consumed more medical supplies and medications than those hospitalized for non-COVID-19 causes. This difference also occurred regarding LOS, causing high costs differences throughout the hospitalization period. These results are in line with evidence that demonstrates the prevalence and severity of COVID-19 in male patients (CAI, 2020). Among female patients, there were no differences in daily patient costs (indirect); these were only observed in total costs and LOS during the hospitalization period.

The strong impact of COVID-19 on inpatient costs, as observed in results, is similar to the high costs of ICU hospitalization considering patients affected by sepsis. By using a bottom-up approach for determining the direct costs of 385 patients admitted to the ICU with severe sepsis, a study revealed a long length of stay (mean 16·6 days), a high mortality rate, and substantial expenses for treating this disease, especially considering the high costs of medications used in the effort of keeping patients alive (MOERER *et al.*, 2002). Such similarity in costs between patients with COVID-19 and sepsis could be explained by the hypothesis of a process named viral sepsis being crucial for the COVID-19 disease mechanism (LI *et al.*, 2020a). The impact of COVID-19 on ICU costs can also be associated to a high proportion of patients who require mechanical ventilation (BHATRAJU *et al.*, 2020). The mean cost and length of stay in the ICU of patients requiring mechanical ventilation were US$ 31 600 and 14·4 days, respectively, while those of patients who did not require mechanical ventilation were US$ 13 000 and 8·5 days (DASTA *et al.*, 2005).

The results of the study indicate higher expenses considering patients with COVID-19 than other ICU admissions. Econometric evidence has shown that patients with the new coronavirus disease generated significant (direct: 36%) increases in ICU costs. Cost of illness can be an excellent economic tool to inform decision-makers, as long as the study design is innovative and capable of measuring the real cost to society (TARRICONE, 2006). The economic evidences of the study regarding the ICU contribute to explaining the cost pressure on the health care system Porter; Teisberg (2006), whether in prices charged by health insurances, in society's access to hospital services, or ultimately in the budget of public health care systems. Based on our results, the high spread rates of this virus, and the number of hospitalizations, we can estimate that the costs of COVID-19 should increase this pressure on the whole health care system.

Researchers are currently working to understand the effectiveness of therapies that aim to cure and save the lives of people with COVID-19. At the same time, this study revealed that the therapies used so far have spent a significant amount of resources, either related to medications and medical supplies or due to the excessive time spent on the care of these patients. The potential severe respiratory syndrome in patients with COVID-19 led different therapies to be tested, suggested, and performed (MATTHAY; ALDRICH; GOTTS, 2019). Even though some health systems offer advanced therapies, no local or regional coordination, or even a national reference protocol, have been established (MATTHAY; ALDRICH; GOTTS, 2019). In addition to the absence of an effective drug, these factors lead to a lack of standard treatment protocols for patients with COVID-19 and ultimately increase ICU costs. We speculate that the development of an effective treatment may contribute to a reduction in the resources directed to patients hospitalized with COVID-19, which could possibly result in a reduction of the high costs shown in this study.

Based on the study results, table 10 summarises the main conclusions around the research hypotheses.

Table 10 – Synthesis of the set of conclusions

Hypothesis	Results	Conclusions
H1: Patients hospitalized with COVID-19 severely add costs to intensive care units.	Confirmed	Patients with COVID-19 consume more direct resources (medications and medical supplies) than other ICU admissions. This increase is 36%.
H1a: Men hospitalized with COVID-19 have higher costs than men hospitalized for other causes in ICU.	Confirmed	The costs of men with COVID-19 are higher, mainly direct costs and costs during the total period of hospitalization (due to the extended stay).
H1b: Age positively influences the costs of patients with COVID-19 hospitalized in the ICU.	Non-Confirmed	Age was not considered a variable that influences ICU costs. However, in the group-specific of patients over 60 years and with COVID-19, high costs were identified.
H1c: LOS positively influences the costs of patients with COVID-19 hospitalized in the ICU.	Confirmed	Costs of patients hospitalized with COVID-19 are elastic to the length of ICU stay. The high LOS of patients with COVID-19 influences costs during the hospitalization period.
H1d: Severity positively influences the costs of patients with COVID-19 hospitalized in the ICU.	Confirmed	Severity is a variable that can "double" the costs of patients hospitalized with COVID-19 in the ICU.

