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The Effect of Intracranial Hemorrhage and SARS-CoV-2 Association on Mortality

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Abstract

Objective: SARS-CoV-2 is a pandemic that still causes high mortality and morbidity in our world. We observed and wanted to examine the high mortality and morbidity rates of SARS-CoV-2 due to lung and other organ involvement, and even more mortality in the presence of accompanying intracranial events.

Methods: This study is a single-center retrospective cohort study. Patients who applied to Afyonkarahisar State Hospital between June 2020 and June 2021, who were evaluated as SARS-CoV-2 in their current state and who were found to have an intracranial hemorrhage, were evaluated.

Results: Of the 13 patients in our cohort, 7 (54%) had comorbidities such as hypertension, diabetes mellitus, and chronic renal failure. The intraparenchymal hematoma was observed in 5 patients, chronic subdural hematoma in 2 patients, acute subdural hematoma in 1 patient, and subarachnoid hemorrhage in 4 patients. Decompressive craniectomy and hematoma evacuation were performed on 5 patients in our study. Nine of the patients included in our study died as a result of their follow-up and treatment in the intensive care unit, and the mortality rate was 69%.

Conclusion: Intracranial hemorrhages may occur rarely in patients with SARS-CoV-2 infection, and it is observed that intracerebral hemorrhages, which are already quite mortal, are more mortal. In addition, COVID-19 infection is thought to be a risk factor for intracranial hemorrhages.

Keywords: Intracranial Hemorrhages, Anticoagulants, Covid-19, Mortality

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INTRODUCTION

"Severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) is a pandemic that still causes high mortality and morbidity in our world. Cases of intracranial events are seen in the literature in patients who are active or have had SARS-CoV-2 active recently. In a study conducted in Wuhan, the incidence of neurological symptoms in patients with SARS-CoV-2 infection was 36.4%, and the rate of acute cerebrovascular disease was 5.7% (1). Although many factors are blamed for this, it is argued that SARS-CoV-2 causes endothelial cell damage and endotellitis and may cause thrombosis in the venous and arterial system with the effect of platelet activation and stasis in blood flow (2,3). At the same time, there is an opinion in the literature that it predisposes to bleeding due to depletion of coagulation factors (4,5). In addition, anticoagulant treatment regimens are used to prevent thrombosis in the current guideline of SARS-CoV-2 treatment, and it is known that anticoagulant treatments increase intracranial bleeding. And it is argued that this may be a predisposing factor for intracranial hematomas in patients with SARS-CoV-2 (6). Intracerebral hematomas constitute 10-15% of all ischemic brain diseases, and 1-year mortality rates range from 51% to 65% (7). In the study of Cheruiyot et al. (8), the mortality rate of SARS-CoV-2 and the intracerebral hematoma was found to be 48.6%. We observed and wanted to examine the high mortality and morbidity rates of SARS-CoV-2 due to lung and other organ involvement, with a more mortal course in the presence of accompanying intracranial events.

METHODS

This study is a single-center retrospective cohort study. Ethics committee approval was obtained from Afyonkarahisar Health Sciences University on 06.08.2021 with the decision numbered 427.

Patient Population

In our study, between June 2020 and June 2021, intracranial hemorrhage was detected in the application to Afyonkarahisar State Hospital, followed up and treated in our hospital, and evaluated as SARS-CoV-2 in its current state (with positive nasopharyngeal SARS-CoV-2 polymerase chain reaction (PCR) test and/or patients with typical radiological thoracic computed tomography (CT) findings) or patients who were admitted to our hospital again within 1 month after discharge were included. Traumatic intracranial hemorrhages and patients under 18 years of age were not included in the study.

Data Collected

The patient data used were obtained from Afyonkarahisar State Hospital's electronic health records and patient files. Demographic characteristics of the patients (age, gender), comorbidities and related anticoagulant drug use, complaint at admission, SARS-CoV-2 diagnosis time, anticoagulant drug use after SARS-CoV-2 diagnosis, intracranial bleeding time (if detected at the time of application It was evaluated as "initial apply", it was evaluated as "late apply" if it was detected after re-admission within 1 month after SARS-CoV-2 treatment), anticoagulant drug use after intracranial hemorrhage, an antiviral medication used after SARS-CoV-2 diagnosis, intracranial treatment for

bleeding (surgery/follow-up) and mortality were evaluated.

