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Acute intracranial hemorrhage in 76 COVID-19 patients during the first and second pandemic waves

Akutno intrakranijalno krvarenje kod 76 bolesnika obolelih od COVID-19 u prvom i drugom talasu pandemije

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Abstract

Background/Aim. There is limited data on the frequency of intracranial hemorrhage (ICrH) in the first wave [beta variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)] and second wave (delta variant of SARS-CoV-2) coronavirus disease 2019 (COVID-19) pandemic. The aim of this study was to analyze the appearance of ICrH in COVID-19 patients (CP). **Methods.** Among 505 CP treated at the Special Hospital for Cerebrovascular Diseases "Sveti Sava" intermittently during the 2020–2021 period, ICrH was diagnosed in 76 (15.1%) patients. The available information from the medical records regarding clinical, demographic, as well as radiological data (multislice computed tomography examination of the endocranium) was collected and analyzed. **Results.** In the first wave, out of 308 CP, 63 (20.5%) were diagnosed with ICrH. In the second wave, out of 197 CP, ICrH was diagnosed in 13 (6.6%) patients, which was a statistically significant difference ($p < 0.002$). There was no statistically significant difference for the presence of hypertension ($p = 0.271$), diabetes mellitus ($p = 0.558$), and chronic obstructive pulmonary disease ($p = 0.794$) among CP with ICrH comparing the two waves of the pandemic. However, a statistically significant difference was proven in the frequency of patients with atrial fibrillation and anticoagulant drug therapy ($p = 0.021$ each). There was no statistically significant difference in the frequency of patients with fever ($p = 0.637$), fatigue ($p = 0.587$), hemiparesis ($p = 0.831$), respiratory symptoms ($p = 0.289$), and loss of consciousness ($p = 0.247$). D-dimer values in the second pandemic wave were statistically significantly lower ($p = 0.003$). The combination of ischemic stroke and ICrH was six times more common in the second wave ($p = 0.003$). However, cerebral parenchymal hemorrhage was two times less frequent ($p = 0.001$) in the second wave but with statistically higher frequencies of multifocal (23.1%) and diffuse type (36.4%) of ICrH ($p = 0.007$). Combined hemorrhages, as well as subarachnoid and subdural subtypes, were more common in the second wave (23.1% each). Fatal outcomes occurred in 38.1% of patients in the first wave compared to 69.2% in the second wave ($p = 0.039$). **Conclusion.** In the first pandemic wave of COVID-19, ICrH in CP was significantly more frequent and D-dimer was singled out in laboratory analyses, the values of which were statistically significantly higher in comparison with second wave. In the second wave of COVID-19, parenchymal ICrH was less frequent and multifocal and diffuse ICrH were more common in CP with ICrH. The mortality rate was very high in the second wave.

Key words:
covid-19; fibrin fragment d; intracranial hemorrhage; mortality; risk factors; serbia; tomography, x-ray computed.

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Apstrakt

Uvod/Cilj. Nedovoljno je podataka o učestalosti intrakranijalnih krvarenja (IKK) u prvom talasu (beta varijanta virusa *severe acute respiratory syndrome coronavirus 2* – SARS-CoV-2) i drugom talasu (delta varijanta virusa SARS-CoV-2) pandemije izazvane koronavirusom 2019 (*coronavirus disease 2019* - COVID-19). Cilj rada bio je da se analizira pojava IKK kod obolelih od COVID-19 (CB). **Metode.** Od 505 CB koji su lečeni u Specijalnoj bolnici za cerebrovaskularne bolesti „Sveti Sava" tokom 2020–2021, IKK je dijagnostikovana kod 76 (15,1%) bolesnika. Prikupljeni su i analizirani dostupni podaci iz medicinske dokumentacije: klinički, demografski i radiološki (multislajsna kompjuterizovana tomografija endokranijuma). **Rezultati.** U prvom talasu je od 308 CB bilo njih 63 (20,5%) sa IKK. U drugom talasu je od 197 CB kod 13 (6,6%) bolesnika dijagnostikovana IKK, što je bila statistički značajna razlika (p < 0,002). Poređenjem dva talasa pandemije utvrđeno je da nije bilo statistički značajne razlike u postojanju hipertenzije (p = 0,271), dijabetesa melitusa (p = 0,558) i hronične opstruktivne bolesti pluća (p = 0,794) kod CB sa IKK. Međutim, pokazana je statistički značajna razlika u učestalosti bolesnika sa atrijalnom fibrilacijom i bolesnika koji su lečeni antikoagulantnim lekovima (p = 0,021 za obe učestalosti). Nije bilo statistički značajne razlike u učestalosti bolesnika sa temperaturom (p = 0,637), umorom (p = 0,587), neurološkim deficitom (p = 0,831), respiratornim simptomima (p = 0,289) i gubitkom svesti (p = 0,247). Vrednosti D-dimera u drugom talasu pandemije bile su statistički značajno niže (p = 0,003). Kombinacija ishemijskog moždanog udara i IKK bila je šest puta češća u drugom talasu (p = 0,003). Međutim, cerebralno parenhimsko krvarenje bilo je dva puta ređe (p = 0,001) u drugom talasu, ali sa statistički višom učestalošću multifokalnog (23,1%) i difuznog (36,4%) IKK (p = 0,007). Kombinovane hemoragije, kao i podtipovi subarahnoidna i subduralna hemoragija, bili su češći u drugom talasu (23,1% svaki podtip). U prvom talasu, bilo je 38,1% fatalnih ishoda, u odnosu na 69,2% tokom drugog talasa pandemije (p = 0,039). **Zaključak.** U prvom pandemijskom talasu COVID-19, u poređenju sa drugim talasom, IKK su bile znatno češće kod CB, a u laboratorijskim analizama se izdvajao D-dimer, čije su vrednosti bile statistički značajno više. U drugom talasu COVID-19, kod CB sa IKK, parenhimalna IKK je bila manje učestala a multifokalne i difuzne IKK bile su češće. Stopa mortaliteta bila je veoma visoka u drugom talasu pandemije.

