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NEUROLOGICAL PROFILE IN PATIENTS WITH STROKE: POSITIVE AND NEGATIVE FOR SARS-COV-2 INFECTION - A RETROSPECTIVE OBSERVATIONAL STUDY

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Abstract

Sars-CoV-2 infection is linked to an increased risk of both ischemic and hemorrhagic strokes, influenced by factors such as inflammation, coagulopathy, and endothelial dysfunction.

This study aimed to evaluate the prevalence of different types of stroke, assess the severity of initial neurological deficits using the National Institutes of Health Stroke Scale (NIHSS), and examine neurological disability or dependence on daily activities after treatment using the Modified Rankin Scale (MRS) in patients both positive and negative for Sars-CoV-2. Additionally, the study sought to compare the types of strokes and the degree of neurological deficits and disabilities between these two groups.

This retrospective observational cohort study included 91 stroke patients hospitalized in the Department of Neuropsychiatry at the General Hospital of Ohrid during the period from January 1, 2021, to December 31, 2021, which corresponds to the post-COVID period. The findings revealed that Sars-CoV-2 positive patients were generally younger than those who tested negative. Most patients admitted with an initial diagnosis of stroke were classified within the ischemic stroke group, regardless of their COVID-19 status. A significant number of Sars-CoV-2 positive patients exhibited severe to moderate strokes based on the NIHSS classification. Following treatment, the majority of these patients experienced moderate to severe disabilities.

The results of this study enhance our understanding of the relationship between stroke incidence and current or prior infections with SARS-CoV-2.

Keywords: NIHSS, Sars-CoV-2, Hemorrhagic stroke, Ischemic stroke

Introduction

As is well known, stroke is one of the leading causes of death worldwide. Among all neurological diseases in adults, cerebrovascular diseases rank highest in terms of frequency and importance in terms of morbidity, mortality, and disability. Nearly 50% of neurological diseases in hospitals fall into this category [1,2].

Stroke is the third leading cause of death in developed countries, following coronary diseases and cancer. It affects 0.2% of the population and is fatal in one-third of cases. At least half of stroke survivors are permanently disabled.

The global incidence of stroke is 3 to 4 per 1,000 inhabitants. For example, in the United States, about 800,000 people experience a stroke each year. Around 75% of strokes are first occurrences, while 1 in 4 are recurrent.

The prevalence of strokes increases with age: in the 65–74 age group, it is 4.2%, while in the 75–84 age group, it is 7.8%. Stroke is the leading cause of disability in people over 65 years old [3, 4]. Globally, 30 billion dollars are spent annually on stroke prevention [5].

Among stroke survivors, 30% suffer from dementia, and 50% remain physically disabled [6].

Acute stroke (AS) is defined as a focal or global disturbance of brain function that occurs suddenly and is the result of a disruption of cerebral circulation or insufficient blood flow to meet the metabolic needs of neurons for oxygen and glucose.

Depending on the mechanism, AS can be classified into two main groups: Acute ischemic stroke (AIS): caused by vessel occlusion due to thrombosis or embolism; it is much more common and occurs in about 75–80% of patients;

Acute hemorrhagic stroke (intracerebral hemorrhage [ICH] or subarachnoid hemorrhage [SAH]): occurs in the remaining 20–25% of patients and Transient ischemic attack (TIA). More recent classifications also include, in addition to ischemic and hemorrhagic (arterial) strokes, cerebral venous thrombosis and spinal cord infarctions.

AIS is a clinical syndrome characterized by acute loss of brain function that lasts more than 24 hours or leads to death. It presents with a sudden loss of body function, speech, or consciousness because of interrupted blood supply. The brain requires constant oxygen and glucose to function properly, which it receives through the blood.

If the blood flow disruption is not corrected within the first few hours, brain tissue dies and permanently loses function. The most common cause of arterial narrowing in the brain is vessel wall thickening—atherosclerosis. Ischemic strokes account for the majority of all strokes [7-10].

The symptoms of stroke can vary depending on the type of stroke and the part of the brain affected. However, some early warning signs, based on recent research, are: Ataxia or weakness of the body, especially if it affects only one side; Sudden changes in vision in one or both eyes; Difficulty swallowing; Sudden severe headache; Dizziness and loss of balance; Confusion and Difficulty speaking and/or understanding speech.