Source: The author

The study confirmed the central hypothesis that patients with COVID-19 add extra costs in the ICU, especially concerning direct resources. Except for hypothesis H1b (age), the other secondary hypotheses were confirmed, emphasising the importance of severity as one of the main factors of influence on the costs of patients with COVID-19 hospitalized in the ICU.

6. FINAL REMARKS

This study aimed to calculate the influence of COVID-19 on the costs of ICU patients in comparison to patients admitted forother causes. Data were collected from 544 patients hospitalized in an ICU of a private hospital in southern Brazil. Among these, 40 identified with COVID-19 and 504 with other causes. Data were collected from a systematic process, including direct and indirect cost data and patient characteristics variables. All these data were submitted to statistical and econometric tests.

The study results showed that patients hospitalized with COVID-19 have a substantial economic impact in intensive care units, as they require a large volume of resources, especially with the use of medical supplies and medications. The evidence of this research confirms that, in addition to a severe public health problem and macroeconomic impacts, COVID-19 may substantially impact health financing, given the high cost of treating these patients in intensive care units.

The study results confirm that ICU patients with COVID-19 had a very long length of stay, especially compared to other hospitalization causes. As a result, their expenses during the total period of hospitalization are high. They are patients who consume more medical supplies and medications. Besides, the use of these patients' materials and medications, as revealed in this study, has a higher average cost than other hospitalizations. Based on this evidence, the lack of knowledge about the disease and the absence of an effective treatment protocol seems to be influencing the additional expenses of affected patients and hospitalized by SARS-Cov-2, which is justified by the high use of resources.

This research also aimed to identify the ICU costs originated by COVID-19 according to hospitalized patients' profile. In this case, the study revealed that older patients (over 60 years of age) consume significant ICU resources. Their expenses were very high compared to other causes of hospitalization, which can be ten times higher. High costs were also found in male patients. These results are in line with studies that revealed greater disease severity in elderly patients and men.

The econometric model helped identify the main factors that influence the costs of patients with COVID-19 in ICU. Among the main results, severity is the variable with the most significant influence on direct costs (medical supplies and medications); that is, the costs of ICU patients with COVID-19 are very sensitive to the severity score, with an elasticity of 2.067. The costs were also elastic to the LOS variable. In this case, daily costs increase with each additional day of hospitalization. Although group over 60 years of age with COVID-19 add extra costs in the ICU, we reject the hypothesis that age is a variable of influence on ICU costs. Finally, analyzing all 544 hospitalizations and considering patients with COVID-19 as a dummy variable, the econometric model revealed that hospitalizations by COVID-19 increase ICU costs by 36%.

This research can serve as a reference to generate knowledge and initial data about COVID-19 for future research in health economics. Its costs can serve as a subsidy or reference for cost-effectiveness or cost-utility models. Given the high consumption of resources by these patients and the restrictions on health agents' financial capacity, understanding the effectiveness of treatments becomes a fundamental issue for the decision-making process of allocating and managing resources to treat patients with COVID-19.

Further studies are required on the economic impacts of this pandemic on health care, as more data on hospitalization costs are revealed. This study is consistent in stating that COVID-19 exerts intense pressure on ICU costs but has a limitation when comparing it with the costs of all other diseases. It may still be necessary to compare it with the costs of similar health issues such as other respiratory diseases. Given the high number of cases currently with COVID-19, new studies on economic impacts are suggested, with more robust samples, to obtain results with more statistical robustness. Similarly, studies, including new variables in econometric models, are suggested to understand better the factors affecting ICU costs.

In conclusion, this study contributes to understanding the behavior of ICU costs, especially considering patients diagnosed with COVID-19. Our results could help the medical community, health care administrators, and governments in the management and allocation of resources, especially at a time when the COVID-19 pandemic is exhausting the capacity of hospitals and limiting ICU resources.

