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CHARACTERISTICS OF ISCHEMIC STROKE IN PATIENTS WITH CONFIRMED CORONAVIRUS DISEASE 2019 INFECTION IN VOJVODINA, SERBIA

KARAKTERISTIKE ISHEMIJSKOG MOŽDANOG UDARA KOD PACIJENATA SA POTVRĐENIM COVID-19 U VOJVODINI, SRBIJA

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Summary

Introduction. The World Health Organization declared a pandemic of coronavirus disease 2019 on March 11, 2020. The literature has shown that coronavirus disease 2019 is associated with thromboembolic complications, including ischemic stroke. This retrospective study aims to present the characteristics of ischemic stroke in patients with coronavirus disease 2019. **Material and Methods.** This retrospective study was conducted in the period from April 2020 to January 2022 at the Clinical Center of Vojvodina, and included 58 patients with confirmed coronavirus disease 2019 and a new-onset ischemic stroke. **Results.** The reason for hospitalization in 42 (72.41%) patients was a new-onset ischemic stroke and 16 of them (38.09%) had a previously confirmed coronavirus disease 2019. In 16 patients (27.58%), ischemic stroke occurred during hospital treatment due to severe clinical manifestations of coronavirus disease 2019. In most coronavirus disease 2019 positive patients the etiology of ischemic stroke was unknown. In most cases (43.1%), the ischemic stroke was a partial infarction of the anterior circulation. Nine patients (15.51%) received intravenous thrombolytic therapy (alteplase) in the appropriate time frame. Lethal outcome occurred in 21 patients, of which in 11 patients complications of coronavirus disease 2019 were the cause of death. **Conclusion.** A large number of cases with stroke and thrombotic complications in patients with coronavirus disease 2019 is a good indicator that severe acute respiratory syndrome coronavirus 2 does not only cause respiratory infections, but is a systemic infection. The etiology of most ischemic strokes was unknown, which is probably related to difficult functioning of the health system during the pandemic.

Key words: Ischemic Stroke; COVID-19; SARS-CoV-2; Thromboembolism; Demography; Risk Factors; Treatment Outcome

Sažetak

Uvod. Svetska zdravstvena ogranizacija je 11. marta 2020. godine proglasila pandemiju koronavirusne bolesti 2019 (COVID-19). Podaci iz literature ukazuju na povezanost COVID-19 i tromboembolijskih komplikacija, uključujući ishemijski moždani udar. Cilj ove retrospektivne studije bio je da prikaže karakteristike ishemijskih moždanih udara kod pacijenata obolelih od COVID-19. **Materijal i metode.** Ova retrospektivna studija je sprovedena u Univerzitetskom kliničkom centru Vojvodine i obuhvatila je 58 pacijenata u periodu od aprila 2020. do januara 2021. godine koji su imali udružen COVID-19 sa novonastalim ishemijskim moždanim udarom. **Rezultati.** Razlog za hospitalizaciju kod 42 pacijenta (72,41%) bio je novonastali moždani udar, 16 od njih (38,09%) imalo je prethodno potvrđen COVID-19. Ishemijski moždani udar kod 16 pacijenata (27,85%) nastao je tokom hospitalnog lečenja zbog teške kliničke slike COVID-19. Najčešći etiopatogenski mehanizam nastanka ishemijskog moždanog udara kod COVID-19 pozitivnih pacijenata bio je nepoznate etiologije. U najvećem broju slučajeva (41,1%) ishemijski moždani udar je bio parcijali infarkt prednje cirkulacije. Devet pacijenata (15,51%) je primilo intravensku trombolitičku terapiju (alteplazu) u odgovarajućem "vremenskom prozoru". Smrtni ishod se desio kod 21 pacijenta, od kojih su kod 11 pacijenata uzroci smrti bile komplikacije COVID-19. **Zaključak.** Veliki broj udruženih slučajeva moždanog udara i trombotskih komplikacija kod COVID-19 pozitivnih pacijenata je pokazatelj da SARS-CoV-2 nije samo uzročnik respiratorne infekcije, nego sistemske infekcije. Etiologije većine ishemijskih moždanih udara je bila kriptogena, što je verovatno povezano sa otežanim funkcionisanjem zdravstvenog sistema u periodu pandemije.

