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RISK FACTORS IN HOSPITALIZED PATIENTS WITH STROKE POSITIVE ON SARS-COV-2-INFECTION

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Abstract

Numerous reports indicate an increased number of strokes in the period after the peak of Covid 19, describing the presence of "COVID strokes" in young individuals with atypical thromboembolic events.

The main goal of this investigation was to assess/identify risk factors and coexisting comorbidities, in patients first time hospitalized for diagnosis of stroke at the Neuropsychiatric Department at the Public Health Institution (PHI) General Hospital Ohrid, positive for Sars-Cov-2-infection, from 6 months prior to the day of hospital admission in comparison to Sars-Cov-2 negative patients who met the same criteria.

All 54 patients who met the criteria to be included in the study, after giving written consent, answered the modified European Stroke Awareness Questionnaire (SAQ). Traditional stroke risk factors were highly prevalent in our cohort (Sars-Cov-2-infected patients with stroke) with more than 80% of individuals having had at least 1 documented risk factor such as obesity (significantly more prevalent in our cohort), sedentary lifestyle and presence of two or three coexisting comorbidities such as hypertension, dyslipidemia, diabetes, or heart disease.

The investigation will contribute to the development of new models and strategies for the prevention of stroke in patients with Covid-19- infection.

Key words: stroke, risk factors Covid-19, obesity, comorbidity.

Introduction

In March 2020, the World Health Organization (WHO) declared the coronavirus disease-19 (Covid-19) a global pandemic [1]. Since then, hospitals and surgical departments around the world have been forced to restructure the way healthcare is delivered.

Numerous organizations, including the American Heart Association/American Stroke Association (AHA/ASA), disseminated guidelines to optimize procedural safety, while many reports indicated an increased risk of thromboembolic complications due to the disease as well as an increased number of strokes associated with Covid-19. However, a reduced incidence of strokes and a sharp decline in the number of stroke patients during the pandemic have also been observed [2-10].

Although there is a clear impact of Covid-19 on reducing the number of strokes, its overall impact on stroke presentation characteristics and, importantly, on clinical outcomes has yet to be

determined. Numerous reports indicate an increased number of strokes in the period after the peak of infection, describing the presence of "COVID strokes" in young individuals with atypical thromboembolic events [11].

Importantly, even patients with mild or asymptomatic Covid-19 may have an altered coagulation profile or continue to have aberrant coagulation even after recovery from the illness. Severe acute respiratory syndrome coronavirus 2 viral infection has been found to considerably increase one's risk of stroke, and this condition could be the result of many factors such as dysregulated host immune response to the virus persisting several months after the infection. Many studies reported mixed data on the role of traditional risk factors such as hypertension, dyslipidemia, and diabetes in stroke pathogenesis of Covid-19-positive patients [12,13].

The main goal of this investigation was to assess/identify risk factors and coexisting comorbidities, in patients first time hospitalized for diagnosis of stroke at the Neuropsychiatric Department at the Public Health Institution (PHI) General Hospital Ohrid, positive for Sars-Cov-2-infection from 6 months prior to the day of hospital admission in comparison to Sars-Cov-2 negative patients who met the same criteria for hospitalization.

Patients and methods

In the Republic of North Macedonia, from 3 January 2020 to 3:56 pm CEST, 6 September 2023, there have been 348,411 confirmed cases of COVID-19 with 9,941 deaths, reported to WHO. The last wave of Covid-19 was on June 27, 2022. until October 3, 2022. with a peak on July 25, 2022. (4845 confirmed cases) according to WHO [1].

This study was carried out in the post-covid period (after the end of the last wave of Covid-19) from January to September 2023. at PHI General Hospital Ohrid at the Department of Neuropsychiatry. A total of 54 patients were hospitalized for the first time for stroke, meeting the criteria for diagnosis according to the American Stroke Association Stroke Council Recommendations [14] with positive/negative Covid-19 infection from 6 months prior to the day of hospital admission (confirmed by PCR-polymerase chain reaction Corona Covid 19 test) were included in the study. Patients included in the study consciously and voluntarily agreed to participate in the investigation and gave permission for their laboratory, neurological, and tomographic findings to be used.

The Ethics Committee of the PHI General Hospital in Ohrid approved this investigation. Exclusion criteria were: absence of consent to voluntarily participate in the investigation due to the patient's own decision or due to impaired consciousness until the end of hospital treatment; patients who have previously suffered an ischemic or hemorrhagic stroke or patients hospitalized for suspected re-stroke; patients who had a repeated stroke during hospitalization; patients who have 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).