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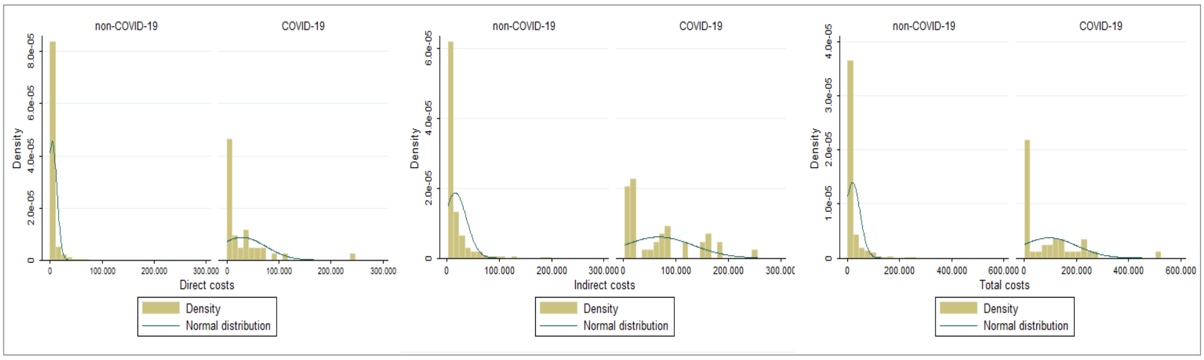
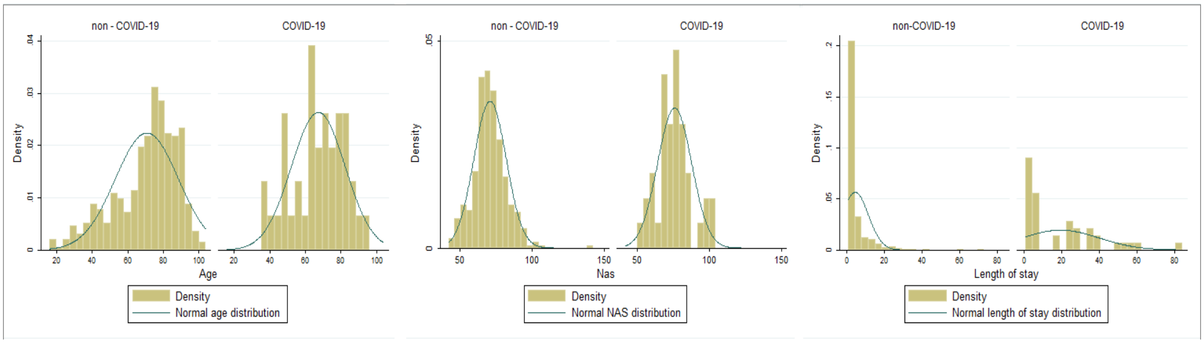
APENDIX A - HISTOGRAM OF HOSPITALIZATION COSTS: NON-COVID-19 X COVID-19



Source: The author
Note: Distribution of direct, indirect, and total costs in the sample of patients admitted to the intensive care unit.

APPENDIX B - HISTOGRAM OF AGE, SEVERITY, AND LENGTH OF STAY: NON-COVID-19 X COVID-19



Source: The author

APPENDIX C - TEST FOR EQUALITY OF DISTRIBUTION FUNCTIONS: KOLMOGOROV-SMIRNOV (K-S).

	Obs		**Combined K-S**		
Variable	**Non-COVID-19**	**COVID-19**	**D**	**p-value**	**Corrected**
Length of stay	504	40	0.4175	0.000	0.000
Age	504	40	0.1885	0.144	0.105
Severity (NAS)	504	40	0.2480	0.021	0.013
Daily hospitalization costs					
Direct costs	504	40	0.3698	0.000	0.000
Indirect costs	504	40	0.1480	0.391	0.320
Total costs	504	40	0.1548	0.337	0.270
Total hospitalization costs					
Direct costs	504	40	0.4262	0.000	0.000
Indirect costs	504	40	0.4687	0.000	0.000
Total costs	504	40	0.4625	0.000	0.000

Source: The author

Note: The Kolmogorov-Smirnov test was used to analyze whether there was a difference between variances of the sample. The analysis has corroborated the results of median, where all differences were statistically significant (p-value < 5%) except for age and daily indirect and total costs.