Clinical Evaluation

SARS-CoV-2 treatment was arranged according to the general conditions, respiratory parameters, vital signs, and thorax CT evaluations of the patients, and the need for mechanical ventilator/non-invasive mechanical ventilation was evaluated. In terms of cranial, Surgery/follow-up decision was made according to brain CT/MRI evaluations. In patients with intracranial hematoma, the surgical intervention was decided considering the location of the hematoma, the amount of hematoma, the midline shift effect, herniation findings, and the general condition of the patient. Patients who did not undergo surgical treatment were followed up closely in our intensive care unit clinically, neurologically, and radiologically.

Radiological and Laboratory Evaluation

The patients included in our study were patients who applied to our emergency department with neurological and respiratory symptoms and had intracranial hemorrhage findings according to brain computed tomography (CT) or brain magnetic resonance (MR) imaging. Nasopharyngeal SARS-CoV-2 PCR test and thoracic CT are taken routinely from all patients who are planned to be hospitalized in the intensive care unit in our hospital. Thoracic CT scans were evaluated using the "Radiological Society of North America (RSNA) Chest CT Classification System" and the "COVID-19 Reporting and Data System (CO-RADS)" (9,10). These classifications were used both for diagnosis and for predicting the severity of the infection. Intracranial hemorrhage findings were classified as intraparenchymal, subarachnoid, and subdural hemorrhage according to the type of hemorrhage. In laboratory findings, white blood cell (WBC), hemoglobin (Hb), urea, creatinine, platelet, prothrombin time (PT), active partial thromboplastin time (aPTT), international normalized ratio (INR), C-reactive protein (CRP), sedimentation, ferritin values were checked.

Anticoagulant Use

As is known, SARS-CoV-2 infection generally predisposes to thrombosis. For this reason, anticoagulant therapy is often started in patients with risk factors. Although the use of anticoagulant drugs is contraindicated in patients with intracranial bleeding; Considering the general condition of the patient clinically and radiologically, it can be given by close neurological and radiological follow-up according to the benefit-harm ratio. We evaluated the previous use of anticoagulant medication and the initiation/continuation of anticoagulant therapy after intracranial hemorrhage, depending on SARS-CoV-2 infection or the type of bleeding in our cohort.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 22.0 (IBM Corporation, Armonk, NY). Frequency analysis was used for demographic analyses. In descriptive statistics, the data were presented as mean ± standard deviation for parametric, median (range) for non-parametric continuous, and number (percentage) for categorical variables.

RESULTS

Demographic Findings and Comorbid Diseases

The demographic information of the patients is summarized in Table 1. The mean age was 66.5 ± 20.2 (median 66, range 25-91). 61% of the patients

were female (n=8). Seven of the patients in our cohort (54%) had comorbidities such as hypertension (HT), diabetes mellitus (DM), and chronic renal failure (CRF). Only 1 patient had used clopidogrel for cardiac reasons unrelated to SARS-CoV-2 infection.

Anticoagulant Use

Three patients included in the study were diagnosed with hemorrhagic cerebrovascular accident (CVO) accompanied by subarachnoid hemorrhage; Vascular pathology was not considered because of the location and clinic of the bleeding. The therapeutic dose of enoxaparin Na was started in these 3 patients, taking into account the benefit-risk ratio, for close clinical and radiological follow-up. In addition, 1 patient in our study was started on a prophylactic dose of enoxaparin Na due to SARS-CoV-2 in the last 1 month and was discharged; In the next period, he applied to the emergency department with the complaint of left hemiparesis and was operated with the diagnosis of right temporoparietal intraparenchymal hematoma. For this reason, the patient's anticoagulant treatment was discontinued. Other patients in our cohort were not given anticoagulant therapy after detecting intracranial hemorrhage. Information on the use of anticoagulant drugs is shown in Table 1.