Each stroke manifests differently, and the symptoms depend on the affected brain region and its size. In most cases, symptoms and signs appear suddenly and are immediately noticeable. In some patients, they may occur during the night while sleeping, with the patient noticing them when waking up. The sudden and rapid onset of symptoms is the most recognizable sign of stroke.

Thus, if symptoms develop slowly and worsen over days, weeks, or months, it is unlikely to be a stroke [11,12].

It is of crucial importance to understand the connection between COVID-19 and strokes. COVID-19 is associated with an increased risk of ischemic and hemorrhagic strokes due to factors such as inflammation, coagulopathy, and endothelial dysfunction.

Ischemic strokes, mainly as a result of thrombus formation, are more common in patients with COVID-19, while hemorrhagic strokes tend to occur in severe cases, often linked to anticoagulant therapy or virus-induced coagulopathy.

Studies have shown worse outcomes for stroke patients with COVID-19, with increased mortality, especially in those with pre-existing conditions and low socio-economic status [13–15]. In March 2020, the World Health Organization (WHO) officially declared COVID-19 a global pandemic.

Numerous organizations, including the American Heart Association/American Stroke Association (AHA/ASA), have issued guidelines aimed at improving safety in healthcare.

Many scientific studies have highlighted the increased risk of thrombosis due to the disease, along with a significant number of strokes associated with COVID-19. Several studies reported an increase in stroke cases in the period following the "peak of the COVID-19 pandemic." These studies also emphasized the "COVID episodes in young people" who experienced atypical thrombosis.

However, there were also numerous studies that suggested the opposite—that the number of hospitalized stroke patients decreased during the course of the pandemic [15-17].

Due to the symptoms mentioned above, the patient seeks neurological evaluation. Upon admission, a clinical and neurological examination is performed. The National Institutes of Health Stroke Scale (NIHSS) is a clinical assessment tool used by healthcare professionals to measure the severity of stroke. It helps determine the degree of neurological damage and guides treatment decisions.

The NIHSS scoring system is used to evaluate the effect of acute cerebral infarction on levels of consciousness, language, neglect, loss of visual field, extra-ocular movement, motor

strength, ataxia, dysarthria, and sensory loss. NIHSS structure consists of 15 items (domains), scored from 0 (no impairment) to higher numbers indicating greater severity.

The maximum score is 42, representing the most severe impairment [18]. In terms of clinical use and significance, NIHSS is used at initial assessment (to determine stroke severity) and during hospital stay to monitor progression or improvement.

It is most applied when deciding on treatment options (e.g., thrombolytic therapy) in acute strokes. NIHSS results help predict results. Higher scores often correlate with worse functional outcomes and greater long-term disability. However, there are limitations, as NIHSS is only one of many tools to assess stroke severity and can miss subtle deficits or be influenced by the patient's level of consciousness. It may not fully assess certain brain functions, such as emotional or behavioral changes and higher cognitive processes [18,19].

The modified Rankin scale (mRS) has been the gold standard for grading stroke outcomes in clinical trials for many years. Therefore, it has become the most used tool for measuring stroke-related disability in both observational studies and the daily clinical practice of stroke units (SU) and rehabilitation wards (RW).

Due to this simple-to-use scale, which assesses disability from no symptoms (0 points) to death (6 points), the whole spectrum of functional states can be described.

The purpose of this study was to evaluate and identify the prevalence of different types of cerebral stroke, assess the grades of initial neurological deficits using the National Institutes of Health Stroke Scale (NIHSS), and analyze the outcomes after the treatment period using the Modified Rankin Scale (MRS) in patients who tested positive (from the day of hospital admission up to six months prior to admission) and negative for Sars-CoV-2.

Additionally, the study aimed to compare the types of strokes, neurological deficits measured by NIHSS, and levels of neurological disability and dependence assessed by M RS between patients positive for SARS-CoV-2 and those negative for the virus.

Patients and methodology

This is a retrospective observational study that included stroke patients who were hospitalized in the Department of Neuropsychiatry at the General Hospital of Ohrid during the period January 1, 2021 – December 31, 2021, i.e., in the post-COVID period

Patients who were hospitalized for the first time for stroke, meeting the diagnosis criteria according to the American Stroke Association Stroke Council Recommendations [19], with positive/negative COVID-19 infection from 6 months prior to the day of hospital admission (confirmed by the COVID-19 PCR polymerase chain reaction test) were included in the study.