Ključne reči: ishemijski moždani udar; COVID-19; SARS-CoV-2; tromboembolija; demografija; faktori rizika; ishod lečenja

Introduction

On March 11, 2020, the World Health Organization declared a pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). By October 2, 2022, 615 million cases were confirmed, with a mortality rate of 1.05%. In the Republic of Serbia, the total number of patients by October 4, 2022, was 2,369,456, and the mortality rate was 0.72% [1]. The severity of the clinical symptoms in patients with COVID-19 varies, from asymptomatic form of the disease, mild and more severe clinical presentation with bilateral pneumonia, to life-threatening acute respiratory distress syndrome and multiorgan dysfunction that can lead to death.

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Abbreviations

COVID-19	– coronavirus disease 2019
SARS-CoV-2	– severe acute respiratory syndrome coronavirus 2
ACE2	– angiotensin-converting enzyme 2
vWF	– von Willebrand factor
CT	– computed tomography
Ang	– angiotensin
IL	– interleukin
NIHSS	– National Institutes of Health Stroke Scale
TACI	– total anterior infarction
PACI	– partial anterior infarction
POCI	– posterior circulation infarction
LACI	– lacunar infarction
mRS	– modified Rankin Scale
TOAST	– Trial of (Org 10172) Acute Stroke Treatment

Neurological symptoms are common in COVID-19 positive patients, such as loss of the sense of smell and taste, headache, dizziness, and symptoms that are related to the development of ischemic stroke. The incidence of stroke in COVID-19 patients is estimated to be 0.5 - 1.5% [2]. In a retrospective study from the beginning of the pandemic that included 214 hospitalized COVID-19-positive patients from Wuhan, 5.7% of patients developed a stroke [3]. Hemorrhagic stroke is much less common than ischemic stroke in COVID-19 patients [4, 5].

Arterial and venous thrombosis

There is a lot of evidence of arterial and venous thrombotic complications in patients infected with COVID-19. In the study by Klok et al., 31% of COVID-19 patients had thrombotic complications, most often deep vein thrombosis, pulmonary thromboembolism, myocardial infarction, and ischemic stroke [6].

Autopsies of COVID-19 patients showed numerous micro- and macrovascular thrombosis of the blood vessels in the lungs, liver, spleen, kidneys, and heart. Acute respiratory insufficiency may be caused by microvascular thrombosis in the lungs [6]. Pulmonary thromboembolism is the cause of death in a large percentage of COVID-19-positive patients [7].

The exact cause of thrombotic complications has not been established, but it is considered to be multifactorial. One of the possible explanations for the pathophysiological mechanism of thrombotic complications in patients infected with COVID/19 is Virchow's triad [8].

Endothelial injury

The first factor of Virchow's triad is endothelial injury, which may be a result of direct effect of the virus on the cells or as part of a systemic inflammatory response - a cytokine storm [8]. Endothelial cell damage changes the vascular wall and causes platelet activation, and enhances procoagulant activity.

Direct endothelial cell damage

Coronavirus binds to the angiotensin-converting enzyme 2 (ACE2) which is widely expressed in multiple organs. The SARS-CoV-2 binds to ACE2 receptors with antigenic protein spikes ("spike" antigen) and enters the cell through processes involving the cell surface transmembrane protein serine 2 (TMPRSS2). The viral genome ribonuclric acid is released and replicates inside the host cell's cytoplasm. The newly formed genomic ribonucleic acid is packaged into vesicles containing the virion, fuses with the cell membrane, and thus releases the virus. This process enables the circulation of the virus. The ACE2 receptors are expressed widely in multiple organs, including the lungs, heart, kidneys, and intestines [9]. Underneath the endothelial cells is von Willebrand factor (vWF) coagulation, which is released after endothelial cell damage. The vWF plays a role in platelet adhesion and binds to factor VIII in the blood, thus prolonging its half-life, and also plays a role in starting the coagulation cascade [10].

Cytokine storm

Cytokine storm, as a complication of COVID-19, is an uncontrolled response to SARS-CoV-2 infection with the synthesis of interleukin (IL)-6 and other inflammatory mediators. This condition damages cells, produces numerous pro-inflammatory markers, and initiates coagulation process via the complement system, and thus induces a state of hypercoagulability. As part of COVID-19, an increase in cytokine values was recorded, including IL1B, IFNγ, IP10, MCP1, and IL-6, especially in patients with a more severe form of the disease and with higher mortality [9].

