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Assessment of Decompressive Craniectomy in Patients with Malignant Cerebral Infarction and Co-Occurring SARS-CoV-2 Infection

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Abstract

Background: Malignant ischemic stroke is a known cerebrovascular complication in patients with SARS-CoV-2 infection, and decompressive craniectomy has been proposed as a treatment option. However, there is limited data available on the outcomes of patients with malignant stroke and concurrent SARS-CoV-2 infection. This study aimed to investigate whether decompressive craniectomy is beneficial for patients with malignant stroke and SARS-CoV-2 infection. **Methods:** This case-control study was conducted between March 2020 and December 2021, involving patients diagnosed with malignant stroke who underwent decompressive craniectomy. A total of 52 patients were included and divided into two groups: Group 1 consisted of patients with malignant ischemic stroke and concurrent SARS-CoV-2 infection (n = 20), while Group 2 comprised patients with malignant ischemic stroke without SARS-CoV-2 infection (n = 32). Medical data were collected for analysis. **Results:** The data analysis included variables such as diagnosis of COVID-19 and clinical outcome of death. Statistical tests, including the Chi-squared test with Yates's correction ($p = 0.9094$), Fischer's Exact Test ($p = 0.7708$), Coefficient φ (0.0568), and Odds Ratio (1.273, 95% CI: 0.4332 - 4.343), were conducted using a contingency table. The results showed no significant association between SARS-CoV-2 infection and the clinical outcome of death. **Conclusion:** The findings indicate that patients with SARS-CoV-2 infection benefit from decompressive craniectomy for the treatment of malignant stroke to the same extent as patients without viral infection. This study provides valuable insights into the efficacy in patients with malignant stroke and SARS-CoV-2 infection. Further research is warranted to confirm these findings and explore additional factors that may influence patient outcomes in this context.

Keywords

Ischemic Stroke, Decompressive Craniectomy, RNA, Viral, Case-Control Studies, COVID-19, Stroke

1. Introduction

Since the emergence of COVID-19 in December 2019, it has posed significant logistical challenges for healthcare services worldwide. This situation has been particularly complex in developing countries, where limited resources, both human and material, have exacerbated the difficulties. The pandemic has necessitated adaptations across various medical specialties, including neurosurgery, which has faced challenges such as reduced availability of intensive care unit beds. Furthermore, COVID-19 has resulted in a decrease in surgical volume, increased reliance on telemedicine, redeployment of surgeons to non-surgical medical duties, and significant physical, mental, and emotional strain on healthcare professionals (Khalafallah et al., 2020; Zoia et al., 2020).

COVID-19 is an infectious disease caused by an RNA virus called SARS-CoV-2, which belongs to the *Coronaviridae* family. The disease manifests itself, in most cases, through mild to moderate respiratory symptoms. Nevertheless, some patients develop critical varieties, such as Severe Acute Respiratory Syndrome (SARS). Human-to-human transmission occurs via the respiratory route by inhaling droplets released by coughing, sneezing, or by direct contact with infected secretions taken to the mouth, nose, or eyes (Habas et al., 2020; Du et al., 2020). Shi et al. (2020), in a review study, pointed out that the most common clinical manifestations are fever, fatigue, cough, myalgia, and dyspnea. A death rate of 2% to 3% is estimated.

As COVID-19 spread around the world, evidence of an association with cerebrovascular disease, as well as other varieties of vasculopathy, increased. This type of manifestation appeared in 13 (6%) of 221 patients with COVID-19 in a retrospective series of cases from Wuhan. Other studies in Spain, the United States, and China indicated that 1% to 1.6% of hospitalized patients were affected by cerebrovascular diseases (Almqvist et al., 2020). In Milan, Italy, nine (2%) of the 388 hospital patients diagnosed with COVID-19 developed Cerebrovascular accidents (CVA). Although the most predominant and crucial symptom is a respiratory disease, neurological manifestations are being increasingly recognized (Ellul et al., 2020). There is also evidence that SARS-CoV-2 infection makes patients with pre-existing cardiometabolic illnesses more vulnerable to critical vascular events, such as stroke (Aghayari Sheikh Neshin et al., 2021). Ischemic brain injury appears to be most common in the course of more severe disease. In a Chinese study, for example, 20% of deceased patients with SARS-CoV-2 showed signs of hypoxic encephalopathy, in contrast to only 1% of patients who recovered (Almqvist et al., 2020; Dominguez, Robinson, & Holmes,

2009; Romero-Sánchez et al., 2020).