The Ethics Committee of the PHI General Hospital in Ohrid approved this investigation and gave permission for the laboratory, neurological, and tomographic findings from the medical records to be used. Patients who had previously suffered an ischemic or hemorrhagic stroke or patients hospitalized for suspected re-stroke;

Patients who had a repeated stroke during hospitalization; patients who had been hospitalized a few days after the onset of the stroke; patients who have come with complaints of transient ischemic attacks, which cannot be confirmed by clinical examination;

Patients whose clinical findings were unclear (that is, patients in whom the computed tomographic finding excluded vascular suffering) and hospitalized patients whose identity was unknown (John Doe-patients) were excluded from the study.

A total of 213 patients were hospitalized during this period. A total of 91 patients met the criteria for inclusion in the study. 30 of them were SARS-CoV-2 positive from the day of hospital admission up to six months before. The following data were collected and analyzed:

- Sex (male/female)

- Age (in defined age ranges)
- Laboratory and imaging findings
- Type of stroke:
- ischemic stroke
- hemorrhagic stroke
- Severity of neurological deficit using the National Institutes of Health Stroke Scale (NIHSS)- to grade neurological findings at hospital admission. NIHSS consists of 15 items (domains), scored from 0 (no impairment) to higher numbers indicating greater severity. The maximum score is 42, representing the most severe impairment.

NIHSS Scoring system:

- Score 0: No signs of stroke
- Mild stroke: 1–4
- Mild to moderate stroke: 5–15
- Severe stroke: 16–20
- Very severe stroke: ≥21. A score> 25 is often associated with a high risk of severe disability or death.

The M Rankin Score was used to measure the degree of disability and dependence after treatment.

- No symptoms at all: 1
- No significant disability despite symptoms; capable of carrying out all usual duties and activities:2
- Slight disability; unable to carry out all previous activities, but able to take care of himself without assistance:3
- Moderate disability; requires some help, but can walk without assistance:4
- Severe disability; unable to walk without assistance and unable to attend to their own bodily needs without assistance:5
- Dead: 6

Statistical analysis was performed using SPSS software (version 25, Chicago, Ill, USA). Descriptive statistics were used. Categorical data from all patients were summarized using proportions and percentages. Categorical variables were analyzed using the chi-square test. The results were presented in tables and graphs. Statistical significance was set at $p \leq 0.05$.

Results

During the study period, a total of 91 patients were included in the study; 50 (54.9%) of them were males and 41 (45%) were females. The distribution of the patients by sex and age is presented in Table 1.

Table 1. Distribution of Patients by Sex and Age group

Age group (years)	**Males n (%)**	**Females n(%)**	**Total n (%)**
<50	2 (2.2%)	3 (3.3%)	5 (5.6%)
50–59	4 (4.4%)	7 (7.7%)	11 (12%)
60–69	24 (26.4%)	9 (9.9%)	33 (36.3%)
≥ 70	20 (22%)	22 (24.2%)	42 (46.2%)
Total	**50 (54.9%)**	**41 (45%)**	**91 (100%)**

Stroke was more common in males. In SARS-CoV-2 positive patients, stroke was more frequent in females,16 (53.3%), compared to males, 14 (46.7%). In SARS-CoV-2 negative patients stroke more males had a stroke compared to females, Fig.1.