Clinical Findings

The most common reason for admission of patients in our cohort was the loss of consciousness with 54% (n=7). In addition, 5 patients (38%) were admitted to the hospital with neurological symptoms such as hemiparesis and headache. Only 1 patient (7%) was admitted to the hospital due to dyspnea. When we consider patients diagnosed with COVID-19 for the first time; We see that 91% of them present with neurological symptoms.

Decompressive craniectomy and hematoma evacuation were performed on 5 patients in our study. Anticoagulant treatment was not given to any of the patients who underwent surgery in the postoperative period. Patients who were not planned for surgery were followed closely clinically and radiologically. Cranial surgery was not required in the follow-up of all patients who did not undergo surgery at the first admission. Considering the general clinical condition, respiratory parameters, and imaging findings of the patients, 9 (69%) patients were followed up with a mechanical ventilator.

All patients newly diagnosed with SARS-CoV-2 were started on favipiravir treatment as an antiviral treatment. 2 patients in our study; Since favipiravir treatment was given for SARS-CoV-2 within 1 month and SARS-CoV-2 infection was not considered clinically, laboratory and radiologically in her current application, favipiravir was not started.

Nine of the patients included in our study died as a result of their follow-up and treatment in the intensive care unit, and the survival rate in our cohort was 31%. The clinical findings of the patients are summarized in Table 1.

Radiological Findings

CO-RADS and RSNA classifications were used in the diagnosis of SARS-CoV-2 infection and the evaluation and prediction of clinical progression of the patients. These classifications are shown in Table 2 and Table 3. As it is known, there is a possibility that the SARS-CoV-2 PCR test may be false-negative, and although the PCR test is negative in some cases, the diagnosis can be made clinically and

Table 1. Baseline Demographic, Clinic, and Radiological Characteristics

Demographic characteristics	**Mean age ± SD** 66.5 ± 20.2 (median 66, range 25-91) **Gender (female)** 61% (n=8)												
	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**	**Patient 7**	**Patient 8**	**Patient 9**	**Patient 10**	**Patient 11**	**Patient 12**	**Patient 13**
Age	87	82	66	63	91	83	84	47	78	40	63	25	56
Gender	M	M	F	F	F	F	M	F	M	F	F	F	M
Comorbidity	-	DM	CRF	HT	DM	DM	HT, CRF	-	-	-	-	-	HT, CRF
Use of anticoagulant	-	-	-	-	-	-	-	-	-	-	-	-	Clopidogrel
Clinical characteristics													
COVID time	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Late apply	Late apply	Initial apply
Presenting complaint	unconsciousness	Unconsciousness	Unconsciousness	Unconsciousness	Unconsciousness	Dyspnea	Unconsciousness	Headache	Left hemiparesis	Headache	Left hemiparesis	Right hemiparesis	unconsciousness
Haemorrhage time	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Late apply	Late apply	Initial apply
COVID medication	Favipiravir	Favipiravir	Favipiravir	Favipiravir	Favipiravir	Favipiravir	Favipiravir	Favipiravir	Favipiravir	Favipiravir	-	-	Favipiravir
Anticoagulant initiated with COVID	-	-	-	Enoxaparin Natrium	-	Enoxaparin Natrium	-	-	-	Enoxaparin Natrium	Enoxaparin Natrium	-	-
Use of anticoagulant after haemorrhage	-	-	-	Enoxaparin Natrium	-	Enoxaparin Natrium	-	-	-	Enoxaparin Natrium	-	-	-
Surgery	-	+	-	-	+	-	-	-	+	-	+	+	-
Mortality	+	+	+	+	+	-	+	+	-	-	+	-	+
Radiological characteristics													
RSNA	İndeterminate	İndeterminate	İndeterminate	Typical	Typical	Typical	Typical	Negative	Negative	Typical	Negative	Negative	Typical
CO-RADS	4	6	4	6	5	5	5	6	6	5	1	1	6
Pneumonia	+	+	+	+	+	+	+	-	-	+	-	-	+
Type of intracranial haemorrhage	ICH	Acute SDH	Spontaneous SAH	Haemorrhagic stroke	Acute SDH	Haemorrhagic stroke	ICH	ICH	Chronic SDH	Haemorrhagic stroke	ICH	Chronic SDH	ICH
Haemorrhage localization	Left temporal and intraventricular	Left frontotemporal	Diffuse Fisher Grade 4 SAH	Left occipital	Left frontotemporal	Left parietal	Left thalamic	Left thalamic	Left frontoparietal	Left parietal	Right parietal	Left temporoparietal	Left parietooccipital
Laboratory characteristics													
Hb	13,9	12,1	10,6	15	11,6	12	13	14,3	12	12	14	12	14,7
WBC	12,8	4,3	5,7	8,3	25	6	8	9	9	6	5	7	16,1
Platelet	124	104	270	299	300	368	102	291	316	443	384	318	107
PT	11,3	12,7	11,3	13,1	10,1	11,1	11,1	12,2	14,5	12	11	11,3	12,4
aPTT	24,3	27	25,3	26,1	20,4	20,1	23,8	23,6	27,7	22,9	25,2	29,9	35,7
Creatinine	0,95	1,04	5,37	1,03	1,53	0,89	1,02	0,64	0,62	0,45	0,66	0,72	4,8
CRP	304	80	39,4	205	119	72	182	7	58	25	1	6,8	57,1
Sedimentation	36	53	61	43,5	71	28	76	17	85	61	14	13	36
INR	1,3	1,2	1,1	1,3	1,3	1,1	1,2	1,1	1,2	1,1	1,1	1,1	1,3
Ferritin	-	208	1708	1668	505	-	799	47,4	576	331	-	-	531
COVID-19 PCR	Negative	Positive	Negative	Positive	Negative	Negative	Negative	Positive	Positive	Negative	Negative	Negative	Positive