Dysregulation of the renin-angiotensin system

Dysregulation of the renin-angiotensin system is also a cause of cell damage and thrombotic complications. The virus invades alveolar epithelium and cardiomyocytes using ACE2 as a transmembrane receptor. The ACE2 receptors are part of the renin-angiotensin system that participates in the control of arterial pressure. The ACE2 is a counter-regulatory peptide that degrades angiotensin (Ang) II into Ang 1 - 7, thereby attenuating the biological effects of the AT1 receptor. Angiotensin 1 - 7 is a protective peptide and has vasodilatory and anti-inflammatory effects. Depletion of ACE2 receptors stops the enzymatic conversion of Ang II to Ang 1 - 7. A deficiency of ACE2 reduces the production of Ang 1 - 7 and leads to disruption of endothelial function and increases oxidative stress. The hormone Ang II leads to an increase in blood pressure and has a pro-inflammatory and atherogenic effect on blood vessels that causes lung damage and damages organs such as the heart and brain. An elevated level of the Ang II hormone was registered in 90% of critically ill patients with COVID-19 [9].

Hypercoagulability

The hypercoagulable state is one of the most significant indicators of a poor outcome in COVID-19 with high D-dimer values and decreased platelet values as a consequence of consumption (disseminated) coagulopathy. In some patients with confirmed COVID-19, elevated values of antiphospholipid antibodies (anticardiolipin and anti-beta-2 glycoprotein antibodies) were observed, which can lead to thrombotic events.

Transiently elevated antiphospholipid antibodies have been observed in critically ill patients [10].

Stasis of blood flow

The last factor of Virchow's triad is blood stasis, which occurs as a result of the immobility of COVID-19 patients due to their poor general condition and dependence on oxygen support [8]. Because of that, it is necessary to include patients in early rehabilitation treatment.

Cardioembolism

Cardiomyopathy in COVID-19 patients can be explained by several mechanisms, such as a direct effect of virus particles via ACE2 receptors, systemic inflammatory reaction of the body (cytokine storm), a reduction of ACE2 receptor regulation and increased effect of the hormone Ang II, as well as hypoxemia and respiratory insufficiency as a consequence of lung tissue damage. All these contribute to the development of myocarditis and heart rhythm disorders, which increases the risk of cardioembolic stroke [11].

Material and Methods

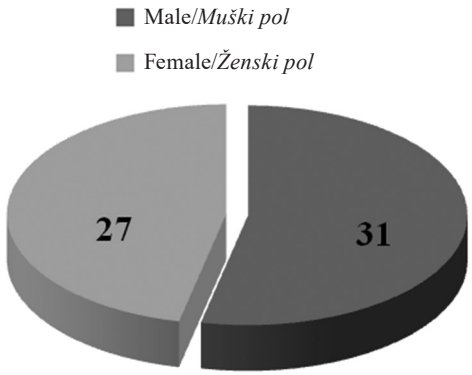
This retrospective study was conducted at the University Clinical Center of Vojvodina, and it included all patients treated from April 2020 to January 2022, who required treatment in a tertiary healthcare institution. Patients had a COVID-19 confirmed by rapid antigen or PCR testing and ischemic stroke.

We studied data related to the demographic and clinical characteristics of patients and the characteristics of ischemic stroke. The National Institutes of Health Stroke Scale (NIHSS) was used for clinical assessment. Based on the clinical manifestations and radiological findings, ischemic strokes were classified into one of four possible types based on the Oxfordshire Community Stroke Project (OCSP) classification (total anterior infarction (TACI), partial anterior infarction (PACI), posterior infarction (POCI), and lacunar infarction (LACI). The neurological outcomes of patients were based on modified Rankin Scale (mRS). We discussed the etiology of ischemic stroke based on the Trial of Org Acute Stroke Treatment (TOAST) classification.