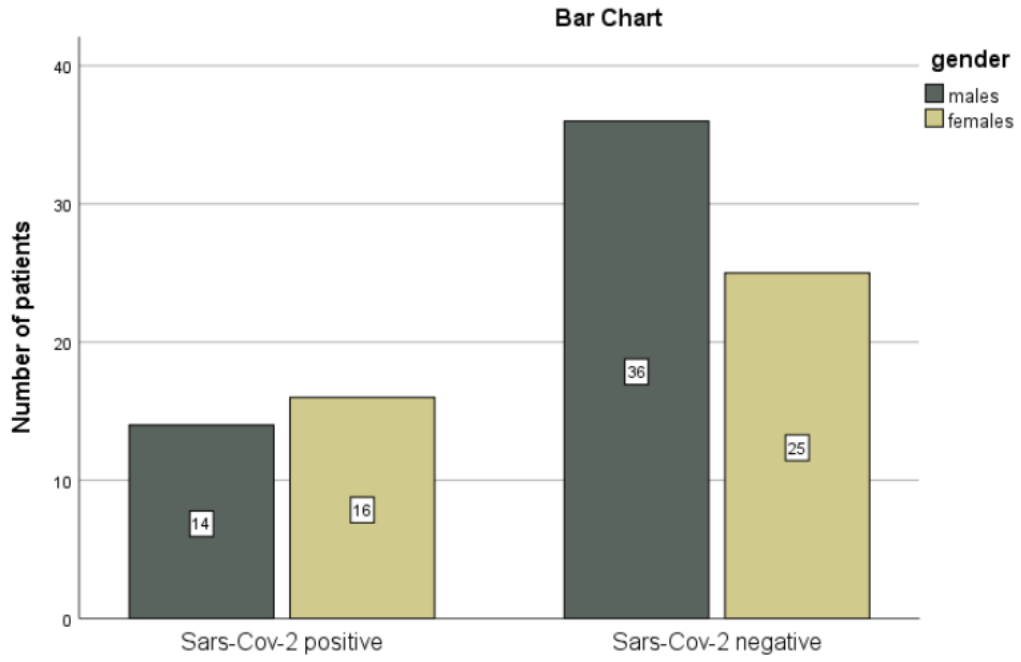

Fig.1 Gender Distribution of Stroke in SARS-CoV-2 Positive and Negative Patients

Stroke was most common in the 70- and older-age group of patients, 42 (46.2%), followed by the 60–69 years old patients' group, 33 (36.3%), and the 50-59 years old patients, 11 (12%). In contrast to these findings, the majority of SARS-CoV-2 patients were younger and belonged to the 60-69 years old age group, Fig.2.

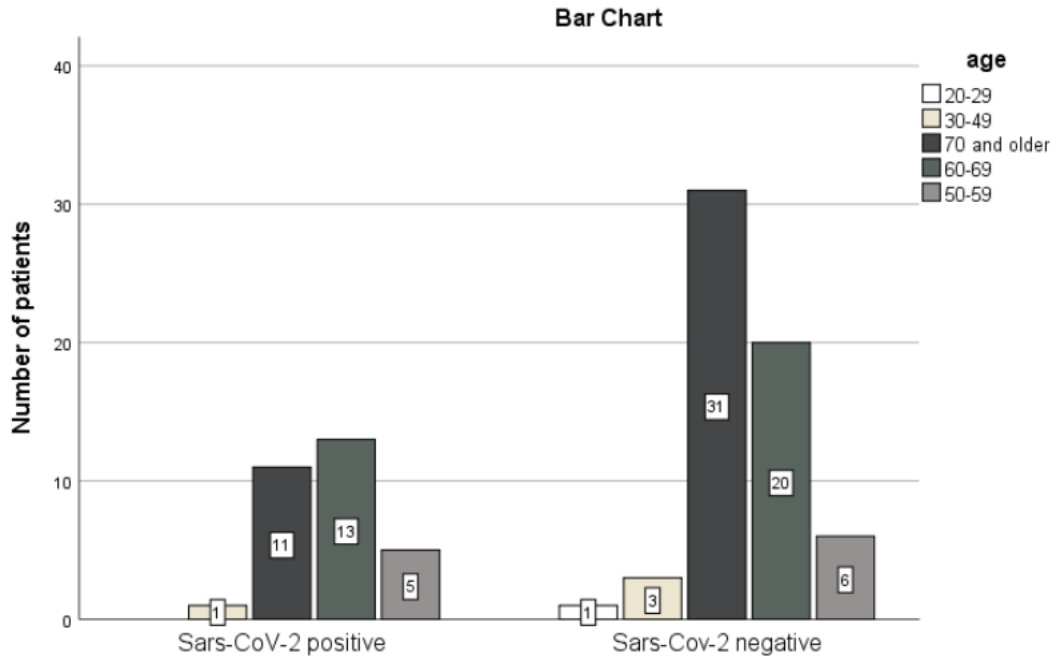

Fig 2. Age Distribution of Stroke in SARS-CoV-2 Positive and Negative Patients

The most frequent type of stroke was ischemic stroke in 74 (81.3%) patients, followed by hemorrhagic stroke in 17 (18.7%) patients. The distribution of the ischemic and hemorrhagic strokes in Sars-CoV-2 positive and negative patients is presented in Table 2.

