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COVID-19 Impact on Intraparenchymal Hemorrhage and Surgical Outcomes: A Comprehensive Analysis

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ABSTRACT

AIM: To investigate the possible association between COVID-19 infection and intraparenchymal hemorrhage (IPH) by examining changes in the preoperative and postoperative periods, mortality, and the impact of COVID-19 on IPH survival times.

MATERIAL and METHODS: This cross-sectional retrospective analysis included 82 IPH cases operated on and treated between January 2021 and March 2023. Brain computed tomography/magnetic resonance imaging scans were used to confirm the diagnosis of IPH and provide evidence of neurological damage. The information was gathered using a predesigned form of hospital records. Participants were included if they had a positive COVID-19 result or displayed no symptoms, indicating a past infection.

RESULTS: The study included 82 people, nine (11%) of who tested positive for COVID-19 and 73 (89%) tested negative. There was no difference in mortality rates between the two groups (p=0.651). The hematoma volume decreased from the preoperative (82.4 ± 42.4) to the postoperative (23.7 ± 44.8) measurement (p<0.001). The midline shift value decreased from the preoperative (9.26 ± 4.71) to the postoperative (5.16 ± 5.06) assessment (p<0.001). Patients without COVID-19 infection had a mean survival time of 31.5 days and a median survival time of 23 days, whereas patients with COVID-19 infection had a survival time of 25.7 days and a median survival time of 8 days.

CONCLUSION: Our findings show that hematoma volume and midline shift improve significantly after surgery, although GCS scores remain unaltered. Except for AST and ALT levels, there were no significant differences in mortality rates, demographic, clinical, and most laboratory results between COVID-19-positive and COVID-19-negative patients.

KEYWORDS: COVID-19, Hematoma volume, Intraparenchymal hemorrhage, Mortality

INTRODUCTION

Intraparenchymal hemorrhage (IPH) is a serious neurological disease defined by unexpected bleeding within brain tissue, with high mortality and morbidity rates (17). It is classified into two types: traumatic and nontraumatic (2). The primary causes of nontraumatic IPH include hypertension, vascular abnormalities, and anticoagulant medications (10). However, the COVID-19 pandemic has recently affected millions globally and emerged as a novel and potentially dangerous trigger for IPH (9).

COVID-19, discovered in 2019, has resulted in the loss of millions of lives worldwide and has impacted healthcare systems (1). This sickness, caused by the $SARSCoV_2$ virus, damages the pulmonary tissue and affects other systems in the human body (19). COVID-19 complications include coagulation abnormalities, blood vessel inflammation, and endothelial dysfunction, all associated with thromboembolic and vascular issues (6). In the scientific literature, the number of studies addressing the neurosurgical effects of COVID-19 is increasing (8). Notably, Sharifi-Razavi et al. emphasize the development of IPH in COVID-19 patients, whereas Dogra et al. emphasize the risk of IPH in COVID-19 patients associated with anticoagulant medications (7,14). Beyrouti et al. found that 31% of patients with ischemic stroke caused by COVID-19 had a hemorrhagic transformation (4). Altschul et al. discovered that hemorrhagic stroke increased the risk of death in COVID-19, with a mortality rate of 38.5% (3). Yaghi

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et al. also found that IPH occurred in 8% of COVID-19-related hematological stroke cases (20).

The present study investigates the potential association between COVID-19 infection and IPH. In this study, we also evaluate changes in the preoperative and postoperative periods, mortality, and the COVID-19 impact on the survival times of IPH.

MATERIAL and METHODS

Study Design

This cross-sectional retrospective analysis included the 82 IPH cases operated on and treated in the Department of Neurosurgery between January 2021 and March 2023. This study was carried out in accordance with relevant ethical principles, and human participants' anonymity and data security were protected (No: 2023.05.181).