Ključne reči:
covid-19; d-dimer; krvarenje, intrakranijalno; mortalitet; faktori rizika; srbija; tomografija, kompjuterizovana, rendgenska.

Introduction

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), manifesting as coronavirus disease 2019 (COVID-19), often causes rapidly progressive interstitial pneumonia [1]. The virus exerts its pathogenic effect mainly by binding its spike glycoprotein to the angiotensin-converting enzyme II (ACE 2) surface receptors to enter target host cells [1–3]. Since these receptors are distributed throughout the body, COVID-19 is, in fact, a multiorgan disease.

The central nervous system can also be affected due to the virus neurotropism and neuroinvasive capability based, among others, on the presence of the ACE 2 receptors on cerebrovascular endothelial cells, arterial smooth muscle cells, neurons, and glial cells [1–7]. In this case, there is a leakage of the blood-brain barrier, i.e., an increase of vascular permeability and extravasation of the blood cells and plasma [7]. Those cerebral vessel abnormalities can lead to parenchymal hemorrhage (PH), subarachnoid hemorrhage (SAH), epidural, subdural, intraventricular hemorrhage, or a combination of these types. Consequently, intracranial hemorrhage (ICrH) can cause severe morbidity and mortality [1, 6–11].

The hemorrhagic stroke was mostly diagnosed in less than 1% of the COVID-19 patients [6, 12–14]. Although infrequent, ICrH is clinically very important due to a high morbidity and mortality rate [11]. In addition, there are less than 40 reports [7], with a corresponding statistical analysis, regarding ICrH in COVID-19 patients, and an even smaller number of articles about ICrH in various epidemic waves [3, 4, 9, 14–19].

Accordingly, the aim of this study was to determine the frequency and characteristics of ICrHs in COVID-19 patients in the first and second epidemic waves.

Methods

The study was designed as a single-center cross-sectional study. Namely, the research included patients from two time periods who were hospitalized at the Special Hospital for Cerebrovascular Diseases "Sveti Sava" due to neurological symptoms and COVID-19 infection. The research was conducted according to the valid permission received by the Ethics Committee of the Special Hospital for Cerebrovascular Diseases "Sveti Sava" (No. 03/3116-3, from June 30, 2021). Written consents were provided by all patients or their relatives.

Some other centers transferred their patients with cerebrovascular diseases to our institution. All these patients tested positive for SARS-CoV-2 following a nasopharyngeal swab examination by reverse transcription polymerase chain reaction, and most of them had positive pulmonary signs in radiograms or computerized tomography (CT) scans.

Patient enrollment and selection

The first wave (wave 1) of epidemics in our country occurred from November 2020 to February 2021 (dominant beta variant SARS-Cov-2), while the second wave (wave 2) happened from August until December 2021 (dominant delta variant SARS-Cov-2). In total, 505 patients were hospitalized in our COVID care center. Among them, 76 patients with ICrH were enrolled. The following spontaneous hemorrhages were noted: PH, SAH, subdural hematoma (SDH), and intraventricular hemorrhage (IVH), as well as their various combinations.

Patient examination

Demographic data (age, gender), clinical data (risk factors: hypertension, diabetes mellitus, chronic obstructive pulmonary diseases), disease symptoms (fever, headache, fatigue, hemiparesis, respiratory symptoms, atrial fibrillation, anticoagulant therapy, consciousness disorders), and laboratory analyses [leukocytes, lymphocytes, C-reactive protein (CRP), D-dimer] were analyzed. Clinical severity was quantified using the National Institutes of Health Stroke Scale (NIHSS) on admission and at discharge. The patient's functional status was assessed by applying a modified Rankin scale.