The principal pathophysiological substrates for cerebrovascular complications are hyperinflammation-mediated endotheliopathy and consumption hypercoagulopathy. Endothelial dysfunction is known for potentially leading to systemic and cerebral vascular complications. In addition, hypercoagulopathy may be related to sepsis, cytokine storm, or immune dysregulation. Pro-inflammatory cytokines (e.g., TNF-alpha, IL-1, and IL-6) and immune dysregulation following extensive tissue injury lead to further activation of coagulation pathways. Researchers also speculate that the direct infection caused by SARS-CoV-2 in the endothelial cells of the cerebral microvasculature may contribute to the pathophysiology of strokes (Ellul et al., 2020; Najjar, Najjar, Chong, Pramanik, Kirsch, Kuzniecky, Pacia, & Azhar, 2020).

Based on the current literature, it is impossible to predict how long COVID-19 survivors would be prone to an increased risk of ischemic stroke (IS) or hemorrhagic stroke (HCVA). It is known that advanced age, hyperlipidemia, diabetes mellitus, arterial hypertension, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, rheumatic diseases, malignant neoplasm, obesity, and smoking are associated with intense COVID-19 effects, and, consequently, increasing the risk of stroke in this group of patients (Aghayari Sheikh Neshin et al., 2021).

The multicenter studies DECIMAL (Vahedi et al., 2007), DESTINY (Jüttler et al., 2007; Jüttler et al., 2011), and HAMLET (Hofmeijer et al., 2009) have established decompressive craniectomy as the gold standard procedure for managing severe ischemic stroke. However, the efficacy of this surgical intervention in patients with malignant ischemic stroke and concurrent SARS-CoV-2 infection remains uncertain. Therefore, the primary objective of this investigation is to determine the potential benefits of procedure in treating patients with malignant ischemic stroke and SARS-CoV-2 infection.

Preliminary discussions have indicated limited evidence based on case reports and small case series (Bhatia et al., 2021; Chan, Salonga, & Khu, 2021; Liang et al, 2020; Sáez-Alegre et al., 2021), suggesting a suboptimal response to this surgical approach. These findings warrant further exploration of alternative strategies. As such, this study aims to contribute to the existing knowledge by evaluating the use of decompressive craniectomy for managing malignant ischemic stroke within the context of the ongoing COVID-19 pandemic.

2. Methods

2.1. General Plan

This study follows an observational analytical case-control design. The medical records of patients diagnosed with malignant ischemic stroke who underwent decompressive craniectomy between March 2020 and December 2021 were examined. The survey was conducted in the medical accounts sector of the General Hospital of Fortaleza (HGF).

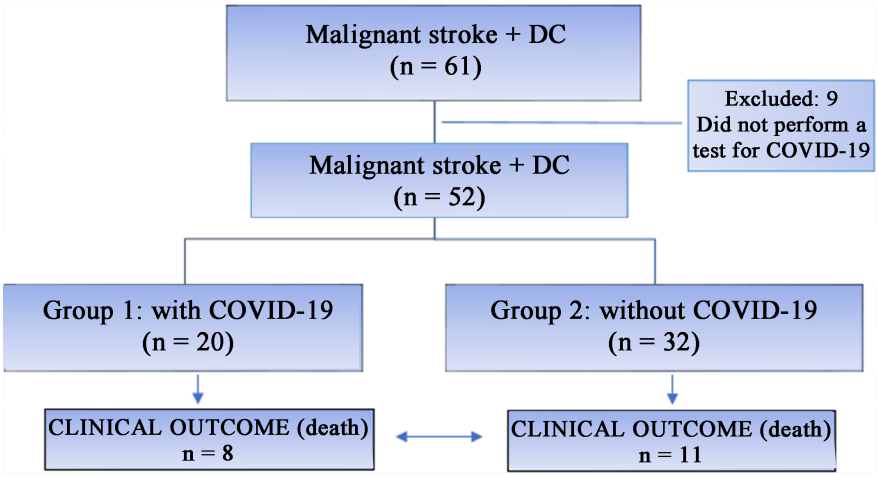


Figure 1. Schematic diagram of the case-control study. Stroke, ischemic stroke; DC, decompressive craniectomy.