Definition of IPH

Brain computed tomography/magnetic resonance imaging scans were used to confirm the diagnosis of IPH and provide evidence of neurological damage. When brain imaging or autopsy examinations were unavailable, clinical symptoms such as headaches and vomiting, decreased consciousness or a comatose state, and a gradual decline culminating in death within 24 hours of symptom onset were used to make a probable IPH diagnosis due to the presence of increased intracranial pressure. Cases that could not be conclusively identified as ischemic, hemorrhagic, or subarachnoid bleeding due to insufficient clinical indicators or lack of confirmatory tests were classified as unclassified cerebrovascular occurrences and were excluded from the study. Within the hospital system, evaluations were carried out.

Data Collection

Patient demographic details, test results, symptoms, blood pressure, neurological examination findings, length of hospital stay, mortality rates, and neurological outcomes were all recorded using a predesigned form of hospital records. Participants were included if they had a positive COVID-19 test result showing a past infection or if they did not exhibit any symptoms (fever, cough, shortness of breath, and loss of taste or smell). Individuals were eligible for the study if they had a confirmed COVID-19 diagnosis based on a positive viral RNA RT-PCR assay result. Patients with trauma-related IPH, insufficient data in the hospital dataset, or who did not have COVID-19 testing were excluded from the study.

Data Analysis

The SPSS-v26.0 program (IBM Corp., New York) analyzed the patients' data. Numerical data were presented as mean ± standard deviation and categorical data as frequency and percentage. The cross-table relationship between IPH and COVID-19 was evaluated using the chi-square test. GCS scores, hematoma volume (in cubic centimeters, cm^3), and midline shift (in millimeters, mm) were examined using paired sample *t* tests within each pair. The mean–median survival times of patients with and without COVID-19 infection were compared. We used the Kaplan–Meier analysis method (Figure 1) to present the survival curves, compare the survival times to evaluate the data, and obtain the mean–median survival times for each patient group with 95% confidence intervals and standard errors. To establish if there was a difference in survival distributions for COVID-19 infection, we used the log-rank (Mantel–Cox) test to assess the equality of survival time distributions between the two patient groups. A p-value of < 0.05 was considered significant.

RESULTS

Demographics

The demographic, clinical, and laboratory data of patients with and without COVID-19 were compared in this study (Table I). There were 82 people in the research, with nine (11%) testing positive for COVID-19 and 73 (89%) testing negative. On average, COVID-19-positive patients were 52.1 ± 15.4 years old, whereas COVID-19-negative patients were 60 ± 16.9 years old (p = 0.189). The average length of stay in the hospital was 38.8 ± 40.2 days for those on COVID-19 and 40.7 ± 42.3 days for those without (p=0.896). The average follow-up length for both groups was 34.2 ± 38.7 days for COVID-19-positive patients and 33.7 ± 31.6 days for COVID-19-negative patients (p=0.963). In terms of gender distribution, 55.6% (n=5) of the COVID-19-positive patients were male, and 44.4% (n=4) were female. On 61.6% (n=45) of COVID-19-negative were male and 38.4% (n=28) were female (p=0.722).

There was no difference in comorbidities between the two groups (p=0.593). Anisocoria was found in 33.3% (n=3) of COVID-19-positive individuals and 28.8% (n=21) of COVID-19-negative individuals (p=0.776). neurological deficit was found in 11.1% (n=1) of COVID-19-positive patients but not in 4.1% (n=3) of COVID-19-negative individuals (p=0.358). Postoperative infarction occurred in 62.5% (n=5) of COVID-19-positive patients and 63.8% (n=44) of COVID-19-negative patients (p=0.944).

In terms of laboratory values, there were differences between the two groups for AST (p=0.005) and ALT (p=0.002). The mean AST level in COVID-19-positive patients was 44.3 ± 37.2 U/L, whereas 27.6 ± 12.1 U/L in COVID-19-negative individuals. Similarly, the mean ALT level in COVID-19-positive patients was greater (54.9 ± 49 U/L) than in COVID-19-negative individuals (21.9 ± 18.3 U/L). Other indicators, such as glucose, uric acid, albumin, urea, creatinine, LDH, CRP, globulin, leukocyte, neutrophil, lymphocyte, and platelet levels, did not differ between COVID-19 positive and negative patients (Table I).