Computerized tomography imaging

First, each patient underwent a radiography or CT chest examination to confirm the clinical COVID-19 diagnosis. For stroke imaging, we have used a 160-slice CT machine, Toshiba Aquiline Prime, by applying field of view (FOV) 240 and a slice thickness of 2.0 mm. The type, number, and location of the hemorrhages in the multislice CT scans were determined in each patient of both waves.

Statistical analysis

Statistical analyses were performed using the statistical software SPSS v22.0. Statistical tests are 2-sided, and $p < 0.05$ was considered statistically significant. Continuous variables are shown using mean (standard deviation) and median (interquartile range) and compared by applying the nonparametric Mann-Whitney *U* test for all non-normally distributed data. Categorical variables were reported as frequency rates and percentages and compared by Chi-square (χ^2) tests.

Results

Among the total of 505 patients (308 were hospitalized in wave 1, and 197 in wave 2), 76 had ICrH (15.1%). In total, patients were aged 72.9 ± 7.8 (53–89) years, with a median of 73 years. The average interval between the onset of symptoms of COVID-19 infection and diagnosis of ICrH was a median of three days: patients developed ICrH 0–45 days after infection.

Patients in the first wave

Out of the 308 COVID-19 patients in the first wave, 63 (20.5%) experienced ICrH, and all of them were nonvaccinated since the national vaccination program was at its beginning in the general population**.** They were 73.1 ± 8.1 (53–89) years old, with a median of 73 years, without gender differences in frequency. Hypertension (93.7%), diabetes (30.2%), and chronic obstructive pulmonary disease (12.7%) were among the most frequent risk factors. Atrial fibrillation was present in 19.0% of patients, and all of them were taking anticoagulant treatment. Fever (81.0%), fatigue (88.9%), and hemiparesis (85.7%) were the most frequent symptoms and signs, in addition to respiratory disorders (58.7%) and consciousness alterations (57.1%). There were no statistical differences in the mentioned parameters between patients in different COVID-19 waves (Table 1).

Table 1

Clinical and demographic characteristics of the coronavirus disease 2019 patients with intracranial hemorrhage in the first (n = 308) and second (n = 197) waves

Patient characteristics	First wave (n = 308)	Second wave (n = 197)	*p*-value
Patients with ICrH	63 (20.4)	13 (6.6)	< **0.001**
Age, years	73.1 ± 8.1	71.7 ± 6.4	0.551
Male/female, %	50.8/49.2	69.2/30.8	0.225
Hypertension	59 (93.7)	11 (84.6)	0.271
Diabetes mellitus	19 (30.2)	5 (38.5)	0.558
COPD	8 (12.7)	2 (15.4)	0.794
Fever	51 (81.0)	9 (75.0)	0.637
Headache	35 (55.6)	4 (33.3)	0.158
Fatigue	56 (88.9)	10 (83.3)	0.587
Hemiparesis	54 (85.7)	10 (76.9)	0.831
Respiratory symptoms	37 (58.7)	9 (75.0)	0.289
Atrial fibrillation	12 (19.0)	6 (50.0)	0.021
Anticoagulant therapy	12 (19.0)	6 (50.0)	0.021
Consciousness disorder	36 (57.1)	9 (75.0)	0.247
Leukocytes × 10^9/L (RR 3.4–9.7)	11.7 ± 9.1	11.1 ± 5.1	0.854
Lymphocytes × 10^9/L (RR 1.2–3.4)	1.4 ± 0.9	1 ± 0.4	0.242
CRP, mg/L (RR 0.0–5.0)	41.1 ± 67.2 (13.4)	71.6 ± 69.2 (67.4)	0.155
D-dimer, ng/mL (RR 0–570)	1,646.9 ± 269.0	730.3 ± 125.8	**0.003**

Table 1 (continued)

Patient characteristics	First wave (n = 308)	Second wave (n = 197)	*p*-value
Isolated ICrH	95.9	69.2	**0.003**
ICrH + ischemic stroke	4.8	30.8	
NIHSS score on admission	14.8 ± 9.2	14.8 ± 8.4	0.778
NIHSS score at discharge	23.3 ± 15.8	31.7 ± 16.5	0.086
Mortality rate, %	38.1	69.2	0.039

ICrH – intracranial hemorrhage; COPD – chronic obstructive pulmonary disease; RR – reference range; CRP – C-reactive protein; NIHSS – National Institute of Health Stroke Scale.
Values are given as numbers (percentages), mean ± standard deviation, or mean ± standard deviation (median) unless otherwise indicated.

The CRP values were high (49.9 ± 12.2 mg/L), as well as D-dimer (1,646.9 ± 269.0 ng/L). Mainly spontaneous, pure ICrHs were registered, while the association of ICrH and ischemic stroke (IS) was very rare (4.8%, $p < 0.001$) (Table 1).

