Aneurysmal Subarachnoid Hemorrhage in Covid-19 Patients Predicts Worst Clinical Presentation and Higher Mortality

Hemorragia Subaracnoidea Aneurismática em Pacientes com Covid-19 é Preditor de Pior Apresentação Clínica e Maior Mortalidade

Lucas Crociati Meguins
Dionei Freitas de Morais
Ricardo Lourenço Caramanti
Carlos Eduardo Dall’Aglio Rocha
Raquel Cristina Trovo Hidalgo
Crescêncio Alberto Pereira Centola
Eberval Gadelha Figueiredo

ABSTRACT

Objective: The aim of the present study is to identify the consequences of COVID-19 infection and intracranial aneurysmal rupture.

Methods: The investigation was performed as a nonrandomized retrospective observational study.

Results: In the group of SARS-CoV-2-negative patients, one hundred sixty-six (72.81%) were admitted with a Hunt-Hess (HH) Scale I-III (HH I: 5 [2.19%]/HH II: 111 [48.68%]/HH III: 50 [21.93%]) and 62 (27.19%) were HH IV-V (HH IV: 55 [24.12%]/HH V: 7 [3.07%]). In total, 104 (45.61%) patients were admitted with a Glasgow Coma Scale (GCS) score of 15 points, 46 (20.18%) with a GCS score of 13-14 points, 56 (24.56%) with a GCS score of 7-12 points and 22 (9.65%) with GCS score of 3-6 points. In the group of SARS-CoV-2-positive patients, two (18.18%) were admitted to with a Hunt-Hess (HH) Scale score of I-III (HH I: 0 [0%]/HH II: 1 [9.09%]/HH III: 1 [9.09%]), and 9 (81.82%) patients had a score of HH IV-V (HH IV: 4 [36.36%]/HH V: 5 [45.45%]). One (9.09%) patient was admitted with a GCS score of 15 points, 3 (27.27%) with a GCS score of 13-14 points, 2 (18.18%) with a GCS score of 7-12 points, and 5 (45.45%) with a GCS score of 3-6 points.

In the group of SARS-CoV-2-negative patients, of all 228 individuals treated, 138 (60.53%) had a modified Rankin Scale (mRS) score ≤3, 35 (15.35%) had a mRS score of 4-5, and 55 (24.12%) died. On the other hand, in the group of SARS-CoV-2-positive patients, of all 11 individuals treated, 2 (18.18%) had a mRS score ≤3, 2 (18.18%) had a mRS score of 4-5, and 7 (63.64%) died.

Conclusion: COVID-19 has the most severe clinical presentation and higher mortality in patients with aSAH.

RESUMO

Objetivo: O objetivo do presente estudo é investigar as consequências da infecção do COVID-19 em pacientes com aneurisma roto.

Métodos: A investigação foi realizada como um estudo observacional retrospectivo não randomizado. Resultados: No grupo de pacientes SARS-CoV-2-negativos, 166 (72,81%) foram admitidos com uma escala Hunt-Hess (HH) I-III (HH I: 5 [2,19%]/HH II: 111 [48,68%]/HH III: 50 [21,93%]) e 62 (27,19%) foram HH IV-V (HH IV: 55 [24,12%]/HH V: 7 [3,07%]). Em total, 104 (45,61%) pacientes foram admitidos com pontuação na Escala de Coma de Glasgow (ECG) de 15 pontos, 46 (20,18%) com pontuação na GCS de 13-14 pontos, 56 (24,56%) com pontuação na GCS de 7-12 pontos e 22 (9,65%) com pontuação na GCS de 3-6 pontos.

Keywords: Aneurysmal subarachnoid hemorrhage; COVID-19; Clinical presentation; Mortality
Aneurysmal subarachnoid hemorrhage (aSAH) is a serious life-threatening condition that is associated with poor clinical and neurological outcomes in many patients. Despite a significant reduction in mortality, from over 50% to nearly 35% of cases, this disease still presents elevated morbidity and mortality. Approximately one-quarter of patients suffering aSAH die immediately after aneurysm rupture or before reaching medical care, and one-third remain permanently dependent on nursing care. The clinical outcome varies according to the severity of the acute bleed, the patient's initial presentation, early rebleeding and delayed cerebral ischemia. Clinical complications, such as pulmonary and cardiac complications, are also prognostically relevant. This severe neurological disease reaches an even more dramatic condition and unknown stage in adult patients who are positive for coronavirus disease 2019 (COVID-19). The pandemic has challenged neurosurgeons dedicated to the treatment of aSAH and forced the implementation of security protocols. However, few studies have investigated the clinical characteristics and outcomes of individuals with aSAH who were actively or very recently infected with severe acute respiratory syndrome coronavirus 2.