There was no difference in mortality rates between the two groups, with COVID-19-positive patients dying at 66.7% (n=6) and COVID-19-negative patients dying at 58.9% (n=43, p=0.651). The mean follow-up length for COVID-19-positive patients was 17.1 ± 14.7 days, whereas 18.6 ± 16.1 days for COVID-19-negative (p=0.302).

Paired Analysis

The study evaluated 82 observations' preoperative and

Table I: Demographic and Laboratory Data of IPH According to COVID-19

Variables		COVID-19 Infection		p-value
		(-) (n=73)	(+) (n=9)	
Age (years)		60 ± 16.9	52.1 ± 15.4	0.189
Hospitalization (days)		40.7 ± 42.3	38.8 ± 40.2	0.896
Gender; n (%)	Male	45 (61.6)	5 (55.6)	0.722
	Female	28 (38.4)	4 (44.4)	
Follow-up (days)		33.7 ± 31.6	34.2 ± 38.7	0.963
Mortality (days)		18.6 ± 26.1	17.1 ± 34.7	0.302
Comorbidity; n (%)	≤1	37 (50.7)	3 (33.3)	0.593
	2	16 (21.9)	3 (33.3)	
	≥3	20 (27.4)	3 (33.3)	
Anisocoria; n (%)	No	52 (71.2)	6 (66.7)	0.776
	Yes	21 (28.8)	3 (33.3)	
Neurodeficit; n (%)	No	3 (4.1)	1 (11.1)	0.358
	Yes	70 (95.9)	8 (88.9)	
Postop infarct; n (%)	No	25 (36.2)	3 (37.5)	0.944
	Yes	44 (63.8)	5 (62.5)	
Mortality; n (%)	No	30 (41.1)	3 (33.3)	0.651
	Yes	43 (58.9)	6 (66.7)	
Glucose (mg/dL)		174.7 ± 70.7	190 ± 90.7	0.555
Uric acid (mg/dL)		4.7 ± 2	6.3 ± 1.1	0.293
Albumin (g/dL)		40.1 ± 6.7	37.3 ± 5.1	0.342
Urea (mg/dL)		42.5 ± 25.5	45.8 ± 20.2	0.715
Creatinine (mg/dL)		1.1 ± 0.9	1.2 ± 1	0.616
AST (U/L)		27.6 ± 12.1	44.3 ± 37.2	**0.005**
ALT (U/L)		21.9 ± 18.3	54.9 ± 49	**0.002**
LDH (U/L)		261.1 ± 95.1	286.3 ± 120.1	0.634
CRP (mg/L)		23 ± 48.4	38.6 ± 48.4	0.425
Globulin (g/dL)		29 ± 5.1	31.3 ± 6.1	0.329
Leukocyte ($\times10^3$/μL)		12.4 ± 5.4	15 ± 5.2	0.178
Neutrophil ($\times10^3$/μL)		10.4 ± 10	12.4 ± 5.3	0.568
Lymphocyte ($\times10^3$/μL)		2.2 ± 1.8	1.3 ± 0.6	0.14
Platelet ($\times10^3$/μL)		231.4 ± 80.6	213.2 ± 113.7	0.544

Note: *Numerical data were presented as mean ± standard deviation, and categorical data were presented as frequency and percentage.*
AST: *Aspartate aminotransferase;* ***ALT:*** *Alanine aminotransferase;* ***LDH:*** *Lactate dehydrogenase;* ***CRP:*** *C-reactive protein.*