Table 2. Distribution of Stroke type in Sars-CoV-2 Positive and Negative patients

Sars-CoV-2 infection	**Ischemic stroke n (%)**	**Hemorrhagic stroke n (%)**	**Total n (%)**
Positive	24 (80%)	6 (20%)	30 (100%)
Negative	50 (82%)	11(18%)	61 (100%)
Total	**74 (81.3%)**	**17(18.7%)**	**91 (100%)**

Significantly more patients with an ischemic type of stroke were hospitalized compared to patients with a hemorrhagic type of stroke. Similar findings presented Sars-CoV-2 positive and Sars-CoV-2 negative patients, p=0.05

Neurological deficit was assessed using the NIHSS. When grouped by severity, most patients were classified as having very severe and severe neurological deficits, 46 (50.6%), followed by moderate, 34 (37.4%), and mild to moderate stroke, 11 (12.1%).

Regarding the Sars-CoV-2 infection, among the Sars-CoV-2 negative patients, the majority of patients were with moderate stroke, 25 (41%), followed by 16 (26%) patients with severe stroke, 13 (21%) patients with very severe, and 7 (11%) patients with mild to moderate stroke.

Most Sars-CoV-2 negative patients had moderate and severe stroke. In Sars-CoV-2 positive patients the majority of patients were with very severe stroke, 10 (33%), 9 (30%) patients were with moderate type of stroke, 7 (23%) of them were hospitalized with severe and 4 (13%) of them with mild to moderate types of stroke, Fig.3. Many Sars-CoV-2 positive patients were with very severe and moderate stroke.

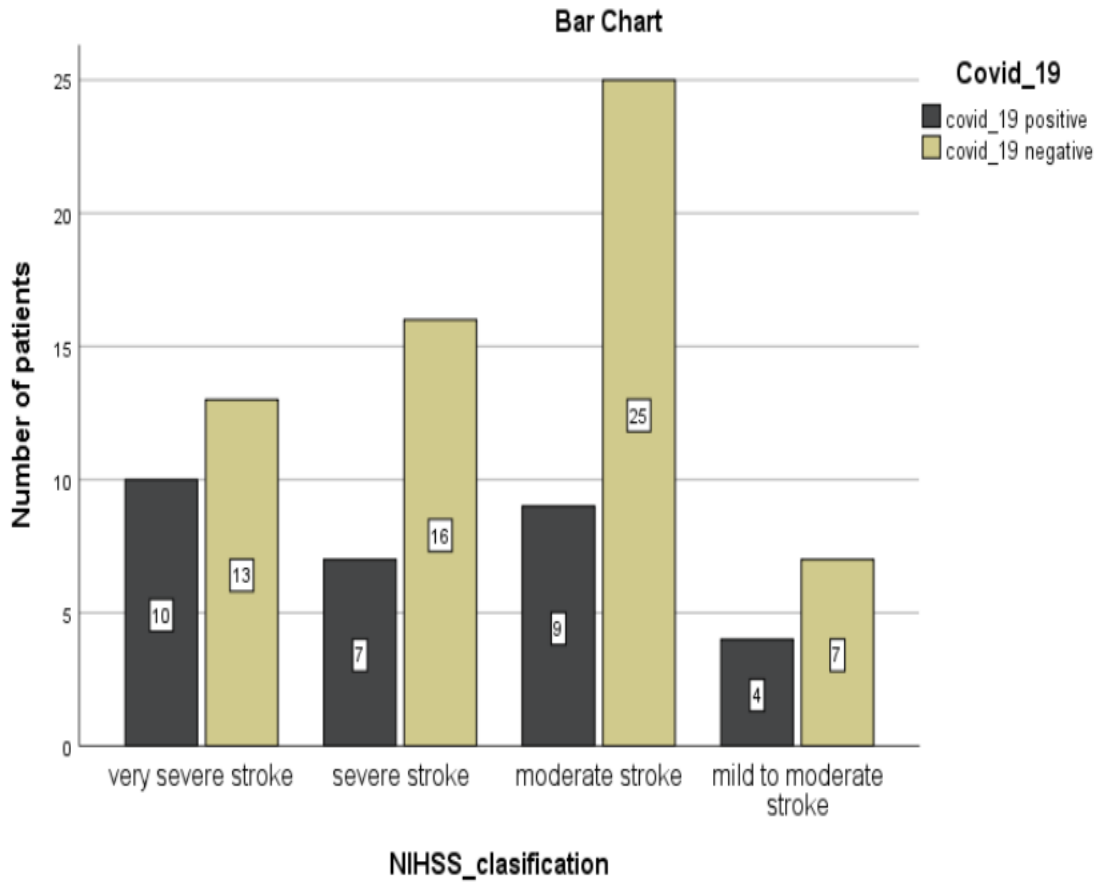

Fig.3. Distribution of Nneurological deficits (NIHSS) in Sars-CoV-2 Negative and Positive Patients with Stroke

To measure the degree of disability or dependence in the daily activities of people who have suffered a stroke, the Modified Rankin Scale was used in patients after they were discharged from the hospital.