Both physical and digital medical records were utilized as data sources to collect information on the following variables: COVID-19 diagnosis, sex, age, comorbidities, NIHSS admission, Glasgow Coma Scale (GCS) upon admission, stroke date, decompressive craniectomy date, and clinical outcome.

In the study, **Figure 1** provides a visual representation of the patient distribution and grouping. Among the initial pool of 61 patients who underwent the procedure, nine were excluded due to insufficient clinical information. The remaining 52 patients were divided into two distinct analytical groups based on their condition. Group 1 comprised patients (n = 20) who underwent decompressive craniectomy for malignant ischemic stroke while also being diagnosed with SARS-CoV-2 infection. It's important to note that inclusion in Group 1 was limited to patients who had a confirmed diagnosis of COVID-19, supported by various factors such as epidemiological, clinical, and radiological evidence, and validated through serological tests or RT-PCR. On the other hand, Group 2 consisted of patients (n = 32) who underwent decompressive craniectomy for malignant ischemic stroke but did not have a SARS-CoV-2 infection.

The compiled data was inputted into software to verify the information and conduct a comparative analysis of the collected observations. Through data standardization and information processing, the researchers obtained a critical analysis that could provide answers to the initial research question.

2.2. Ethics Statement

It is research that contains quantitative and qualitative variables developed at the Neurosurgery Service of the General Hospital of Fortaleza (HGF). The project was approved by the Comitê de Ética em Pesquisa (Research Ethics Committee) of the HGF, via Plataforma Brasil, following opinion No. 59300022.4.0000.5040. All patients received information of participation in this study and provided written informed consent.

2.3. Patients

Table 1 contains the list of patients included in the study. A total of 52 patients were admitted, consisting of 20 belonging to the COVID-19 (+) group and 32 to the COVID-19 (−) group.

Table 1. Patients are separated into two groups of carriers and non-carriers of COVID-19.

PATIENT	COVID-19	SEX	AGE	COMORBI.	NIHSS	GCS	ICTUS	DC	CLINICAL OUTCOME
MDFS	YES	F	57	SAH/CKD	22	15	03/05/2020	03/09/2020	DEATH
MOS	YES	F	68	SAH	23	11	03/22/2020	03/24/2020	DEATH
MLPS	YES	F	61	SAH/DM2	20	11	07/04/2020	07/05/2020	RELEASE
MPRS	YES	F	56	SAH	20	14	08/14/2020	08/15/2020	RELEASE
FSM	YES	F	67	SAH	16	15	10/14/2020	10/17/2020	RELEASE
RGSS	YES	F	46	SAH	32	11	11/21/2020	11/22/2020	RELEASE
MAMC	YES	M	41	SAH/DM2	18	15	01/01/2021	01/04/2021	RELEASE
FIGL	YES	M	58	DM2	21	14	01/15/2021	01/16/2021	RELEASE
MFC	YES	M	50	NO	25	11	02/12/2021	02/15/2021	DEATH
FBM	YES	M	70	SAH	14	12	03/14/2021	03/16/2021	DEATH
MGS	YES	M	74	DM2	21	11	03/22/2021	03/25/2021	DEATH
RBA	YES	F	47	SAH	28	10	03/25/2021	03/29/2021	RELEASE
FVSF	YES	M	56	SAH	24	15	03/28/2021	03/29/2021	RELEASE
RRB	YES	F	38	SAH/DM2	11	13	05/11/2021	05/12/2021	DEATH
JAN	YES	M	63	SAH	24	9	05/16/2021	05/17/2021	DEATH
PIOB	YES	M	61	SAH/DM2	14	13	05/25/2021	05/27/2021	RELEASE
FER	YES	M	40	NO	26	13	05/30/2021	06/01/2021	RELEASE
RMNS	YES	F	44	SAH	20	9	06/10/2021	06/10/2021	RELEASE
RSR	YES	M	47	SAH/DM2	10	15	06/18/2021	06/20/2021	RELEASE
RVAJ	YES	M	41	NO	20	13	07/23/2021	07/25/2021	DEATH
AAT	NO	M	68	SAH	22	10	05/02/2020	05/03/2020	RELEASE
SNS	NO	M	48	NO	21	10	06/10/2020	07/01/2020	RELEASE
TFS	NO	F	29	NO	25	14	07/02/2020	07/04/2020	RELEASE
MSPP	NO	F	51	NO	16	14	07/16/2020	07/18/2020	RELEASE
MSSR	NO	F	49	SAH/DM2	24	14	08/10/2020	08/10/2020	RELEASE
MESM	NO	F	55	NO	25	10	10/05/2020	10/06/2020	DEATH
WBL	NO	M	54	SAH	19	15	10/06/2020	10/07/2020	RELEASE
MILM	NO	F	60	SAH/DM2	24	9	10/31/2020	11/01/2020	RELEASE