PH was more frequent (77.8%) among the ICrH findings. It usually was of a lobar, subcortical location (46.0%), with various radiologic signs: a swirl sign, a satellite bleeding, or a blend sign (Figure 1). The isolated lobar PH can occur in any of the cerebral regions, but the posterior lobar was the most frequent one (40.3%), while the corpus callosum hemorrhage was rare (1.8%) (Figure 2). Occasionally, multifocal (9.5%) or both lobar and multifocal PH appeared (25.5%, $p < 0.001$). A diffuse multifocal type involving several hemispheric lobes was less frequent (8.8%) (Figure 3).

Deep intrahemispheric PH type occurred in 21.1%, and it mainly involved the basal ganglia or the thalamus (Figure 4). The brain stem and cerebellum were also rarely affected (the latter in 5.3%). In any case, the supratentorial location was more often present (88.2%) than the infratentorial one (11.8%) (Figure 5).

Other ICrH subtypes, e.g., SDH and SAH, were less frequent, i.e., only 1.6% and 11.1%, respectively. A former hemorrhage was present either in the infratentorial compartment or the supratentorial space, while SAH always had a supratentorial position (Figure 6). The IVH was associated with other subtypes of the hemorrhage, e.g., with SAH, PH, and SDH (Figures 6 and 7).

Finally, the NIHSS score of the patients was 23.3 on average at discharge, and the mortality rate reached 38.1% (Table 1).

Fig. 1 – Various appearances of parenchymal hemorrhages (asterisk) in axial computed tomography scans: with a blend sign (A) (red arrowhead), a satellite bleeding (B) (red arrowhead), and swirl sign (C) (red arrow).

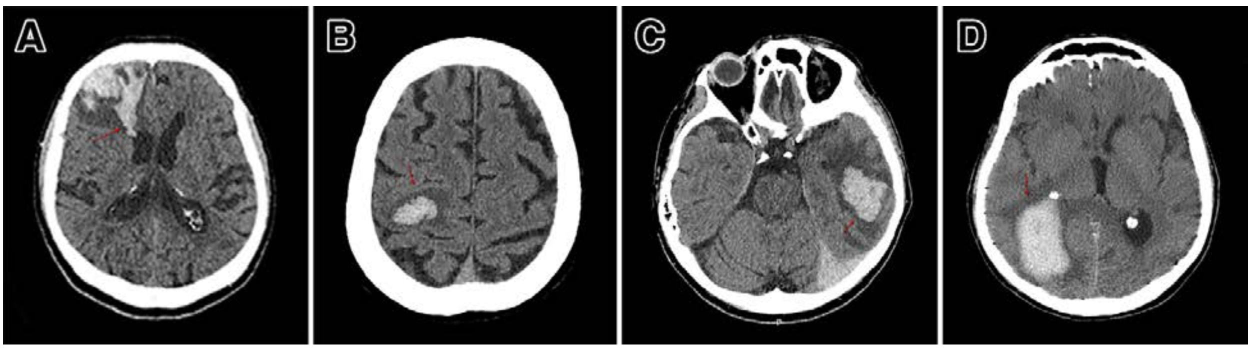

Fig. 2 – Lobar types of intracerebral hemorrhages (red arrows) with various locations in axial computed tomography scans: frontal (A), parietal (B), temporal (C), and temporooccipital (D).

Fig. 3 – Multifocal hemorrhages, the largest being located bilaterally in the frontal lobes (asterisks). A right subdural hematoma (black arrows) was also present, and a left frontoparietal subarachnoid hemorrhage (red arrows) in an axial computed tomography scan.

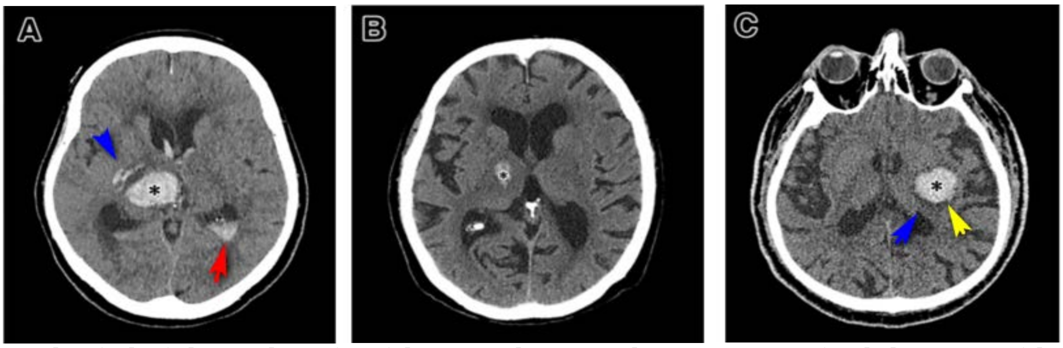

Fig. 4 – Deep hemispheric hemorrhages in axial computed tomography scans. Note entire thalamus (asterisk) affecting the posterior limb of the internal capsule (blue arrowhead) with intraventricular hemorrhage (red arrow) (A); hemorrhage involving the anterior part of the thalamus – asterisk (B); basal ganglia hemorrhage (asterisk) affecting the posterior limb of the internal capsule (blue arrowhead) and the posterior part of the left putamen (yellow arrowhead) (C).