Most of the patients showed slight, 25 (27.5%), and moderate disability, 20 (22%), no significant disability besides symptoms presented 9 (9.9%), while 5 (5.5%) of them were without symptoms. 17 (18.7%) of them presented severe disability, and 15 (16,5%) died during or after the hospital treatment. Regarding the SARS-CoV-2 infection, in Sars-CoV-2 negative patients, 19(31%) patients showed slight and moderate disability, followed by 12 (20%) patients with moderate disability, severe disability presented

10 (16.4%) patients, 7 (11%) patients were without significant disability beside symptoms, 3 (5%) of them were without symptoms, and 10 (16.4%) patients died. Most SARS-CoV-2-negative patients had slight and moderate disability.

Between SARS-CoV-2 positive patients moderate disability presented 8 (27%) patients, followed by 7 (23%) patients with severe disability, 6 (20%) patients with slight disability, without significant disability beside symptoms were 2 (7%), 2 (7%) patients without symptoms, while 5 (16.7%) patients died during or after the treatment, Fig.4. Many SARS-CoV-2 positive patients were with moderate and severe disability.

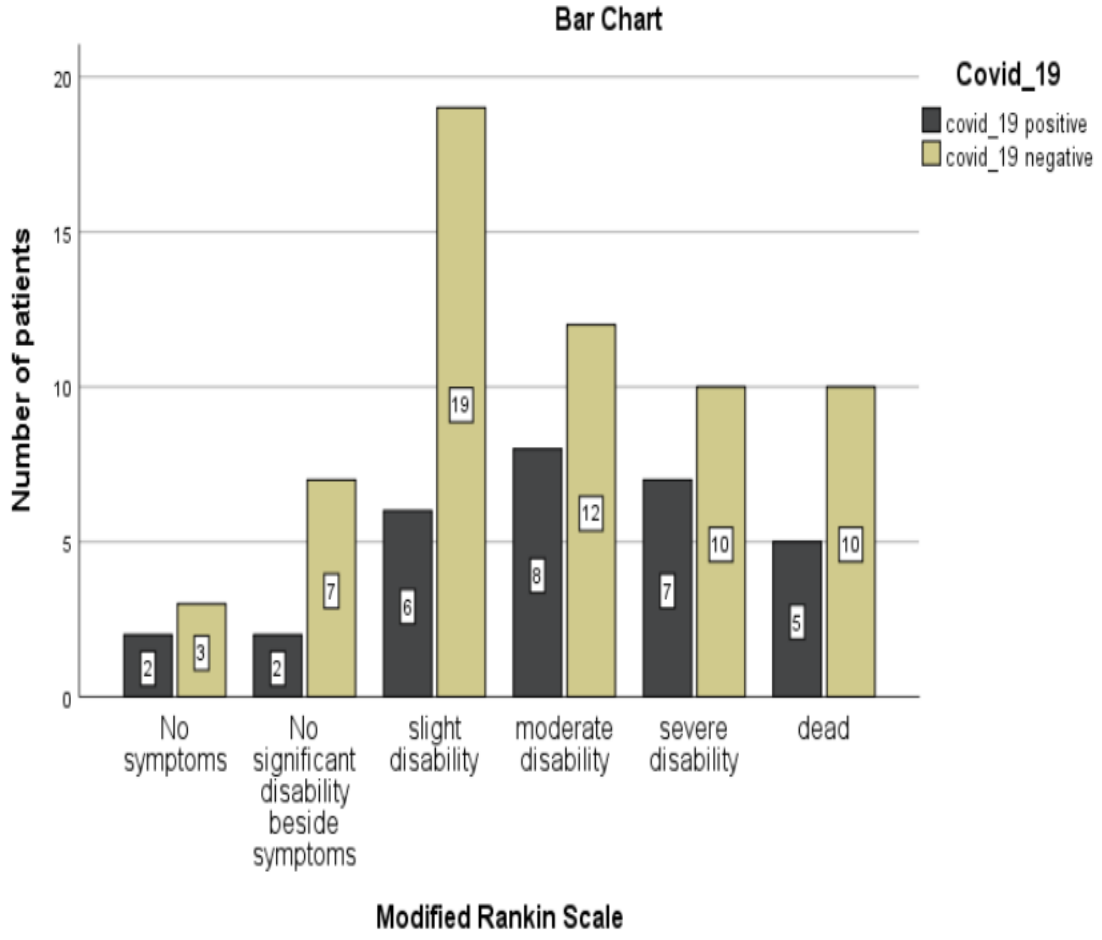

Fig. 4. Distribution of the Grades of Neurologic Disability (M RS) in Sars-CoV-2 Negative and Positive Patients with Stroke