Continued

FJFS	NO	F	49	NO	19	11	11/19/2020	11/20/2020	RELEASE
OMA	NO	M	57	SAH/DM2	20	15	11/30/2020	12/02/2020	RELEASE
JCS	NO	M	66	SAH	25	7	12/19/2020	12/20/2020	DEATH
ATR	NO	M	67	SAH	24	11	01/06/2021	01/07/2021	DEATH
JSS	NO	M	60	SAH	18	15	02/08/2021	02/11/2021	RELEASE
JVF	NO	M	54	SAH/DM2	NR	8	02/20/2021	02/21/2021	DEATH
JMS	NO	M	49	SAH	25	11	02/27/2021	02/28/2021	RELEASE
OMSS	NO	M	37	NO	16	15	04/18/2021	04/19/2021	DEATH
FJS	NO	M	67	SAH	18	15	04/21/2021	04/22/2021	DEATH
AERM	NO	M	42	NO	25	11	05/31/2021	06/01/2021	RELEASE
MFMS	NO	F	68	SAH	15	14	06/16/2021	06/17/2021	RELEASE
WAFS	NO	F	57	SAH	15	14	06/22/2021	06/23/2021	RELEASE
JCS	NO	M	50	DM2	17	15	06/23/2021	05/03/2020	RELEASE
AES	NO	M	57	DM2	19	15	06/28/2021	07/01/2020	DEATH
JPN	NO	M	66	NO	20	12	07/07/2021	07/04/2020	RELEASE
AJS	NO	M	59	PSOR.	NR	13	07/08/2021	07/18/2020	DEATH
PFS	NO	M	64	SAH/DM2	13	15	07/09/2021	08/10/2020	RELEASE
FVR	NO	M	67	SAH	23	11	07/25/2021	10/06/2020	RELEASE
MMDS	NO	F	56	SAH/NEO	24	10	08/02/2021	10/07/2020	DEATH
APC	NO	M	74	SAH/DM2	9	15	08/14/2021	11/01/2020	DEATH
DFG	NO	F	49	SAH	23	11	09/16/2021	11/20/2020	RELEASE
MIS	NO	F	57	SAH	5	15	10/17/2021	12/02/2020	RELEASE
MRR	NO	F	62	SAH	13	15	11/03/2021	12/20/2020	RELEASE
ASDS	NO	F	57	SAH/DM2	10	14	11/05/2021	01/07/2021	DEATH

Comorbi., comorbidities; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; DC, decompressive craniectomy; F, female; M, male; SAH, Systemic arterial hypertension; CKD, Chronic Kidney Disease; DM2, Type 2 Diabetes Mellitus; PSOR, Psoriasis; NEO, Neoplasm. NR, Not registered.

2.4. Statistical Analysis

The data underwent analysis using the GraphPad Prisma 9.3.1 statistics software designed for Windows. The researchers utilized the variables age, NIHSS, and GCS to evaluate the similarity between the COVID-19 (+) and COVID-19 (−) groups. Initially, the Gaussian distribution of these variables was examined using the Shapiro-Wilk test. A comparison was made between the COVID-19 (+) and COVID-19 (−) groups regarding the aforementioned variables using the T-test and Mann-Whitney statistical tests, as displayed in Table 2. A significance level of 5% ($\alpha = 0.05$) was employed for all tests. Missing data was not imputed, except for the NIHSS values of two patients.

Table 2. Statistical tests used. NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale.

Variables	Statistical Tests
AGE	T-test
NIHSS	Mann-Whitney
GCS	Mann-Whitney

To assess the relationship between the COVID-19 variables and clinical death, a 2 × 2 contingency table (with 1 degree of freedom) was constructed using the raw data. The following tests were conducted: Chi-squared test with Yates's correction, Fisher's Exact Test, Coefficient φ, and Odds Ratio.