Fig. 5 – A brain stem hemorrhage in the pons (red arrowhead) (A) and midbrain (asterisk) (B), as an extension of a right thalamic hemorrhage (asterisk) (C) in axial computed tomography scans.

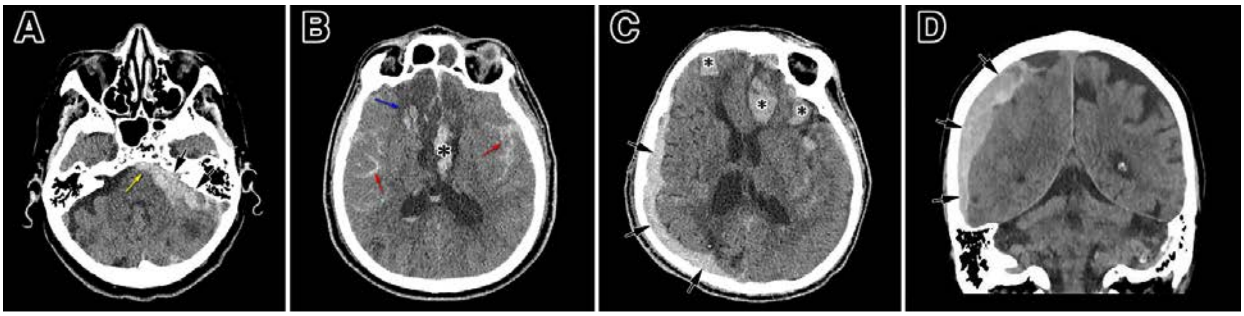

Fig. 6 – Infratentorial subarachnoid hemorrhage (SAH) in the basal cisterns (yellow arrow) and subdural hemorrhage on the left (black arrows) (A) in an axial computed tomography scan. Note a supratentorial SAH (red arrows) associated with a frontal parenchymal hemorrhage (PH) (blue arrow) and the intraventricular hemorrhage (IVH) (asterisk) (B), as well as a subdural hematoma (SDH) (black arrows) in the axial plane (C), and a right SDH (arrows) in the coronal plane (D), along with multifocal PH (D).

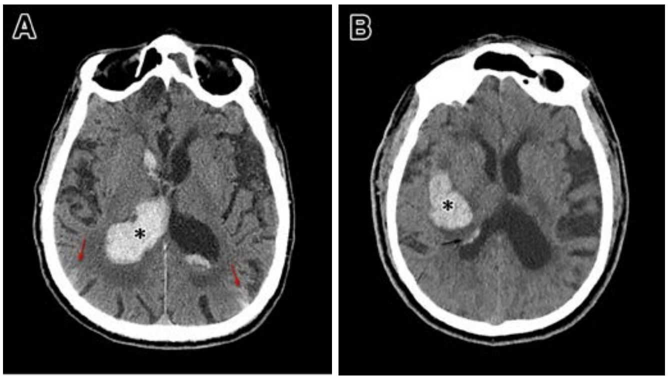

Fig. 7 – Bilateral intraventricular hemorrhage (asterisk) and subarachnoid hemorrhage (red arrows) (A), as well as a small intraventricular hemorrhage (black arrow) associated with a right parenchymal hemorrhage (asterisk) (B) in axial computed tomography scans.

Patients in the second wave

A smaller number of this group of patients with ICrH was revealed, i.e., 13 cases of the total 197 (6.6%), which is significantly less frequent than in wave 1 ($p < 0.001$).

They were aged 71.7 ± 6.4 (57–82) years, with a median of 70 years, i.e., without statistically significant difference to the patient age in the first wave ($p = 0.551$). Males predominated without a statistically significant difference to the patient gender in the first wave ($p = 0.225$). The risk factor frequencies were somewhat lower for hypertension (84.6%, $p = 0.271$) but higher for diabetes (38.5%, $p = 0.558$) in comparison with the first wave. Symptoms like fever (75.0%), headache (33.3%), fatigue (83.3%), and hemiparesis (76.9%) were less expressed, except the respiratory ($p = 0.289$) and the consciousness disorders ($p = 0.247$) which were more frequent (75.0% each) in the second wave. Atrial fibrillation and anticoagulant therapy were present in 50.0% patients each. However, the hemiparesis incidence was somewhat lower (76.9%) in wave 2 ($p = 0.831$), although without a statistical difference (Table 1).