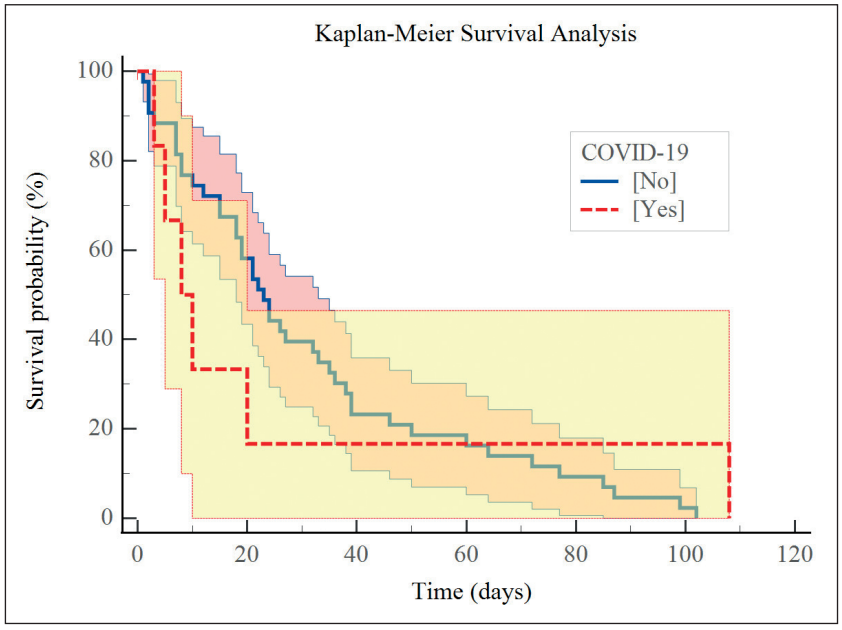

Figure 1: Kaplan–Meier survival analysis for IPH in COVID-19 patients.

Table II: The Paired Analysis of Preoperative and Postoperative IPH Results

Variables	Preoperative	Postoperative	p-value
Glasgow Coma Scale Score	7.5 ± 3.5	7.5 ± 4	0.926
Hematoma volume (cm^3)	82.4 ± 42.5	23.7 ± 44.8	**0.0001**
Midline shift effect (mm)	9.3 ± 4.7	5.2 ± 5.1	**0.0001**

postoperative results across three paired variables (Table II): GCS, hematoma volume (cm^3), and midline shift (mm). The preoperative GCS (7.49 ± 3.49) did not differ from the postoperative GCS (7.45 ± 3.98; 95% CI, −0.74 to 0.82; p=0.926). The paired analysis of hematoma volume, on the other hand, demonstrated a significant reduction from preoperative (82.4 ± 42.4) to postoperative (23.7 ± 44.8; 95% CI, 47.2–70.1; p<0.001). We also discovered a significant reduction in midline shift value from preoperative (9.26 ± 4.71) to postoperative (5.16 ± 5.06; 95% CI, 2.88–5.3; p<0.001).

Survival Analysis

The following statistics apply to IPH case's survival outcomes. The mean and median survival times for the two groups (patients infected with COVID-19 and those who did not) are reported. For patients without COVID-19 infection, the mean survival time was 31.5 days (standard error [*SE*]: 4.2; 95% CI, 23.3–39.7), and the median survival time was 23 days (*SE*: 2.7; 95% CI, 17.6–28.4), whereas for patients with COVID-19 infection, the mean survival time was 25.7 days (*SE*: 16.6; 95% CI, 0–58.3), and the median survival time of 8 days (*SE*: 3.1; 95% CI, 2–14). Overall, the mean survival time was 30.8 days (*SE*: 4.1; 95% CI, 22.7–38.9), and the median survival time was 21 days (*SE*: 2.8; 95% CI, 15.5–26.5). The log-rank (Mantel–Cox) test, which assessed the equality of survival distributions for different levels of COVID-19 infection in the Kaplan–Meier analysis (Figure 1), revealed a p value of 0.348, indicating no significant difference between the two groups.