3. Results

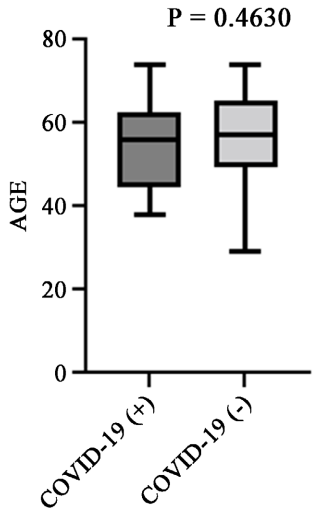
The study aimed to evaluate the effectiveness of decompressive craniectomy in patients with malignant ischemic stroke and co-occurring SARS-CoV-2 infection. The researchers collected data from both physical and digital medical records of 61 patients who underwent the procedure. The analysis of the basic demographic information, comorbidities, NIHSS admission scores, GCS upon admission, stroke dates, decompressive craniectomy dates, and clinical outcomes helps in understanding the impact of COVID-19 on stroke patients. Furthermore, the comparison between COVID-19 positive and negative patients elucidated potential differences in clinical profiles and outcomes, contributing to improved patient management strategies. Among the COVID-19 positive patients, 22 were female, and 30 were male. The age range varied from 29 - 74, with an average age of 54.6. The most prevalent comorbidity was systemic arterial hypertension. NIHSS admission scores ranged from 5 - 32, and the GCS upon admission varied from 7 - 15. Stroke dates and decompressive craniectomy dates were recorded for all patients. The clinical outcomes death showed that eight patients in the COVID-19 positive group and 11 patients in the COVID-19 negative group experienced death, while the remaining patients were released after treatment.

Graphs 1-3 indicate homogeneity between the COVID-19 (+) and COVID-19 (−) groups regarding age, NIHSS, and GCS variables.

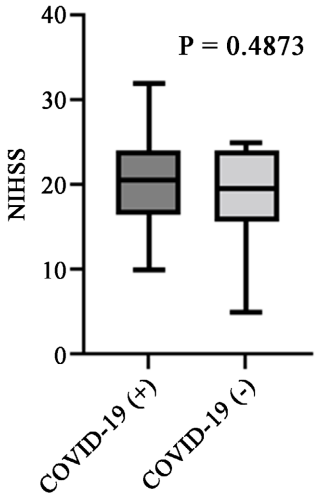
Table 3 expresses the average age, NIHSS, and GCS variables between the COVID-19 (+) and COVID-19 (−) groups.

Table 4 (2 × 2 contingency table; degree of freedom: 1) was created to analyze the association between COVID-19 and the clinical outcome of death in the group of patients with malignant ischemic stroke treated by decompressive craniectomy.

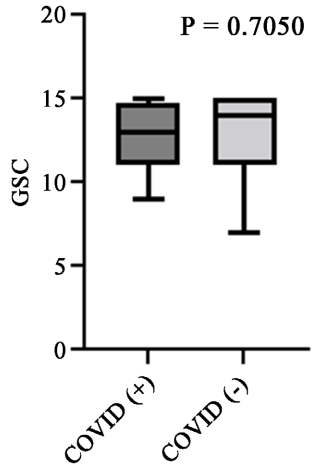
Table 5 shows the statistical tests applied to the contingency table. There is no significant association between the COVID-19 variables and the clinical outcome—death.



Graph 1. Age of patients with COVID-19 (+) and COVID-19 (−).



Graph 2. NIHSS COVID-19 (+) and COVID-19 (−) admission scale of patients with COVID-19 (+) and COVID-19 (−). NIHSS, National Institutes of Health Stroke Scale.



Graph 3. Glasgow Coma Scale for admission of patients with COVID-19 (+) and COVID-19 (−). GCS, Glasgow Coma Scale.

Table 3. The average age, NIHSS, and GCS variables. NIHSS, National Institutes of Health Stroke Scale. GCS, Glasgow Coma Scale.

	COVID-19 (+)	COVID-19 (−)
Age	54.25	56.41
NIHSS	20.45	19.07
GCS	12.50	12.63

Table 4. Relationship between the number of patients with COVID-19 and non-COVID-19 patients with the clinical outcome—death.