D-dimer values were also smaller (mean 730 ng/L, $p = 0.003$), with a statistical difference, but CRP values were higher than in the first wave (mean 71.6 mg/L, $p = 0.155$) without a statistical difference. Lymphocytopenia was registered in these patients. The association of ICrH and IS was more frequent in wave 2, i.e., 30.8%, compared to only 4.8% in wave 1, and this difference was statistically significant ($p = 0.003$) (Table 1).

As for hemorrhage subtypes, PH was more than 2-fold less frequent in wave 2 ($p = 0.001$), as was a lobar PH. However, multifocal hemorrhages (23.1%) and their combination with isolated lobar ones (46.1%) were more frequent ($p = 0.007$), as was a diffuse type (36.4% compared to only 8.8% in wave 1). A posterior lobar PH was much more rare (18.2%) than in the first wave (40.3%), but cerebellar hemorrhages appeared more often (18.2% compared to 5.3%).

A *corpus callosum* hemorrhage was not present in wave 2. On the other hand, there was a much higher incidence of SAH and SDH (23.1% each) and of combined bleeding (23.1% compared to 9.5%, $p = 0.112$).

The NIHSS mean score was higher at discharge than in the first wave (mean 31.7, compared to 23.3) ($p = 0.086$). The mortality rate was significantly higher in wave 2 (69.2%, $p = 0.039$) (Table 1).

Discussion

In our hospital, ICrH occurred in 76 (15.1%) patients. This percentage was high because the hospital became a COVID center for patients with cerebrovascular disorders for Belgrade and the wider area. It was our specificity, which is difficult to compare with other centers.

The authors of some systematic reviews found acute stroke in 1.4% on average of COVID-19 patients, with a usual range of 0.5–8.1% [6, 7, 9, 16]. Acute stroke incidence is higher within certain ethnic and racial groups [10–13].

The ICrH incidence in other groups of COVID-19 patients usually ranged from 0.1% to 3.3% (mean 0.6–0.7%) [6, 7, 10–12]. If compared to the total number of stroke patients with COVID-19, the ICrH frequency can reach 30.0%. Different SARS-CoV-2 strains and variants causing infection most likely influenced the event incidence [3, 18, 19].

Combinations of ICrH and IS, or cerebral venous thrombosis, were reported in some patients [12]. PH was associated with IS in 1.0–39.2% [12], which is, in general, more frequent than in our patients from the first wave (4.8%), but our result from the second wave (30.8%) is within this range.

Of all the COVID-19 ICrH subtypes, PH occurred more often compared to SAH, SDH, epidural hematoma (EDH), and IVH, which were much less frequent [11, 17–23]. Several authors reported only PH in their studies [6, 9, 24–26]. A pure PH incidence among the ICrH patients ranged from 45.8% to 92.6% (mean 65.9%) [10, 11, 20, 21, 23, 27–31], which is in agreement with the incidence in wave 1 (77.8%), but not regarding wave 2 of our patients (30.1%).

Some PHs were associated with other hemorrhagic subtypes. We noted certain associations of PH with SAH and SDH or IVH, which is somewhat more frequent than in certain reports [12, 27].

There were drastic differences regarding a pure SAH incidence, observed in 5.8–71.0% (mean 22.0%) of the ICrH COVID-19 cases [11–13, 20, 21, 23, 29–32]. Our study showed almost the same average frequency in wave 2. SDH was mentioned in 10.9–48.6% (mean 24.4%) of ICrHs [7, 27], similar to our patients in wave 2.

EDH was reported only by several authors, who mentioned it as being about 1% of all ICrHs [7], [27]. This hemorrhage subtype was not registered in our study.

Intracranial hemorrhage in COVID-19 patients in the first wave

In the first wave, hemorrhage incidence commonly was less than 1.0% of all COVID-19 patients, i.e., between 0.1% and 0.9%, and rarely up to 2.0% [10, 26, 29, 32–35]. Hemorrhages were much more frequent in our patients (20.5%) for the mentioned reason.

Patients with ICrH usually had severe COVID-19, including pneumonia [6, 10, 36, 37]. According to certain reports, COVID-19 patients with stroke were younger on average (mean 52.6–65.0 years) than those only with stroke [6, 36, 38, 39], while some others reported the opposite results [12]. The mean age of our patients was 73.1 years in the first wave. Stroke was the main reason for hospital admission in 37.7% of COVID-19 patients, while 77.0% experienced ICrH after COVID-19 symptoms occurrence [6].