APPENDIX D - CORRELATION (COVARIANCE) OF VARIABLES TEST

	Length of stay	Age	NAS
Length of stay	1.0000		
Age	0.0567 (0.1868)	1.0000	
Severity (NAS)	0.3215 (0.0000)	0.1130 (0.0083)	1.0000

Source: The author

Note: The correlation of variables was tested in order to identify whether there was a correlation between the variables to be used in the regression models. A low correlation was found between the variables, thus all of them could be used in the ordinary least squares (OLS) regression without affecting estimates of the best betas. The p-value is shown in parentheses.

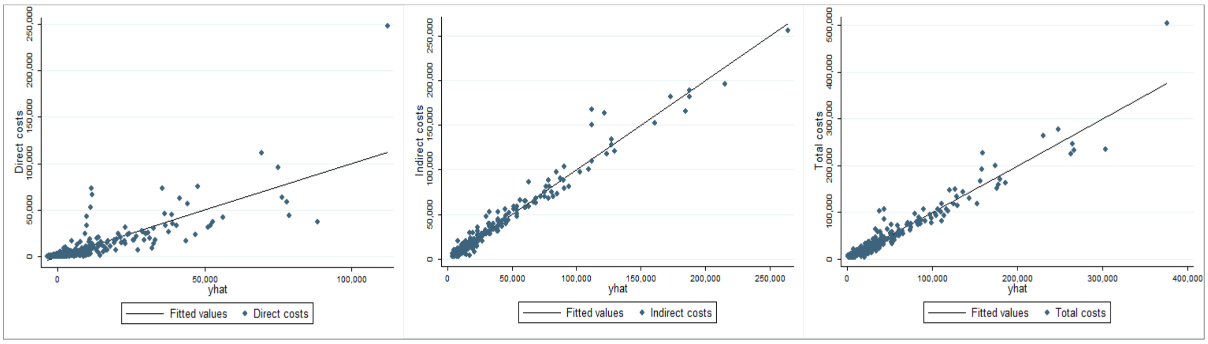
APPENDIX E - ORDINARY LEAST SQUARES – (OLS)

	Direct costs		Indirect costs		Total costs	
	Coefficient	**CI (95%)**	**Coefficient**	**CI (95%)**	**Coefficient**	**CI (95%)**
COVID-19	5,267.477* (3.10)	1,930–8,604	5,976.921*** (6.42)	4,148–7,804	11,244.41*** (5.78)	7,420–15,069
Length of stay	1,281.231*** (26.37)	1,185–1,376	3,045.051*** (114.39)	2,992–3,097	4,326.279*** -77.68	4,217–4,436
Age	-53.316* (-2.30)	-98·8–-7.79	15.235 (1.2)	-9.69–40.17	-38.080 (-1.43)	-90.25–14.10
Severity (NAS)	89.527* (2.37)	15·3–163.73	27.783 (1.34)	-12.87–68.43	117.314** (2.71)	32.25–202.37
Constant	-4,549.431 (-1.54)	-10,367–1,268	-959.903 (-0.59)	-4,146–2,227	-5,509.54 (-1.62)	-12,177–1,158
F(3 , 540)	265.68***		4,535.17***		2,148.14***	
R-squared	0.66		0.97		0.94	
N	544.00		544.00		544.00	

Source: The author

Note: Dependent variables: direct, indirect, and total costs during the hospitalization period, expressed as continuous variables in Brazilian Real (R$). Independent variables: COVID-19 patients (dummy variable) = 1 and non-COVID-19 patients =0, age, severity (NAS), and length of stay. T statistics are shown in parentheses. In the next appendices (F to O), the quality of the presented model was analyzed and tested. ***p-value < 0·001, **p-value < 0·01, and *p-value < 0·05.