The purpose of the present investigation is to describe the clinical presentation and outcome of individuals with aSAH testing positive for COVID-19.
Pre-surgical evaluation
All patients were admitted to the Emergency Department and initially stabilized by the emergency team. After initial care, all patients underwent computed tomography (CT) and angiotomography (CAT) of the brain, and whenever unsatisfactory results of the vascular lesion, irregular shape of the aneurysm or suspicion of vasospasm were found, digital subtraction angiography (DSA) of the four intracranial arteries was performed. Surgical indication was defined on a case-by-case basis and discussed with a multidisciplinary team (neurosurgeon/interventional neuroradiologist) about the scientific guidelines for the management of intracranial aneurysms and SAH were followed.

Surgical technique
The surgical technique was chosen according to three main factors: (A) location of the ruptured intracranial aneurysm; (B) additional unruptured aneurysms (multiple aneurysms); and (C) presence of intraparenchymal hematoma.

Supratentorial aneurysms were treated preferentially by pterional, pretemporal, orbitozygomatic or interhemispheric approaches or using a combination of techniques following the surgical steps previously published. On the other hand, infratentorial aneurysms were treated preferentially by pretemporal transzygomatic or far lateral approaches following the surgical steps previously published.

Outcome assessments and follow-up
Follow-up investigations were carried out in operated patients. By the end of 6 months after surgical intervention, all patients received a neurological examination to evaluate performance status and neurological deficits. In-hospital mortality was documented.

Statistical analysis
Data collected from all patients are organized in tables. Averages are expressed as the mean ± SD for parametric data and as median values for nonparametric data. Statistical analysis was performed using Fisher’s exact test and the chi-square test. A p value<0.05 was considered statistically significant.

Ethical issues
The Ethical Committee of our institution analyzed the project of the present study and approved the investigations. The study complies with the Declaration of Helsinki. Informed consent was obtained from all patients and/or those legally responsible for surgical treatment.

RESULTS

General information
A total of 228 SARS CoV-2 negative patients with aSAH were included in the present investigation. One hundred sixty-nine (74.12%) patients with 221 (76.47%) aneurysms were women, and 59 (25.88%) were men with 68 (23.53%) aneurysms. One hundred forty-five (63.60%) patients were <60 years old (15-30: 5 [2.19%]/30-39: 20 [8.77%]/40-49: 46 [20.18%]/50-59: 74 [32.46%]) and 83 (36.40%) were ≥60 years old (60-69: 54 [23.68%]/70-79: 23 [10.09%]/80-89: 6 [2.63%]).

A total of 11 SARS-CoV-2 positive patients with aSAH and 13 aneurysms were included in the present investigation. Nine (81.82%) patients were asymptomatic for COVID-19 and tested positive on the first day of admission, and two (18.18%) patients with initial mild respiratory symptoms tested positive on the fourth day of admission. Six (54.55%) were women with 7 (53.85%) aneurysms, and 5 (45.45%) were men with 6 (46.15%) aneurysms. Three (27.27%) patients were <60 years old, and 8 (72.73%) were ≥60 years old.

Clinical and radiological presentation
In the group of SARS-CoV-2-negative patients, one hundred sixty-six (72.81%) were admitted with a Hunt-Hess (HH) Scale score of I-III (HH I: 5 [2.19%]/HH II: 111 [48.68%]/HH III: 50 [21.93%]), and 62 (27.19%) with a HH score of IV-V (HH IV: 55 [24.12%]/HH V: 7 [3.07%]). A total of 104 (45.61%) patients were admitted with a GCS score of 15 points, 46 (20.18%) with a GCS score of 13-14 points, 56 (24.56%) with a GCS score of 7-12 points, and 22 (9.65%) with a GCS score of 3-6 points. During radiological investigation, 6 (2.63%) patients had a Fisher Scale score of I, 37 (16.23%) with a Fisher Scale score of II, 29 (12.72%) with a Fisher Scale score of III, and 156 (68.42%) with a Fisher Scale score of IV.