Typical vascular risk factors and comorbid diseases were present in the ICrH patients, especially hypertension (52.6–81.8%), diabetes mellitus (20.5–49.4%), dyslipidemia (16.0–50.6%), obesity (11.0%), smoking (6.5–20.8%), alcohol abuse (8.4%), previous cerebrovascular events (4.3–21.8%, including PH in 18.2% on average), heart disease (20.0–31.1%), chronic renal failure (10.3–19.1%) or acute renal failure (48.7%), liver disorder (15.8%), pulmonary disease (8.3–18.7%), malignancy (17.9%), and rarely amyloid angiopathy, epilepsy, dementia, hypothyroidism, rheumatoid arthritis, and acquired immunodeficiency syndrome [10, 12, 29, 36, 37, 39]. We noted hypertension as high as 93.7%, diabetes mellitus at 30.2%, and atrial fibrillation at 19.0% within our group during wave 1.

In addition, there are also certain other risk and predisposing factors, such as serious COVID-19 illness [16], with an NIHSS score of 11–13 on average, compared to a mean value of 14.8 in our patients. The Glasgow Coma Scale mostly ranged from 8–15, and the Rankin score was 3–6 [28, 39]. According to the literature, other important factors are also endotracheal intubation, prolonged mechanical ventilation (in 70.0–77.0%), extracorporeal membrane oxygenation, immobility, prolonged general hypoxemia, coagulopathy, renin-angiotensin axis disorder, metabolic and enzyme disorder, septic shock, post-viral bacterial superinfection, and multiple organ damage [39–41].

Furthermore, there is occasionally an important role of immune overexpression and hyperinflammation (high CRP levels, cytokine storm, proteases activation), enhanced catecholamine secretion due to stress, changes of blood pressure, loss of brain autoregulation, and anticoagulation treatment (up to 71.0%) [4, 6, 10–12, 27, 30, 37, 42]. The level of D-dimer was commonly higher in the PH patients (mean 3,387 ng/L) [16], but almost 2-fold lower in our study (1,647 ng/L).

ICrH was usually diagnosed in 2–25 days following admission [29]. PH alone may occur on admission or commonly during the first 9 to 14 days on average following the onset of COVID-19 [37]. In general, it may develop 1–32 days after infection [11, 28, 36], and in our study, patients developed ICrH 0–45 days after infection.

The most common symptoms in ICrH patients were impairment or loss of consciousness (32.1%), aphasia (42.3%), motor deficit (9.0–43.5%), severe headache (15.4%), syncope (10.3%), seizures (9.0%), and a changed mental status (16.7%), including signs of encephalitis and meningitis in some cases [4, 31, 39]. In our patients in the first wave, consciousness disorder was more frequent (57.1%) than in other reports, as were hemiparesis (85.7%) and headache (55.6%).

The mortality rate was usually 33.0–59.0% [10, 11, 21, 36]. Our results are within this range (38.1%). According to some reports, the male gender (up to 73.0%), old age (over 65 years on average), smoking, mechanical ventilation, ischemic heart disease, and lower leukocyte and platelet count were predictors of a death outcome [16, 23]. Gender frequencies were almost equal in our patients in the first wave.

PH was the most frequent event compared to other subtypes of ICrH since it occurred in almost 77.8% of our ICrH patients. There were most often single PHs (44.1–67.0%, and 46.0% in our patients) and less frequently multifocal ones (32.0–36.0%, but somewhat lower in our cases) [6, 10, 29].

The isolated PHs were most frequent (44.1–93.5%), particularly in the cerebral white matter (lobar position). A location in the deep hemispheric region occurred rarely (4.9–6.6%), sometimes bilaterally [43], but it was seen in as much as 21.1% of our patients. An atypical callosal hemorrhage was rare [15]. PH was also infrequent in the infratentorial compartment (9.1%), i.e., in the brain stem or the cerebellum (1.1%) [10, 11, 29, 36, 44]. We noted a cerebellar hemorrhage in 5.3% of patients.

The presence of both lobar and deep hematomas was rare in the mentioned reports (4.0–6.0%) [22, 29, 39, 44]. Some of them can enter the ventricular system [22, 36]. Hematomas had an average volume of 45.9 cm^3 [36].

In our study, SAH occurred in 11.1% of patients. In the literature, the presence of SAH is very variable.

Some authors presented only SAH, which is in general less frequent than PH (0.1–0.7%, mean 0.2%) in COVID-19 patients [13]. It was in the range of 5.8–71.0% (mean 22.0%) among the ICrH patients with COVID-19. Various numbers of the SAH individuals were presented in different reports [13, 14, 17, 45–47].

These patients were aged 35 to 54 years (mean 47.0) [48]. The risk and predisposing factors, as well as comorbidity and complications, were similar to patients with PH, but hypertension predominated (68.6%). A previous SAH was registered in 14.0% of the patients [13]. There was a rare combination of SAH with IVH or IS [12], but more often, including PH [11–13, 20, 23, 28–31].