All patients who met the criteria to be included in the study, after giving written consent, answered the Questionnaire which included demographic (age, gender), socioeconomic, and other anamnestic data regarding the health condition of the examinee. For this research, a two-part survey questionnaire of 19 questions, non-standardized European Stroke Awareness Questionnaire (SAQ) has been used, modified/adapted to the conditions of this study [15].

The questionnaire was filled out by the interviewer who was able to redefine and clarify the questions. The modification was carried out after conducting a pilot study in 20 patients from the Neuropsychiatric Department-PHI General Hospital Ohrid. The first part of the questionnaire consisted of general information that focused on the age, gender, level of education, marital status, work status, socioeconomic status, and other general socio-demographic data of the patient. The questions also refer to the interviewee's lifestyle habits regarding cigarette smoking, alcohol consumption, and physical activity. Body mass index (weight in kilograms divided by height in meters squared) was evaluated aa well as the current state of the patient's health, i.e. present comorbidities.

Statistical analysis was performed using the SPSS (version, Chicago, IL, USA). Descriptive statistics were used. Categorical data from all participants were summarized using proportions and percentages. The chi-square test was used to compare risk factors between Covid-19-positive and negative patients with a diagnosis of stroke. A p-value less than 0.05 was considered statistically significant.

Results

From the total of 54 patients 31 (57,4%) were males and 23 (42,6%) were females. Twenty four (44,4%) of them were Covid-19-positive. Between Covid -19 -positive patients, 13 (54,2 %) were males and 11 (45,8%) were females. Between Covid -19-negative patients 18 (60%) were males and 12 (40%) were females.

There was no difference in age distribution between COVID-19-positive and COVID-19 -negative patients. The majority of Covid-positive, 19 (79%), and 22 (73%) of Covid-negative-patients belonged to the groups of 60-69 years and ≥70 years old patients.

Nearly half of the Covid-positive and Covid-negative patients were living in rural areas. The largest number 17 (70,8%) of Covid-19-positive and Covid-19-negative patients, 21 (70%) patients were married.

The majority of the Covid-positive, 20 (83%), and Covid-negative patients, 23 (77%) were with low educational level (elementary and high school level). The largest number of Covid-19-positive, 18 (75%) and Covid-19-negative patients, 16 (53,3%) were retired, and employed, 5 (20,8%) Covid-positive and 9 (30%) Covide-negative patients. In terms of monthly income in Covid-19-positive patients, 15 (62%) patients belonged to the low-income groups. In the Covid-19- negative group, the majority of the patients belonged to the group of patients with low, 9 (30%), and to the group with the highest monthly income 11 (36,7%). There were no differences among Covid-positive and Covid-negative patients regarding the level of education, working position, and monthly income.

Regarding lifestyle habits, 13 (54%) Covid-positive and 16 (53%) Covid-negative patients were daily and occasional smokers. Majority of the Covide-positive and Covide-negative patients didn't consume alcohol or consume it occasionally, 20 (83%) Covide-positive and 25 (83%) Covide- negative patients. According to the physical activity, 22 (92%) of Covid-positive and 26 (87%) of Covid-negative patients belonged to the group with no and to the group with mild physical activity. Only 6 (11%) of all patients declared that they have had intense physical activity.

Body mass index was the only risk factor that showed significant differences between Covid-positive and Covid-negative patients. Persons with a body mass index (BMI) of < 18. are classified as being underweight, between 18.5 and 25.9 kg/m2 as healthy weight range, between 26 and 29.9 kg/m2 as overweight, and ≥ 30 kg/m2 as being obese. Obese patients were significantly more numerous in the group of Covid-19-positive patients (p=0.059) compared to Covid-19-negative patients, (Fig 1). 17 (71%) Covide-positive and 13 (43%) Covide-negative patients had BMI ≥30. Covid-19-positive patients were more obese compared to the Covid-19-negative patients.

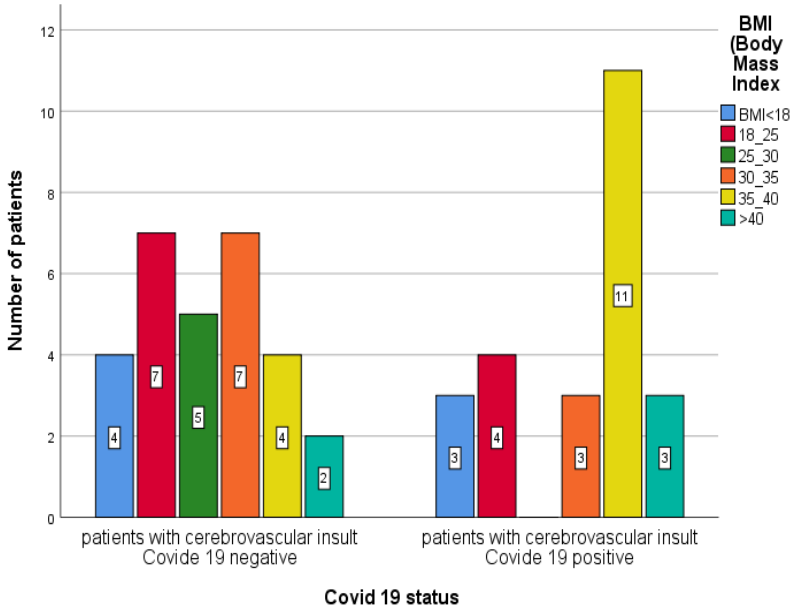

Fig.1 Body mass index (BMI) in Covid-19-positive and Covid-19-negative patients with stroke