In the group of SARS-CoV-2-positive patients, two (18.18%) were admitted with a Hunt-Hess (HH) Scale score of I-III (HH I: 0 [0%]/HH II: 1 [9.09%]/HH III: 1 [9.09%]), and 9 (81.82%) with a HH score of IV-V (HH IV: 4 [36.36%]/HH V: 5 [45.45%]). One (9.09%) patient was admitted with a GCS score of 15 points, 3 (27.27%) with a GCS score of 13-14 points, 2 (18.18%) with a GCS score of 7-12 points, and 5 (45.45%) with a GCS score of 3-6 points.
During radiological investigation, 6 (54.55%) patients had a Fisher Scale score of III, and 5 (45.45%) had a Fisher Scale score of IV.

According to the Hunt-Hess Scale at admission, a statistically significant difference was observed between Groups A and B (Figure 1 and Table 1).

**Aneurysm analysis**

Of the 289 clipped aneurysms in the SARS-CoV-2-negative group, 183 (63.32%) were <6 mm, 64 (22.15%) were 6–110 mm, and 42 (14.53%) were >10 mm. Two hundred eighty-nine aneurysms were clipped, 228 (78.89%) ruptured (Anterior Communicating Artery AComA: 72 [31.58%]/Middle Cerebral Artery MCA: 71 [31.14%]/Posterior Communicating Artery PComA: 60 [26.32%]/Pericallosal Artery PA: 9 [3.95%]/Internal Carotid Artery, Ophthalmic Segment ICA Opht: 7 [3.07%]/Internal Carotid Artery, Bifurcation ICA Bif: 4 [1.75%]/Basilar Artery BA: 3 [1.32%]/Internal Carotid Artery, Choroidal Segment ICA Chr: 1 [0.44%]/Posterior Inferior Cerebellar Artery PICA: 1 [0.44%]), and 61 (21.11%) incidentally found/unruptured (MCA: 28 [48.90%]/AComA: 9 [14.75%]/ICA Opht: 8 [13.11%]/PComA: 7 [11.48%]/ICA Bif: 3 [4.92%]/ICA Chr: 2 [3.28%]/BA: 2 [3.28%]/PA: 1 [1.64%]/Superior Cerebellar Artery SCA: 1 [1.64%]).

Of all 13 clipped aneurysms in the SARS-CoV-2-positive group, 8 (61.54%) were <6 mm, 3 (23.08%) were 6–110 mm and 2 (15.38%) were >10 mm. Six (46.15%) were MCA, four (30.77%) were AComA, and 3 (23.08%) were PComA.

**Follow-up and mortality**

In the group of SARS-CoV-2-negative patients, of all 228 individuals treated, 138 (60.53%) had a modified Rankin Scale (mRS) score ≤3, 35 (15.35%) had a mRS score of 4-5, and 55 (24.12%) died. On the other hand, in the group of SARS-CoV-2-positive patients, of all 11 individuals treated, 2 (18.18%) had a mRS score ≤3, 2 (18.18%) had a mRS score of 4-5, and 7 (63.64%) died.

A statistically significant difference regarding mortality was observed between Groups A and B (Fisher’s exact test, p=0.0079) (Figure 2).

![Figure 1. Clinical presentation of patients with aSAH.](image1)

![Figure 2. Mortality of patients with aSAH.](image2)

**Table 1. Clinical presentation of patients with aSAH.**

<table>
<thead>
<tr>
<th>Hunt Hess</th>
<th>SARS-CoV-2 (-)</th>
<th>%</th>
<th>SARS-CoV-2 (+)</th>
<th>%</th>
<th>p-value</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I - III</td>
<td>166</td>
<td>72.81%</td>
<td>2</td>
<td>18.18%</td>
<td>0.0455*</td>
<td>168</td>
<td>70.29%</td>
</tr>
<tr>
<td>IV - V</td>
<td>62</td>
<td>27.19%</td>
<td>9</td>
<td>81.82%</td>
<td>0.0202*</td>
<td>71</td>
<td>29.71%</td>
</tr>
<tr>
<td>Total</td>
<td>228</td>
<td>100%</td>
<td>11</td>
<td>100%</td>
<td></td>
<td>239</td>
<td>100%</td>
</tr>
</tbody>
</table>

(*: p-value < 0.05 / Fisher Exact Test)
DISCUSSION

The COVID-19 pandemic outbreak has completely changed the way neurological surgeons deal with intracranial vascular disease\textsuperscript{28-27}. A number of novel protocols have been proposed by different institutions around the world to reduce the nosocomial transmission of the virus and its consequences on neurosurgical patients severely affected by intracranial hemorrhages\textsuperscript{8-10}. The methods implemented were found to be safe and effective in reducing new institutional cases and the intrinsic clinical complications of COVID-19\textsuperscript{8-10}. However, very little is known about the clinical characteristics and outcomes of individuals with ruptured intracranial aneurysms who were actively or very recently infected with SARS-CoV-2\textsuperscript{28,29}.