Results

The retrospective study included groups of patients who were hospitalized at the University Clinical Center of Vojvodina with confirmed COVID-19 and ischemic stroke from April 2020 to January 2022. The COVID-19 was confirmed by rapid antigen or PCR testing for SARS-CoV-2. Patients who were infected with COVID-19 during hospital treatment for a stroke were excluded from the study.

By searching the Key Information Summary of the University Clinical Center of Vojvodina, a group of 58 patients was selected, of which 31 were male and 27 were female **(Graph 1).**



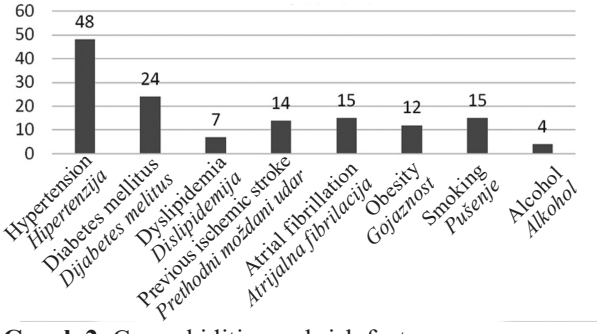
Graph 1. Gender distriburion of patients
Grafikon 1. *Struktura pacijenata po polu*

The average age of the examined patients was 77 years, of which twelve patients were over 80 years old, and nine patients were under 65 years old. The youngest patient was 35 years old with no previous comorbidities.

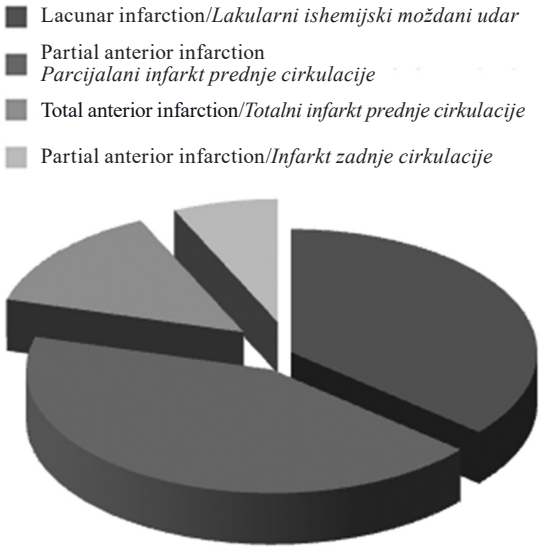
In 42 (72.41%) patients the reason for admission was a new-onset ischemic stroke and 16 (38.09%) had a previously confirmed COVID-19. The median time between the COVID-19 symptoms and stroke onset was 11 days (interquartile range: 4 - 15). In 26 (62%) patients, COVID-19 was confirmed by PCR or antigen test after admission due to new-onset ischemic stroke.

Ischemic stroke occurred in 16 patients (27.58%) during hospital treatment due to the severe clinical picture of COVID-19. In the first week of COVID-19 treatment, stroke occurred in 5 (33.33%) patients, in 4 (26.66%) patients in the second, and in 7 (43.75%) patients in the third week.

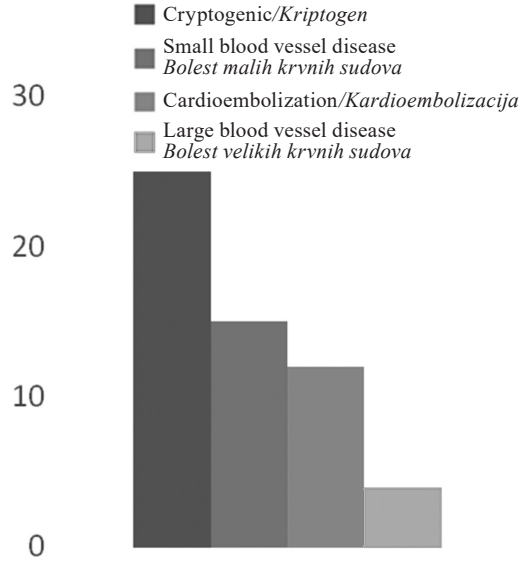
There were 4 patients (6.89%) without previously known comorbidities, while the other patients had at least one risk factor for ischemic stroke. The most prevalent risk factors for stroke were hypertension (82.75%), diabetes mellitus (41.37%), atrial fibrillation (25.86%), obesity (18.96%), and dyslipidemia (12.06%). Previous stroke was reported in 14 patients (24.13%). Fifteen patients (25.86%) reported harmful habits such as cigarette smoking, and 4 patients (6.89%) reported large quantities of alcohol consumption **(Graph 2).** Premorbid mRS in 9 patients (15.51%) was ≥ 3.