Positive family history for cerebrovascular insult was declared in 11 (37%) Covid-19-negative patients and in 7 (29%) Covid-19- positive patients.

Regarding the condition of the patient's health in the group of the Covide-positive-patients only two patients were in good health condition before the accident. Hypertension was declared in 21 (87%), diabetes mellitus in 9 (37%), and dyslipidemia in 5 (26%) Covide-19-positive patients. Presence of two or three coexisting comorbidities was declared in 15 (62%) Covid-positive-patients, most frequently hypertension and diabetes in 4 patients and hypertension, diabetes, and heart disease, in 3 patients. In the group of Covide-19- negative patients, 7 patients were in good health condition before the accident, hypertension was declared in 17 (57%) patients, diabetes mellitus in 5 (17%), and dyslipidemia in 7 (23%) patients. Presence of two or three coexisting comorbidities was declared in 13 (43%) Covid-negative-patients, most frequently hypertension, and dyslipidemia in 4 patients and hypertension and heart disease in 4 patients. Impaired health conditions and existence of two or three comorbidities was more frequent finding in the group of Covide- 19-positive patients.

The most common comorbidities in Covid-19-positive patients were hypertension and diabetes mellitus (Fig.2).

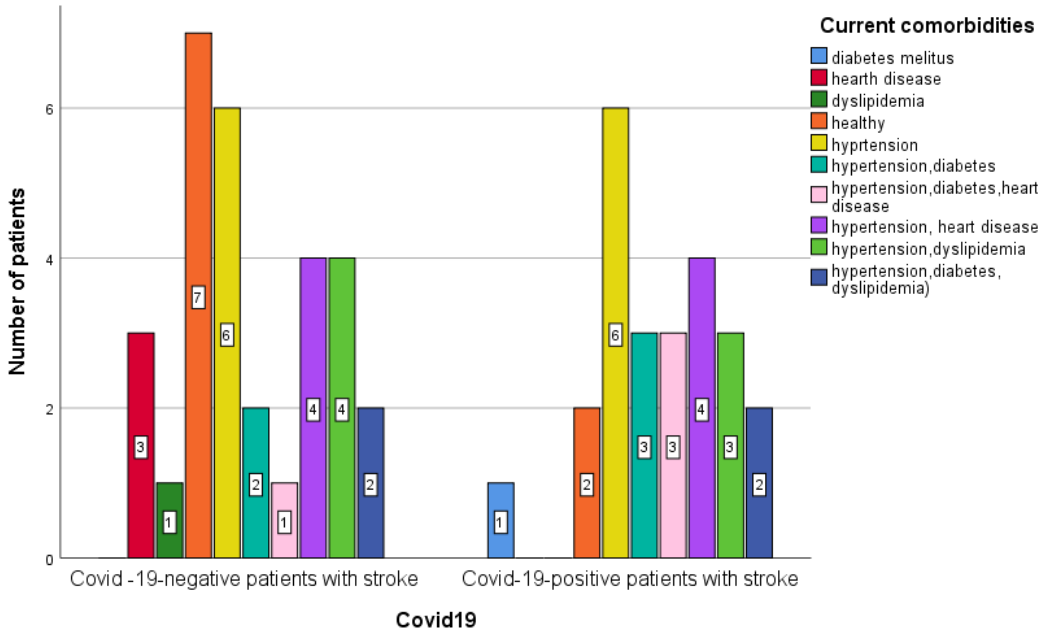

Fig.2 Coexisting comorbidities in Covid-19-positive and Covid-19-negative patients with stroke

Discussion

The motivation for this study was to gain knowledge about the still insufficiently clarified connection between Covid-19-infection and stroke and to contribute to the development of strategies and protocols for the prevention and treatment of these patients. Appropriate treatment of the modifiable risk factors for stroke has been associated with a reduction of stroke. The implementation of measures for primary or secondary stroke prevention may significantly reduce the incidence of stroke among the population [16].