	DEATH	NO DEATH	TOTAL
COVID-19 (+)	8	12	20
COVID-19 (−)	11	21	32
TOTAL	19	33	52

Table 5. Statistical tests of the contingency table, which correlates the variables diagnosis of COVID-19 and clinical outcome—death.

Chi-squared test with Yates's correction (χ^2)	0.01296 ($p = 0.9094$)
Fischer's Exact Test	$p = 0.7708$
Coefficient φ	0.0568
Odds Ratio (OR)	1.273 (IC 95%: 0.4332 - 4.343)

4. Discussion

Brazil, being a continental country with significant socioeconomic disparities across its regions, has experienced varying levels of health impact and resource availability during the COVID-19 pandemic (De Macêdo Filho et al., 2021). Given the restrictions on human and material resources, it is crucial to optimize these scarce resources to ensure effective therapies and avoid unnecessary procedures. Therefore, this study aimed to determine the actual benefit of decompressive craniectomy in patients with malignant stroke and concurrent SARS-CoV-2 infection.

The study period from March 2020 to December 2021 encompassed the most critical months of the pandemic in Brazil. During the research planning phase, careful consideration was given to the importance of designing a control group exposed to similar structural and logistical conditions as the group under analysis.

To assess the homogeneity between the COVID-19 (+) and COVID-19 (−) groups, variables such as age, NIHSS, and GCS were evaluated. Graphs 1-3 demonstrated the homogeneity between the groups, indicating that SARS-CoV-2 infection did not significantly influence the age or neurological condition of patients upon admission.

A contingency table (Table 4) was prepared to analyze the relationship between the diagnosis of COVID-19 and the clinical outcome of death. The results

from the statistical tests (Table 5) indicated that, within the evaluated samples, there was no significant association between viral infection and death. These findings suggest that patients with COVID-19 derived similar benefits from decompressive craniectomy compared to those without viral infection.

A notable gap in the existing literature related to this subject was identified during the literature review. Sudheer et al. (2022) conducted a recent meta-analysis, which included only 13 case reports and series from the early phase of the pandemic, comprising a total of 20 patients (Table 6). The aggregate fatality rate in that meta-analysis was 40%, which aligns with the findings of the present study (40%; 8/20) (Table 4).

In a pre-pandemic study, Goedemans et al. (2020) found a case fatality rate of 20% in patients with malignant ischemic stroke treated by decompressive craniectomy. Multicentric studies, which served as the foundation for current approaches, such as DESTINY, DECIMAL, and HAMLET, showed lethality rates of 18%, 25%, and 22%, respectively. The case-control study presented here considers such parameters inappropriate, for they do not add in the bad conditions, or the "war medicine", caused by the COVID-19 pandemic in health services. Thus, the adoption of a control group submitted to the same adverse conditions as the study group is justified.

The present work has limitations inherent to observational and retrospective studies. From this perspective, the following stand out: 1) not measuring the functionality of surviving patients, which would complement the analysis of the clinical outcome; 2) not performing long-term follow-up of selected patients.

Table 6. Meta-analysis by Sudheer et al. (2022) modified.

N°	Author	Death	No Death	Total
1	Pisano et al. (2020)	1	0	1
2	Alkhaibary et al. (2020)	0	1	1
3	Liang et al. (2020)	1	2	3
4	Rascón-Ramirez et al. (2020)	0	2	2
5	Patel SD et al. (2020)	1	0	1
6	Patel HN et al. (2020)	0	1	1
7	Oxley et al. (2020)	0	1	1
8	Kananeh et al. (2020)	1	0	1
9	Chan et al. (2021)	1	0	1
10	Roy et al. (2021)	1	0	1
11	Scala et al. (2021)	0	1	1
12	Sáez-Alegre et al. (2021)	0	1	1
13	Sudheer et al. (2022)	2	3	5
Total		8	12	20

Even so, the research expresses valid and clarifying information for the understanding of the topic.

5. Conclusion

Based on the analyzed samples, researchers were unable to verify a statistically significant association between the clinical outcome variables death and SARS-CoV-2 infection. Therefore, researchers found that patients with COVID-19 benefit from decompressive craniectomy for the treatment of malignant ischemic stroke as much as patients without viral infection.

Author Contributions

M.W.B.S. organized the database and performed the statistical analysis. M.W.B.S. wrote the first draft of the manuscript. L.M.B.S. and L.W.B.M. conceived and designed the study. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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