DM: Diabetes Mellitus, HT: Hypertension, CRF: Chronic Renal Failure, ICH: Intracerebral Haemorrhage, SDH: Subdural Haemorrhage, SAH: Subarachnoid Haemorrhage, Hb: Hemoglobin, WBC: White Blood Cell, PT: Prothrombin Time aPTT: Active Partial Thromboplastin Time, CRP: C-Reactive Protein, INR: International Normalized Ratio

Table 2. RSNA Classification

COVID-19 pneumonia imaging classification	Rationale	CT Findings
Typical appearance	Commonly reported imaging features of greater specificity for COVID-19 pneumonia	Peripheral, bilateral, GGO* with or without consolidation or visible intralobular lines ("crazy-paving") Multifocal GGO of rounded morphology with or without consolidation or visible intralobular lines ("crazy-paving") Reverse halo sign or other findings of organizing pneumonia (seen later in the disease)
Indeterminate appearance	Nonspecific imaging features of COVID-19 pneumonia	**Absence of typical features AND** **Presence of:** Multifocal, diffuse, perihilar, or unilateral GCO with or without consolidation lacking a specific distribution and are non-rounded or non- peripheral. Few very small GCO with a non-rounded and non-peripheral distribution
Atypical appearance	Uncommonly or not reported features of COVID-19 pneumonia	**Absence of typical or indeterminate features AND** **Presence of:** I solated lobar or segmental consolidation without GCO Discrete small nodules (centrilobular, "tree-in-bud") Lung cavitation Smooth interlobular septal thickening with pleural effusion
Negative for pneumonia	No features of pneumonia	No CT features to suggest pneumonia

**GGO: Ground Glass Opacity*

Table 3. CO-RADS Classification

	Level of suspicion for pulmonary involvement of COVID-19	Summary
CO-RADS 0	Not interpretable	Scan technically insufficient for assigning a score
CO-RADS 1	Very low	Normal or non-infectious
CO-RADS 2	Low	Typical for other infection but not COVID-19
CO-RADS 3	Equivocal/unsure	Features compatible with COVID-19, but also other diseases
CO-RADS 4	High	Suspicious for COVID-19
CO-RADS 5	Very high	Typical for COVID-19
CO-RADS 6	Proven	RT-PCR positive for SARS-CoV-2

radiologically (11). In this context, CO-RADS and RSNA classifications are frequently used in current clinical practice. Eight of the patients in our cohort who were diagnosed with SARS-CoV-2 had a negative PCR test. Two of these patients had SARS-CoV-2 infection in the last 1 month, and it is normal for the PCR test to be negative.