Graph 2. Comorbidities and risk factors
Grafikon 2. *Komorbiditeti i faktori rizika*



Graph 3. Oxfordshire Community Stroke Project classification
Grafikon 3. *Projekt Oksfordširske zajednice za klasifikaciju moždanog udara*



Graph 4. Trial of (Org 10172) Acute Stroke Treatment - classification
Grafikon 4. *Ispitivanje (Org 10172) lečenja akutnog moždanog udara – klasifikacija*

According to the Oxfordshire Community Stroke Project classification of ischemic strokes, TACI was found in 8 patients (13.79%) and PACI in 25 patients (43.1%). Only 4 patients (6.89%) had a POCI, and in 21 patients (36.20%) LACI was verified by brain computed tomography (CT) **(Graph 3).**

In the largest number of patients (43.1%), the etiopathogenic mechanism of ischemic stroke was cryptogenic. Other types of ischemic strokes according to the TOAST classification were results of small blood vessel disease (25.86%), cardioembolization (20.68%), and large blood vessel disease (10.34%) **(Graph 4)**. The median NIHSS was 10 (interquartile range: 8 - 14).

The highest prevalence of ischemic stroke of unknown etiology was probably due to different functioning of the tertiary healthcare system during the COVID-19 pandemic. During hospitalization, 33 patients (56.89%) had no complete diagnostic workup for stroke (arterial duplex scan, CT/magnetic resonance (MR) angiography, and cardiological examinations).

Nine patients (15.51%) received intravenous thrombolytic therapy (alteplase) in the appropriate time frame, of which seven patients (77.7%) had a favorable outcome. Signs of hemorrhagic transformation after intravenous thrombolytic therapy were not registered. No endovascular thrombectomy was performed. During hospitalization, all examined patients were treated by anticoagulant therapy with low-molecular-weight heparin and antiplatelet therapy.

All patients had chest X-rays, and 45 (77.58%) had bilateral pneumonia. All of them needed oxygen support via a mask. In six patients (10.34%), respiratory insufficiency escalated and they required mechanical ventilation.

Almost all examined patients (86.20%) had elevated of C-reactive protein (CRP) values, only 4 patients (6.89%) had D-dimer values within the reference range, while 10 patients (17.24%) had elevated D-dimer values > 10,000 ng/L. Six patients (10.34%) had elevated values of IL-6 during hospitalization.

Eight patients (13.79%) were transferred to another health facility for further hospital treatment and rehabilitation. Twenty-nine (50%) patients were referred for further home treatment with recommendations for controls in the Covid clinic. Thirty-nine (67.24%) patients had a severe disability at discharge, mRS $\geq$ 4. There were 21 (36.2%) lethal outcomes, of which the cause of death in eleven patients were complications of COVID-19. The average length of hospitalization in the examined patients was 16 days.

Discussion

Our retrospective study focused on studying the characteristics and subtypes of ischemic stroke in patients with confirmed COVID-19, as well as the disease outcomes at the end of hospitalization. The average age of patients was high, 77 years, with a predominance of men, in contrast to the study by Shahjouei et al., where 36% of patients were under 55 years of age, and 46% were under 65 years of age [12]. In our study, only 15.51% of patients were under 65 years of age, and the youngest patient was 35 years old with no previous risk factors for stroke. The reason for hospitalization in three-quarters of our patients was a new-onset ischemic stroke, of which 62% had asymptomatic COVID-19, which is comparable to the data from the study by Shahjouei et al. [12]. Some studies have shown that in addition to traditional cerebrovascular risk factors, an associated risk factor in patients with COVID-19 includes hypercoagulability [13]. Our study showed a high prev-

alence of known risk factors in ischemic stroke patients. Only four patients did not have at least one of the previously known comorbidities and risk factors for ischemic stroke. It was established that coagulopathies are often associated with elevated D-dimer values. In our study, only 4 (6.89%) patients did not have elevated D-dimer values, while 17.24% of patients had elevated values > 10,000.