SAH appeared nine days on average following COVID-19 onset. The Rankin scale usually showed 4 points. The mortality rate was 31.4%, which is much higher than in non-COVID-19 patients with SAH (12.2%) [13].

SDH was noticed in 1.6% of patients, with low frequencies compared to other studies [20, 27].

In the literature, the incidence of the non-traumatic SDH was 0.2% on average (range 0.1–0.4%) in COVID-19 patients and 10.9–48.6% (mean 24.4%) within the ICrH group [20, 27, 29]. A combination of SDH, SAH, and PH was rarely reported.

EDH was not observed in our patients. EDH is formed between the *dura mater* and the inner table of the skull. It is extremely rare in COVID-19 patients, i.e., less than 0.1% on average in this group and less than 2.0% within the ICrH groups [27].

An isolated IVH was not seen in our patients, only in combinations with other subtypes. IVH is commonly secondary, as a consequence of the blood entering the ventricular system from PH or rarely from SAH [23, 29]. It accounts for only 0.1–1.4% of COVID-19 patients and less than 2.8% within the ICrH groups [10, 29]. Blood in the ventricles can cause obstruction of the ventricular system and the consecutive hydrocephalus [36].

Intracranial hemorrhage in COVID-19 patients in the second wave

There is limited literature regarding acute stroke in wave 2 compared to the first one [32–35, 45, 46]. In general, stroke admission was 18.4% lower in the second wave, and the acute stroke decline was usually 1.8–2.5%, and rarely up to 8.0% in some reports [32, 35, 45, 46]. As for ICrH in certain countries, a 3.9% decline was observed, but a slight increase was observed in some others [33]. Hemorrhages usually varied from 0.1% to 3.3% [33]. The frequency of ICrH in our patients is much higher (6.6%) for the mentioned reason.

As for ICrH subtypes in wave 2, as much as a 47.0% decline was noted in our study regarding the PH incidence, including its lobar type (23.1% compared to 46.0%). However, there was an increase in multifocal (23.1% vs. 9.5%), combined multifocal and lobar (46.1% vs. 25.5%), diffuse (36.4% vs. 8.8%), and cerebellar PH (18.2% vs. 5.3%), as well as an absence of callosal hemorrhages.

Some authors reported only patients with SAH in their articles [13, 14, 47]. Some others noted a 4.6–8.0% decline of SAH in the second wave [46]. However, SAH in our patients was observed 2-fold more frequently in wave 2 than in wave 1.

SDH was slightly more often present in the second wave (0.9%) [45] but less frequent in some other reports [23, 46]. In our patients, SDH incidence was 23.1% in wave 2, compared to only 1.6% in wave 1. EDH and isolated IVH was not present in our patients. Combinations of various ICrH subtypes were more frequent in the second wave (23.1%) than in the first one (9.5%).

The mean age of patients in the second wave was two years lower than in the first wave, or five years higher in some reports [8], but over 70 years on average in our patients. The type and frequency of the risk factors were reported to be similar in both waves [32] but not in our patients. As regards the symptoms and laboratory findings in wave 2, hypertension, fever, headache, hemiparesis, and the D-dimer value were lower. On the other hand, diabetes, respiratory symptoms, anticoagulant therapy, consciousness disorder, and CRP values were more frequent or higher. Our results are similar to those in another report [18].

According to some authors, less stroke severity was observed in the second wave, i.e., 1–13 NIHSS score compared to 2–16 in the first wave [32]. However, the mean score was 14.8 on admission but 31.7 at discharge in our study. Mortality was also higher in the second wave, e.g., 15.9%, compared to 9.9% in the first wave [49]. According to some authors, there was a 31.0% increased risk of mortality in the second wave [33]. The mortality rate in our study was much higher (69.2%) in wave 2 than in wave 1 (38.1%) and even higher in another report [7].

First of all, the different values of some parameters in wave 2 can be explained by vaccination and better medical treatment [2, 46, 50], but probably by some ethnic characteristics as well [12, 13]. Some others are mainly based on the biological features of new viral lineages and variants, especially regarding the evasion of the previous specific antiviral immunity and increased viral pathogenicity [7, 18, 33].

Conclusion

Intracranial hemorrhage in COVID-19 patients was more frequent in wave 1 with statistical significance. COVID-19 patients with intracranial hemorrhage in wave 2 showed a lower parenchymal hemorrhage incidence but with a higher multifocal and diffuse type, more frequent subarachnoid hemorrhage, subdural hematoma, and cerebellar parenchymal hemorrhage, but an absence of a corpus callosum hemorrhage. Hypertension, fever, and headache were less frequent, while diabetes, respiratory and consciousness disorders, anticoagulant therapy, and D-dimer values were less lower in wave 2. The association of intracranial hemorrhage with ischemic stroke was more often present, as well as combined hemorrhages in wave 2. NIHSS score and the mortality rate were very high in this wave.

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