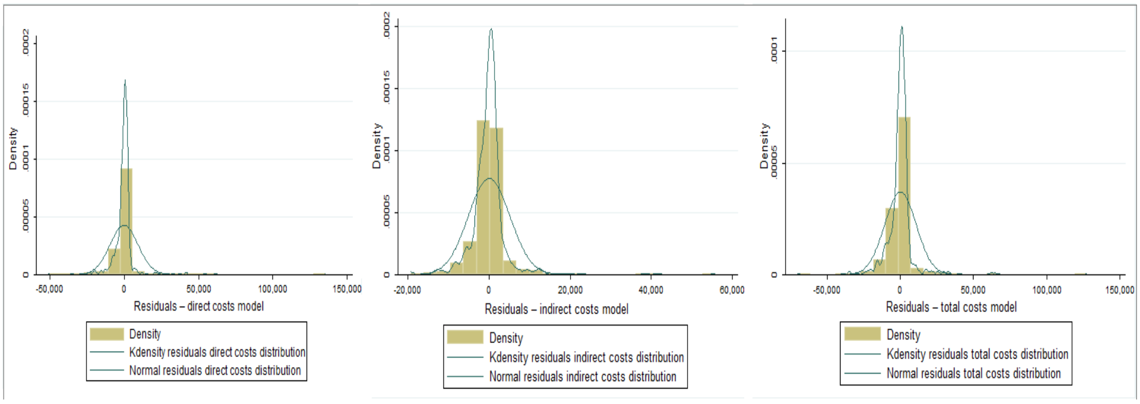
APPENDIX F - TWO-WAY SCATTER PLOT – YHAT ORDINARY LEAST SQUARES



Source: The author

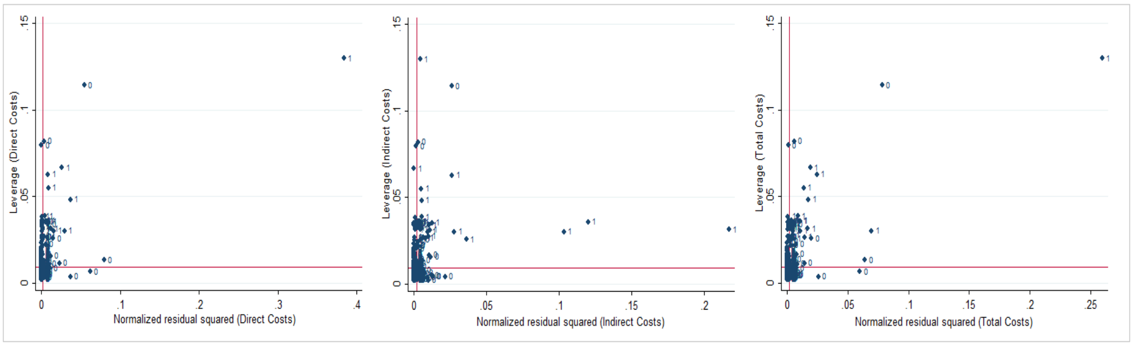
Note: A higher residual dispersion was found in the direct cost model, in addition to one outlier. The best adjustment was obtained in the indirect cost model. The total cost model presented one outlier. Based on the graphical models, the leverage and weight of the residuals should be checked in order to identify whether they might interfere in the beta estimates.

APPENDIX G - RESIDUAL HISTOGRAM



Source: The author
Note: The residuals did not present a normal distribution. In this case, further tests are recommended to identify possible heteroscedasticity problems. It seems that residuals have not presented a homoscedastic pattern.

APPENDIX H - LEVERAGE AND SQUARED RESIDUALS



Source: The author
Note: According to the Cook method, observations located above one are capable of interfering in the model where non-COVID-19 patients = 0 and COVID-19 patients = 1. Residuals with weight and leverage above the recommended value were found in the three models, which may interfere with the residual distribution pattern and affect the estimators.

APPENDIX I - VARIANCE INFLATION FACTOR (VIF) TEST - MULTICOLLINEARITY

Test Multicollinearity

Variable	VIF	1/VIF
Length of stay	1.31	0.760713
COVID-19	1.20	0.831904
Severity (NAS)	1.13	0.887614
Age	1.02	0.980370
Mean VIF	1.17	

Source: The author

Note: This test aimed to identify whether the model presented multicollinearity between the variables. None of the variables had VIF > 10 or 1/VIF < 0·1, thus there was not a perfect linear relationship among the predictors and the regression model estimates could use all variables in the same model.