Based on the TOAST classification, the largest number of patients did not have a clearly defined mechanism for ischemic stroke at the end of hospitalization. In less than half of cases (43.1%), the cause of ischemic strokes was not established, but it was assumed to be related to thrombotic complications as part of COVID-19. A possible cause of the large prevalence of cryptogenic stroke may be associated with the difficult functioning of the health system during the epidemic, the short time of hospitalization, and the impossibility of conducting all necessary neurosonological and neuroimaging diagnostic methods. In our study, 56.89% of patients did not complete neuroserological and neuroimaging diagnostics, as well as cardiological examinations during hospitalization. Two retrospective observational studies from New York showed that the highest percentage were cryptogenic strokes [14, 15]. Small vessel disease was the etiological mechanism in 25.86% of our patients, while neuroimaging analysis indicated LACI in 35.20% of patients. These rates are supported by worldwide studies based on the general population unrelated to COVID-19, small vessel infarction in 21% - 44% and LACI 21 - 30% of patients [16, 17].

In previous studies of COVID-19-positive patients, the incidence of small vessel infarction was 12 - 31%, which coincides with our results [18]. In our study, the lowest incidence was due to large blood vessel disease (10.34%), which can be related to the highest percentage of cryptogenic strokes. The highest incidence of large vessel disease as an etiological mechanism of ischemic stroke was in patients with associated COVID-19, with lower rates of small vessel disease and LACI in most studies [19, 20].

The fact is that LACI and diseases of small blood vessels have smaller deficits and disability [21–23]. During the pandemic, patients with mild to moderate symptoms were less likely to come to medical centers and thus remained less recognized, which could be related to the lower incidence of small blood vessel disease in the examined patients [24].

In our study, 15.51% of patients were treated with intravenous thrombolytic therapy. These rates are similar to a multinational study including 174 infected patients (12.7% intravenous thrombolysis, 5.2% mechanical thrombectomy) [25]. Mechanical thrombectomy was not performed on our patients. A study from Birmingham, as well as a study from New York, showed a significantly worse outcome at the end of hospitalization (NIHSS score) in patients with ischemic stroke associated with COVID-19 than in the population without COVID-19 (NIHSS 19 [23] vs. 8 [12]) [15, 26].

According to a large multihospital retrospective observational study from the United States of America, COVID-19-positive patients had more severe strokes with a worse outcome, 33.3% of patients died [14]. Our study showed similar result and the number of fatal outcomes was 36.2%. Other studies, including colleagues from Italy and New York, have also reported worse outcomes in patients with ischemic stroke associated with COVID-19 [15, 25]. An increase in inflammatory markers was noted in the majority of patients (86.2%) in our study, as well as in other studies worldwide [13–15, 27].

Our study has several limitations, but they may raise ideas for further research. First, this is a retrospective observational study with a small sample size that limits multivariable statistical analyses. Second, not all patients had the same completeness of laboratory data, so some comparisons could not be made. Third, our study did not compare cohorts of ischemic stroke patients with and without COVID-19. Fourth, we do not have all the outcomes at the end of hospitalization, since some patients were sent for further inpatient rehabilitation treatment or transferred to another health facility. Fifth, we did not study hemorrhagic stroke as a subtype.

Conclusion

The coronavirus disease 2019 pandemic, as the consequence of the systemic severe acute respiratory syndrome coronavirus 2 infection, has left an indelible mark on the quality of health care in all parts of the world. Stroke, as the leading cause of disability, is a major burden on the healthcare systems. The large number of strokes and other thrombotic complications in symptomatic and asymptomatic patients with coronavirus disease 2019 is a good indicator that severe acute respiratory syndrome coronavirus 2 is not only the cause of respiratory infections but a systemic infection. In our study, a lower percentage of large blood vessel disease, as an etiological factor of ischemic stroke, was recorded compared to other studies worldwide. A high rate of asymptomatic coronavirus disease 2019 at the time of stroke was also observed. Coronavirus disease 2019 has also caused damage to patients suffering from other chronic non-communicable diseases in terms of the impossibility of regular controls and elective surgeries due to the burden on the health system and insufficient capacities of health institutions.

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