Discussion

This retrospective cohort study analyzed stroke patients hospitalized in the Department of Neuropsychiatry at the General Hospital in Ohrid during the post-COVID period in 2021. The results provide insight into the demographic distribution, types of strokes, and neurological deficits and outcomes after the hospital treatment period in SARS-CoV-2-negative and Positive Patients with stroke.

The findings show that stroke was more common in men (56.8%) than in women (43.2%), which is consistent with previous studies that suggest men are at higher risk for stroke, particularly at younger ages. However, in Sars-CoV-2 positive patients, there were more females with stroke compared to male Sars-CoV-2 positive patients. In Sars-CoV-2 negative patients, male patients with stroke dominated.

Regarding the age of the patients, our data correspond to global epidemiological data, confirming that stroke remains a predominantly elderly disease.

The peak incidence was in the ≥ 70 age group, which corresponds to findings reported in other European populations. In Sars-CoV-2 positive patients, the patients were younger, most of them belonged to the 60-69-year-old age group, compared to Sars-CoV-2 negative patients.

Our findings correspond to the findings of other investigations that confirmed that COVID-positive patients with intracranial hemorrhage (ICH) were younger and had fewer predisposing factors than COVID-negative subjects with ICH [20].

Regarding stroke type, the majority of cases were ischemic (71.4%) in both Sars-CoV-2-positive and negative patients. This distribution reflects the general pattern worldwide, where ischemic stroke accounts for approximately 70–80% of cases.

NIHSS is a 15-item impairment scale that is used to measure stroke severity. The NIHSS is a reliable, valid, and responsive tool for measuring stroke severity; it is useful both in clinical practice and research. It can be used in people with language and cognitive deficits.

Importantly, NIHSS is easy to administer (less than 10 minutes)1 and requires minimal equipment (only a sharp object is required for sensory testing). In addition, resources are free and readily available to help clinicians learn how to administer the NIHSS.

This indicates that despite the burden of the pandemic on healthcare systems, effective acute management and rehabilitation of stroke patients was achieved.

When analyzed by NIHSS categories, Sars-CoV-2 positive patients mostly presented moderate and severe neurologic deficits. These findings are consistent with recent literature that emphasizes that COVID-19 positive patients were more likely to have a large cortical stroke with severe symptoms and poor outcome.

It is important to note that the post-COVID context may have influenced both incidence and outcomes. Several studies have reported a higher risk of thrombotic complications, including ischemic stroke, after COVID-19 infection, likely due to persistent inflammatory and coagulopathic changes. Our findings presented a slight increase in poor outcomes in Sars-CoV-2-positive patients compared to negative patients. Many authors have reported poor stroke outcomes in Sars-CoV-2- positive patients. [20-23].

The limitation of our study is the small number of Sars-CoV-2 positive patients included in the study. More multicenter and prospective studies are needed to better clarify the relationship between COVID-19 and stroke incidence, severity, and outcomes.

Conclusion

This study offers valuable insights into the characteristics of stroke patients hospitalized during the post-COVID period. The majority of these patients were men, and the highest incidence was observed in the age group of 70 and older.

Notably, patients who tested positive for SARS-CoV-2 and experienced a stroke were younger compared to those who tested negative.

Ischemic stroke was the most common type encountered, followed by hemorrhagic strokes. Based on the National Institutes of Health Stroke Scale (NIHSS), most SARS-CoV-2-positive patients presented with either very severe or moderate strokes. In terms of disability following hospital treatment, a significant proportion of SARS-CoV-2-positive patients experienced moderate to severe disabilities.

Furthermore, there was a slight increase in poor outcomes among SARS-CoV-2-positive patients. These findings align with global data on stroke epidemiology and reflect the potential impact of COVID-19 on cerebrovascular health.

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