However, the other 6 patients were diagnosed with SARS-CoV-2; The patients' history, clinical evaluation, and thorax CT scans were placed according to CO-RADS and RSNA classifications. Figure 1 shows typical SARS-CoV-2 involvement in patient 4's thorax ct examination.

When the patients with the first diagnosis of SARS-CoV-2 were evaluated according to the RSNA classification, the findings of 54% of the patients were considered "typical" (n=6). When the same patients were evaluated according to the CO-RADS classification, it was seen that 82% of the patients had high-risk thoracic CT findings in terms of COVID-19 or the PCR test was positive. The evaluations of the patients in our study according to these classifications are summarized in Table 1.

In our cohort, 5 patients had intraparenchymal hematoma, 2 patients had a chronic subdural hematoma (SDH), 1 patient had acute SDH, and 4

patients had subarachnoid hemorrhage (SAH). In Figure 2 brain ct images of patient 11, patient 2, and, patient 12 are shown, respectively. The bleeding of 3 of the patients with SAH was thought to be clinically and radiologically related to hemorrhagic SVO.

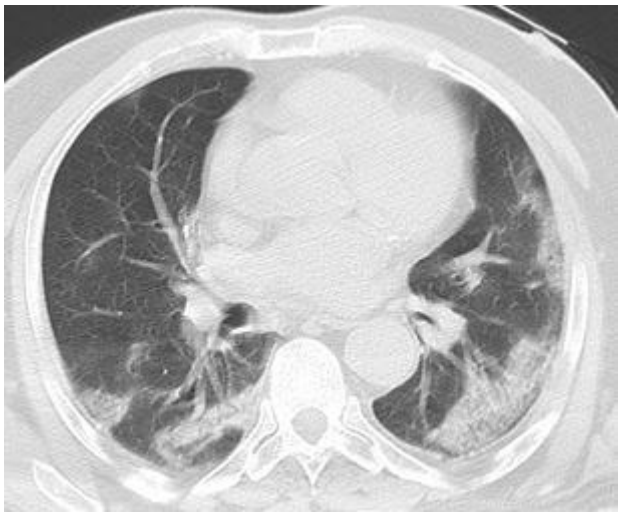

Figure 1. Thorax tomography of fifth patient

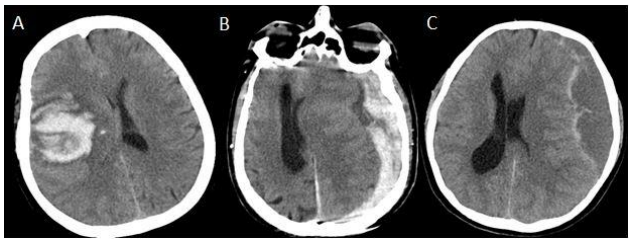

Figure 2. Brain CT images of patient 11, 2 and 12 shown respectively

Aneurysmal SAH was considered in 1 patient, but an advanced radiological examination could not be performed because the patient's general condition was not suitable. These findings are summarized in Table 1.

Laboratory Findings

Routine complete blood count, biochemistry tests, PT, aPTT, INR, and acute phase reactants (CRP, sedimentation, ferritin) were evaluated at the time of admission of the patients in our study. D-Dimer could not be used in our study because it could not be checked in our hospital. It was observed that acute phase reactants, especially CRP and ferritin, were high in patients infected with the newly diagnosed SARS-CoV-2. No bleeding diathesis was observed in any of the patients in our cohort. The creatinine elevation in our 2 patients was associated with the CRF present in these patients. Laboratory parameters are summarized in Table 1.