A lot of authors reported an association between severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and neurological deficits. One of them is the study by Merkler et al. [17] in which patients infected with SARS-CoV-2 were shown to have a higher risk of thrombosis, including stroke, compared with other seasonal viral infections.

The reported incidence of cerebrovascular disease in SARS-CoV-2-positive patients ranges between 1%-6%, with this number expected to rise [18].

The proposed pathophysiological mechanism for these cerebrovascular events is multifactorial: the hypercoagulable state resulting from systemic inflammation and cytokine storm; venous stasis as a result of immobilization; blood hyperviscosity; the post-infectious immune-mediated response and direct viral-induced endotheliitis or endotheliopathy, which subsequently leads to angiopathic thrombosis; the affinity of SARS-CoV-2 for ACE-2 receptors could allow the virus to directly damage intracranial arterial blood vessels, causing rupture of the vessel wall [19,20].

This study showed that Covid-19 occurred in all age groups but predominantly in older regarding the demographic and socioeconomic factors; no differences were evaluated between Covid -19- positive and Covid-negative patients. Obesity is defined as an increase above 25% of the theoretical body weight according to age and sex. "Obesity" is mainly one of the ways to measure "adiposity" which refers to the amount of adipose (fat) tissue. An increase in fat tissue is considered a main risk factor for developing cerebrovascular disease, insulin resistance, diabetes, hypertension, dyslipidemia, vascular diseases, and other diseases. Obese patients hospitalized for stroke and positive for Covid-19-infection had an increased risk of cerebrovascular disease probably due to the preliminary hypercoagulopathy, which can be indirectly shown by the increase in D-dimer in these patients. D-

dimer should be verified and treated carefully in obese Sars-Cov-2- positive patients because of the increased risk for stroke among these patients. Physical inactivity is associated with numerous adverse health effects, including increased risk of total mortality, cardiovascular mortality, and death from stroke [21]. An extensive review by Hankey [22] on potential new risk factors for ischemic stroke included data from a meta-analysis of 23 studies and showed that subjects with high physical activity compared with those with low physical activity had a lower risk of stroke.

Hypertension together with age are leading risk factors for silent or symptomatic cerebrovascular disease [23,24]. High blood pressure multiplies the risk for stroke as much as 4-fold. Our results show that high blood pressure is an even more important risk factor for stroke in Covid-19-positive patients. The risk of cerebral hemorrhage in hypertensive patients is 3.9 times higher than in nonhypertensive individuals [24-28]. The diagnosis and control of hypertension are the main strategies for primary and secondary prevention of stroke [28-30]. According to our results, the control of hypertension is very important for Covide-19-positive patients because of the effect of chronic hypertension on cerebral vessels and tissue (microhemorrhages, silent infarctions, white matter lesions, and atrophy) that is multiplied by the effects of Covid-19-infection itself.

Diabetes is an independent risk factor of ischemic stroke of atherothrombotic cause. Diabetes is the main risk factor following hypertension of cerebral small vessel disease and has been identified as a significant independent variable of stroke [31]. The combination of diabetes and hypertension increases the frequency of stroke in Covid-19-positive patients. Heart diseases are the second cause of acute cerebrovascular events and are diagnosed in one-third of patients with stroke [32, 33]. Atrial fibrillation and atrial flutter are the most important and modifiable risk factors, frequently associated with cardioembolic stroke. The combination of diabetes, hypertension, and heart disease increases the frequency of stroke in Covid-19-positive patients.

Plasma lipids and lipoproteins [total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol] influence the risk of cerebral infarction. Data from prospective studies in male patients have shown that in the presence of total serum cholesterol values > 240 to 270 mg/dL, there is an increase in rates of ischemic stroke [34]. In men, low HDL levels are a risk factor for cerebral ischemia, but data in women are inconclusive. Because high LDL levels are associated with higher cardiovascular risk, adequate control of LDL cholesterol is recommended in Covid-19-positive patients.

The limitation of this observational study is a small sample size that did not allow us to perform further subgroup analyses (division of patients according to the interval between Covid-infection and the onset of stroke symptoms) for a better understanding of the interaction between traditional risk factors for stroke and Sars-Cov-2-Infection.

Conclusion

Traditional stroke risk factors were highly prevalent in our cohort (Sars-Cov2 **-i**nfected patients with stroke) with more than 80% of individuals having had at least 1documented risk factor such as obesity (significantly most prevalent), sedentary lifestyle and impaired health condition with presence of two or three coexisting comorbidities such as hypertension, dyslipidemia, diabetes, or heart disease.

The results of this study will provide more knowledge regarding the connection of stroke and Covid-19 infection. This investigation may contribute to the development of new models and strategies for the prevention of stroke in Covid-19-positive patients and detect the most vulnerable target groups of Covid-19-positive patients.

We declare no conflict of interest.

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