APPENDIX J - BREUSCH-PAGAN (BP) / COOK-WEISBERG TEST FOR HETEROSCEDASTICITY

Ho: Constant variance					
BP: direct costs		BP: indirect costs		BP: totalcosts	
Chi2:	5,304.37	Chi2:	1,274.72	Chi2:	3,815.48
Prob > chi2:	0.0000	Prob > chi2:	0.0000	Prob > chi2:	0.0000

Source: The author

Note: Chi2: chi-squared; Ho: null hypothesis; prob: probability.

The results of this test indicated possible heteroscedasticity problems. Robust matrix models are recommended for correcting this problem.

APPENDIX K - RAMSEY RESET TEST USING POWERS OF THE FITTED COSTS VALUES

Ho: Model has no omitted variables					
Direct costs		Indirect costs		Total costs	
F(3, 536)	124.19	F(3, 536)	13.35	F(3, 536)	69.41
Prob > F	0.0000	Prob > F	0.0000	Prob > F	0.0000

Source: The author

Note: RESET: regression equation specification error test; Ho: null hypothesis; prob: probability.
The RESET adds polynomials to the value estimates to detect general types of non-linear combinations in model specification. The results show functional problems, as Ho has been rejected (p-value < 5%). In addition to the use of robust matrices, the variables were expressed in a logarithmic scale in order to reduce functional problems.

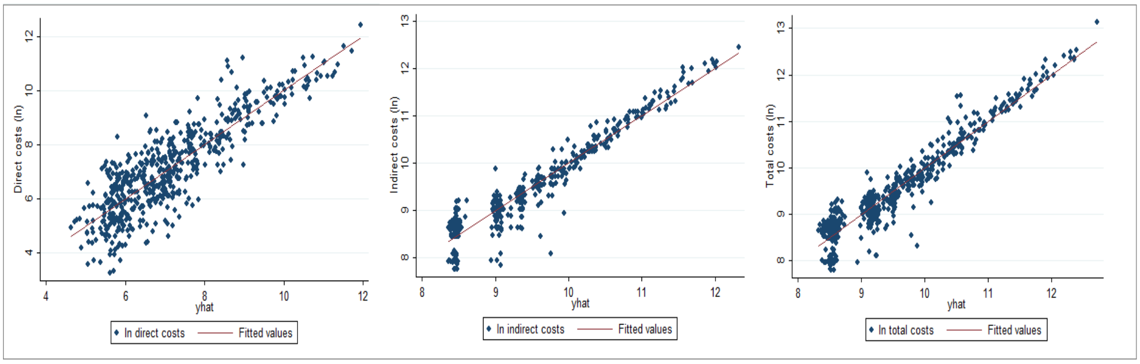
APPENDIX L - ORDINARY LEAST SQUARES (ROBUST)

	Direct costs (ln)		Indirect costs (ln)		Total costs (ln)	
	Coefficient	**CI (95%)**	**Coefficient**	**CI (95%)**	**Coefficient**	**CI (95%)**
COVID-19	0.306** (2.91)	0.09–0.51	0.183*** (3.89)	0.09–0.27	0.196*** (4.01)	0.10–0.29
Length of stay (ln)	1.212*** (33.24)	1.14–1.28	0.820*** (69.78)	0.79–0.84	0.874*** (70.22)	0.84–0.89
Age (ln)	-0.111 (-0.87)	-0.36–0.14	0.022 (0.6)	-0.05–0.09	-0.036 (-0.83)	-0.12–0.04
Severity (NAS)	2.327*** (9.9)	1.86–2.78	0.196* (2.28)	0.02–0.36	0.456*** (5.14)	0.28–0.63
Constant	-3.599*** (-3.26)	-5.77–-1.43	7.533*** (19.83)	6.78–8.27	6.773*** (17·11)	5.99–7.55
F (4 , 539)	623.06***		1823.3***		1928.01***	
R-squared	0.7468		0.9104		0.9141	
N	544		544		544	