DISCUSSION

The present study's findings on nontraumatic intracranial hemorrhage in patients with and without COVID-19 are consistent with some previous research while contrasting with others. The lack of statistically significant variations in mortality rates, follow-up times, and survival outcomes between the two groups implies that COVID-19 may not substantially impact the prognosis of these patients. Furthermore, the postoperative reduction in hematoma volume and midline shift value is consistent with surgical therapies' success in controlling nontraumatic cerebral bleeding.

In the scientific literature, the number of studies addressing the neurosurgical effects of COVID-19 is increasing (8). Beyrouti et al. discovered that a hemorrhagic change occurred in 31% of cases of ischemic stroke connected to COVID-19 (4). Altschul et al. discovered that hemorrhagic stroke doubled the risk of death in COVID-19 patients, with a mortality rate of 38.5% (3). Yaghi et al. also found that IPH occurred in 8% of COVID-19-related stroke cases (20). Sharifian-Dorche et al. discovered a greater mortality rate in COVID-19-positive individuals than in COVID-19-negative patients (15). The mortality rates were the same in both groups, with 66.7% in

COVID-19-positive patients and 58.9% in COVID-19-negative patients. In contrast, the present study indicated increased mortality with no statistical difference between the two groups. Differences in sample size, patient demographics, or treatment modalities could explain the disparity. The survival analysis results are consistent with those of Bhatia et al., who reported no difference in survival outcomes between COVID-19-positive and COVID-19-negative individuals with nontraumatic intracranial hemorrhage (5). Because of this commonality, COVID-19 may not affect the long-term prognosis of nontraumatic intracranial hemorrhage.

The lack of a statistically significant difference in follow-up periods between COVID-19 positive and negative patients may suggest that COVID-19 does not substantially impact the clinical course of nontraumatic intracranial hemorrhage (11,13,16,18). A study conducted by Dogra et al. reported no significant difference in follow-up times between the two groups (7). Notably, Sharifi-Razavi et al. emphasize the development of IPH in COVID-19, whereas Dogra et al. emphasize the risk of IPH associated with anticoagulant drug use in COVID-19 (7,14). The observed reduction in hematoma volume and midline shift value after surgery in our study was consistent with previous research on the efficacy of surgical interventions for nontraumatic intracranial hemorrhage (12). The similar outcomes between COVID-19-positive and COVID-19-negative patients may imply that COVID-19 does not affect surgical treatment success in this context. The findings of this study are consistent with some features of prior research on COVID-19 nontraumatic intracranial hemorrhage. The present study has several limitations.

Various limitations to this study should be considered when interpreting the findings. This study's sample size is limited, reducing the statistical power of the analyses. A bigger sample size may give more robust data and highlight small variations. The retrospective approach of the study could introduce selection bias, information bias, and confounding factors. We conducted the study at a single medical center, which may limit the findings' applicability to other settings and populations. Although the study controlled for several demographic, clinical, and laboratory variables, it is possible that other relevant confounders may not have been accounted for. Factors, such as socioeconomic level, comorbidities, and healthcare access, may influence COVID-19 infection and intracranial hemorrhage results. The study focused on short-term outcomes, with a maximum follow-up length of 38.7 days. Longer follow-up periods could provide valuable information on COVID-19's long-term impact on intracranial hemorrhage prognosis and recovery.

CONCLUSION

Our findings show that hematoma volume and midline shift improves significantly after surgery, although GCS scores remain unaltered. There were no significant differences in demographic, clinical, and laboratory values between COVID-19-positive and COVID-19-negative patients, except for AST and ALT levels. For survival analysis, Kaplan–Meier analysis revealed no difference between the two groups. Additional research with multicenter larger sample sizes and more diverse patient populations is required to corroborate these findings.

AUTHORSHIP CONTRIBUTION

The authors (SD, BC) confirm responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

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