Kostyra et al.\textsuperscript{15} reported a personal experience that was revealed to be effective when treating a patient with ruptured intracranial aneurysm and COVID-19. The authors showed that workflow organization of the operating room reduces surgical time and makes the intervention safe for both the healthcare personnel and the patient\textsuperscript{15}. Additionally, not only does the neurosurgical routine change but also the clinical and epidemiological characteristics of patients with aneurysmal subarachnoid hemorrhage (aSAH) and COVID-19 seem to present a distinct pattern compared with traditional aneurysmal rupture cases, namely, a high frequency of small lesions, dissecting pseudoaneurysms and young individuals\textsuperscript{12}. In our study, all patients with aSAH who were confirmed or suspected to have COVID-19 were treated in an isolated region of the institution with special care to reduce respiratory transmission. No significant difference was observed regarding aneurysmal size and morphology when compared to the prepandemic period. However, we noted a statistically significant worst neurological presentation at admission and higher mortality rates in patients with COVID-19.

Aboukaïs et al.\textsuperscript{14} showed a notorious morbid correlation between the context of the COVID-19 pandemic and the clinical and radiological presentation of patients with spontaneous aSAH. A poor neurological condition and more severe intracranial hemorrhage were observed during the initial months of SARS-CoV-2 circulation, probably correlated with delayed hospital admission\textsuperscript{28}. Moreover, Fiani et al.\textsuperscript{29} raised the suspicion that hypercytokinemia and a hyperinflammatory state are strongly associated with degenerative vascular changes that may predispose individuals with COVID-19 to cerebral aneurysm formation, changes in size or morphology and resultant saccular lesion rupture\textsuperscript{29}. We believe that a combination of premorbid conditions, intrinsic metabolic changes and systemic complications of COVID-19 contribute to the neurological presentation and higher mortality of patients with simultaneous intracranial hemorrhage and viral infection. However, future studies to clearly delineate the correlation are necessary.

Qureshi et al.\textsuperscript{14} conducted an investigation in a large cohort of COVID-19 patients to identify risk factors, comorbidities, and relevant treatment strategies to evaluate outcomes in individuals with concomitant aSAH. The authors observed that aSAH was not increased in patients with COVID-19. However, higher mortality was noted in individuals with aSAH and COVID-19 than in patients without viral infection, probably mediated by a higher frequency of systemic comorbidities\textsuperscript{14}. In our investigation, we also observed higher mortality rates in the group of aneurysmal rupture and COVID-19 patients, but additionally, we also note that patients with concomitant aSAH and viral infection also presented an initial severe neurological manifestation of aneurysmal rupture. We agree that premorbid conditions and initial clinical presentation are the main risk factors for mortality and clinical outcome. Further investigations are necessary to better understand the role of both conditions and explain the mechanisms involved in the worst outcome.

There are several methodological aspects in the present findings, which should be interpreted in the context of a number of limitations. First, this study is a nonrandomized retrospective investigation performed in a highly selected population of a tertiary neurosurgical center. Second, these results cannot be generalized for all types of intracranial hemorrhages or other neurosurgical emergencies. On the other hand, the present study described the surgical outcomes of a relatively large number of patients for a relatively extended follow-up duration.

CONCLUSION

SARS-CoV-2 infection and the pandemic outbreak dramatically changed the routine treatment of patients with ruptured intracranial aneurysms. We highlighted that COVID-19 in adult patients with aSAH predicts the worst clinical presentation and
higher mortality. Further analysis and investigations are necessary to confirm the present observations.

REFERENCES


CORRESPONDING AUTHOR

Lucas Crociati Meguins, MD, PhD
Fundação Faculdade Regional de Medicina de São José do Rio Preto – FUNFARME
Base Hospital
São José do Rio Preto, São Paulo, Brazil
E-mail: lucascrociati@hotmail.com

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