Source: The author

Note: To make estimators less inclined to the influence of outliers (except for the COVID-19 dummy variable), all other values were changed into a logarithmic scale (ln). Regarding the heteroscedasticity problems highlighted in the Breusch-Pagan test, the betas were estimated in robust matrices with expanded variance matrices, adjusting residual weighs. The estimated coefficients represent the elasticity between the dependent and independent variables. The COVID-19 dummy variable represents the variation (after being transformed into an anti-log) of costs concerning other intensive care unit admissions. T statistics are shown in parentheses. ***p-value < 0·001, **p-value < 0·01, and *p-value < 0·05.

APPENDIX M - TWO-WAY SCATTER PLOT – YHAT OLS (ROBUST)



Source: The author

Note: The model with robust matrices and ln variables fulfilled its objective regarding the treatment of outliers and the heteroscedasticity problem.

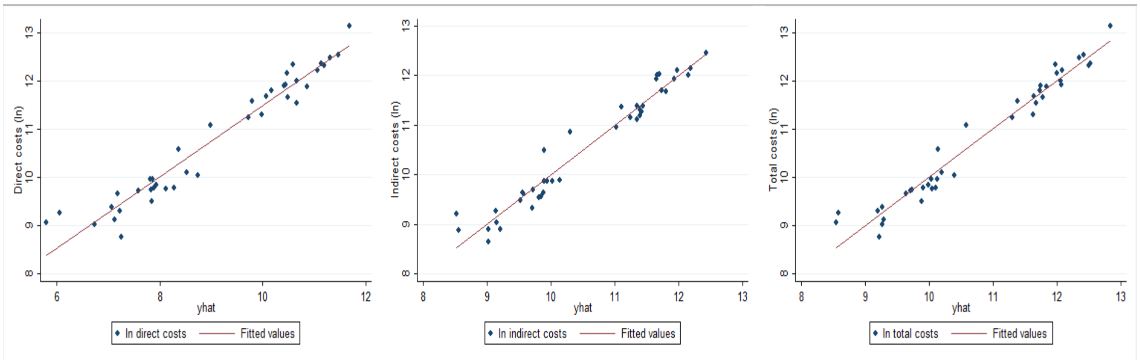
APPENDIX N - ORDINARY LEAST SQUARES (OLS): COVID-19 PATIENTS

	Direct costs (ln)		Indirect costs (ln)		Total costs (ln)	
	Coefficient	**CI (95%)**	**Coefficient**	**CI (95%)**	**Coefficient**	**CI (95%)**
Length of stay (ln)	1.1055*** (12.94)	0.93–1.27	0.9000*** (22.6)	0.81–0.98	0.9427*** (21.22)	0.85–1.03
Age (ln)	0.0382 (0.10)	-0.76–0.83	0.216 (1.27)	-0.12–0.56	0.1788 (1.02)	-0.17–0.53
Severity (NAS_ln)	2.0670* (2.43)	0.34–3.79	-0.3917 (-1.13)	-1.09–0.31	0.0892 -0.25	-0.63–0.81
Constant	-2.5525 (-0.70)	-9.94–4.83	9.2695*** (7.39)	6.72–11.81	7.50*** -5.29	4.62–10.37
F(3 , 36)	94.5***		221.66***		206.64***	
R-squared	0.916		0.9521		0.9585	
N	40		40		40	

Source: The author

Note: The OLS model verifying length of stay, age, and severity as independent variables and direct, indirect, and total costs of patients with COVID-19 as dependent variables. The estimated coefficients represent the elasticity between the dependent and independent variables. Variables were adapted on a logarithmic scale. T statistics are shown in parentheses. ***p-value < 0·001, **p-value < 0·01, and *p-value < 0·05.

APPENDIX O - TWO-WAY SCATTER PLOT – YHAT ORDINARY LEAST SQUARES (ROBUST) – COVID-19 PATIENTS



Source: The author
Note: The residuals are adherent to the slope of the line, which corroborates the results found in appendix M.