DISCUSSION

SARS-CoV-2 infection is more common in the advanced age group, as is the case with intraparenchymal hemorrhages. At the same time, according to studies, the association of intracranial hemorrhage in patients with COVID-19 infection is also seen more frequently in the elderly patient group (8). The mean age of the patients in our study was 66.5 ± 20.2 (median 66, range 25-91). 61% of the patients were female (n=8). In the study of Altschul et al. (12), the mean age was 67.03 ± 15.5 years, and 40% were female. In the study of Melmed et al. (13), the mean age was 61.6 ± 11.2 years and the female gender ratio was 21.1%. Our study observed that the mean age was similar, but the female sex ratio was higher.

Especially in the elderly patient group, comorbidities such as HT and DM are more common than in the normal population. At the same time, the symptoms of infection are more severe in these patients. In this context, elderly patients with comorbidities in COVID-19 infection were accepted as a risk group (13,14). 54% of our patients had at least one comorbidity. In one patient, clopidogrel was used before bleeding due to cardiac reasons. In the study of Mishra et al. (15), the comorbidity rate was 81% and 3 patients were using

antiplatelet/anticoagulant drugs before intracranial hemorrhage. In the study of Nawabi et al. (16), the rate of having at least one comorbidity was 83.3% and the rate of using anticoagulant/antiplatelet medication was 50%. As it is known, comorbidities such as HT, DM, and CRF and the use of antiplatelet/anticoagulant drugs increase the frequency of intracranial bleeding. In our study, the rate of both comorbid disease and anticoagulant/antiplatelet drug use was found to be lower.

As it is known, favipiravir in SARS-CoV-2 infection; is an antiviral agent used to provide effective treatment, reduce mortality, and accelerate discharge (17).

When we evaluate the laboratory findings in our study, we see that acute phase reactants, especially ferritin and CRP, are high in patients with newly diagnosed SARS-CoV-2 infection. Although this situation is primarily related to the picture of infection, acute phase reactants may increase especially in the early period in cases of intracranial hemorrhage. In the current situation, it is difficult to distinguish this. However, high CRP negatively affects mortality (18,19). On the other hand, none of the patients in our cohort had bleeding diathesis, which would be a predisposing factor for bleeding.

It is known that the use of anticoagulants/antiaggregants increases the frequency of intracranial bleeding, especially in elderly patients (20). Pavlov et al. also explained in their study the close association of advanced age COVID-19 patients with comorbidities with intracranial hemorrhage (21). In this context, in the study of Melmed et al. (13), it was found that the use of anticoagulant drugs is closely associated with intracerebral hemorrhage in COVID-19. In our study, only 1 patient had anticoagulant drug use before COVID-19 for cardiac reasons. In addition, one patient, who was accepted as a late admission, was started, and currently using enoxaparin Na at a prophylactic dose as an anticoagulant treatment due to COVID-19 due to risk factors. As seen in the literature, the bleeding diathesis seen in COVID-19 can create a cranial destructive process (13,22). In this context, the rate of anticoagulant use in our cohort was 15.3% (n=2). In the study of Mishra et al. (15), the use of anticoagulant drugs was 54.5%. The rate of use of anticoagulant drugs in our cohort was found to be lower. When we look at the mortality rates, the 1-year mortality rate is 50% in patients with non-traumatic intracerebral hemorrhage (23). In this study, the mortality rate was found to be 69%. According to the literature, although the rate of use of anticoagulant drugs in our study was low, mortality rates were higher than those of intracerebral hematomas, especially independent of COVID-19 infection. In our opinion, the risk of intracranial hemorrhage and mortality increases due to SARS-CoV-2 infection. Although the literature supports this, the rate of use of anticoagulant drugs in our study was low. This situation led us to consider the increased risk of intracranial hemorrhage and mortality rates due to SARS-CoV-2 infection, even without the use of anticoagulants.

CONCLUSION

The SARS-CoV-2 pandemic continues its effectiveness worldwide. In addition to its pulmonary effects, extrapulmonary complications are also present and are still under investigation. In these

patients, intracranial hemorrhages may occur, albeit rarely, and are quite mortal. It is thought that intracerebral hemorrhages, which are already quite mortal, are more mortal due to SARS-CoV-2 infection. In addition, COVID-19 infection is thought to be a risk factor for intracranial hemorrhages. However, further studies involving larger patient groups are needed on this subject.

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