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Research Paper

The Impact of COVID-19 on Clinical Outcomes in Patients With Traumatic Brain Injury

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ABSTRACT

Background: Traumatic brain injury (TBI) is a leading cause of mortality and morbidity worldwide. COVID-19 can impact the central nervous system (CNS) and hematologic system and appears to affect clinical outcomes and the average cerebral hemorrhage volume (ACHV) in patients with TBI.

Objectives: Our study focused on evaluating the effects of COVID-19 on clinical outcomes and the ACHV in TBI patients.

Materials & Methods: In this study, we included TBI patients presenting to an academic trauma center in the North of Iran and categorized them into two groups: infected with COVID-19 and non-infected. A total of 128 TBI patients were identified during 19 months of the COVID-19 pandemic.

Results: Road accidents account for 92.2% of TBI. Among different types of brain lesions, subdural hematoma (SDH) had a significant relationship with COVID-19 (P=0.043). Among patients, 13 (10.2%) were on anticoagulants, with no significant differences between the two groups. Among the COVID-19 patients, those who were anticoagulant users experienced a higher ACHV than those who did not use this medication (P=0.015). The two groups had no significant difference in the ACHV and mortality (P=0.758, P=0.601, respectively). The regression analysis indicates no statistically significant relationship between COVID-19 and ACHV (P=0.983) or between COVID-19 and the mortality rate of TBI patients (P=0.695).

Conclusion: The study highlights that TBI patients with COVID-19 on anticoagulants show higher ACHV levels than those without, a pattern missing in non-COVID patients. This finding suggests a possible synergistic interaction between COVID-19 and anticoagulation, with COVID-19 potentially worsening coagulation disorders.

Keywords: Brain injury, Traumatic, COVID-19, Cerebral hemorrhages

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Highlights

- It appears that COVID-19 can affect the hematological system and cerebral hemorrhage in patients with traumatic brain injury.

- Traumatic brain injury patients with COVID-19 on anticoagulants exhibit a higher average volume of cerebral hemorrhage than those without, a trend not seen in non-COVID-19 traumatic brain injury patients.

Introduction

Traumatic brain injury (TBI) is a leading cause of emergency department visits and a major contributor to mortality and morbidity worldwide [1, 2]. TBI is a significant socioeconomic issue that burdens healthcare systems and affects individuals' lives [1-3]. The incidence of severe consequences, such as intracranial hemorrhages, is mainly associated with TBIs following road traffic accidents rather than other types of traumatic injuries [3]. In addition to the initial brain damage, some avoidable secondary processes, such as progressive hemorrhagic injury (PHI) following intracranial bleeding, can deteriorate the general condition [4]. Hence, risk factors related to PHI should be addressed [4]. Evidence of a direct association exists between PHI and several risk factors, including a high D-dimer level, thrombocytopenia, leukocytosis, and prolonged prothrombin time (PT) [1, 4, 5]. Therefore, it seems rational to accept that coagulation disorders may contribute to poor prognosis in patients with TBI. Moreover, there is a correlation between higher mortality rates after TBIs and comorbidities such as hematologic malignancies and coagulation disorders [4, 6-8].

Coronavirus disease 2019 (COVID-19) emerged as a new infectious disease outbreaking in late December 2019. The disease originated in China and rapidly spread globally [9]. Therefore, in March 2020, the World Health Organization (WHO) declared that the COVID-19 outbreak became a pandemic and a primary global concern [10].

COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an RNA virus [11]. Due to the virus's high mutation rate, many subtypes have emerged that can impact symptoms' incidence and severity. SARS-CoV-2 can lead to high morbidity and mortality rates, which can simultaneously affect various body organs, including the respiratory, cardiovascular, gastrointestinal, central nervous and hematopoietic systems [11, 12]. Although initially manifesting as a respiratory tract infection, subsequent data noted that it should be considered a systemic disease [11]. COVID-19 can impact the hematopoietic system remarkably, often associated with a hypercoagulability state [11]. Main hematologic findings include lymphocytopenia, thrombocytopenia, elevated D-dimer, and prolonged PT [11]. Also, a high rate of arterial and venous thromboembolisms at the first 24 hours of admission is reported among several COVID-19 patients [13, 14].

Angiotensin-converting enzyme 2 (ACE2) is an essential component of the renin-angiotensin-aldosterone system, which plays a crucial role in maintaining homeostasis [15]. It is a pro-inflammatory agent and vasoconstrictor, expressed in almost all organs [16]. ACE2 in lung pneumocytes type 2 can act as a receptor for SARS-CoV-2 [17]. This attachment inhibits ACE2 and facilitates virus entry into cells, followed by boosting cell infection [15, 16]. ACE2 receptors are also present in cerebrovascular endothelial cells, which regulate various brain functions, including autoregulation of cerebral perfusion [15]. Thus, COVID-19 can disrupt autoregulation in CNS and peripheral nervous system [16, 18-23]. Several researchers investigated the most common cranial hemorrhagic patterns both before and after the COVID-19 era, consisting of SDH, SAH and brain contusions, together with falling, which is the most frequent head trauma mechanism [13, 24].

Considering the effects of COVID-19 on various organs, especially the CNS and hematologic system, we aimed to assess the impact of COVID-19 infection on mortality and the average cerebral hemorrhage volume (ACHV) in patients with TBI.

Materials and Methods

In this comparative cross-sectional study, we included hospitalized patients with TBI who presented to our trauma center. They were categorized into two groups: 33 confirmed COVID-19 patients and 95 uninfected patients. All 33 COVID-19 patients were diagnosed before their hospitalization for TBI, with most confirmed

through PCR testing. These patients were identified during the 19-month COVID-19 pandemic (commencing in March 2020 and culminating in September 2021). The patient's clinical data were collected by reviewing their medical records, registered files in the hospital information system and the imaging modalities in the picture archiving and communication system.

We collected documented data based on a checklist including demographic information of patient's age, gender, and underlying diseases, hypertension as blood pressure above 140/90 mm Hg, diabetes based on American Diabetes Association criteria, history of ischemic heart disease based on past medical history, other clinical information (smoking, mechanism of trauma, severity of brain injury, neurological defects and CT scan findings) and risk factors of intracranial complications (anticoagulant drug use, reduced level of consciousness and also type of treatment, suffering from Covid-19 and duration of hospitalization). There are two methods to estimate the intracerebral hemorrhage volume: ABC/2 and computer-assisted planimetric analysis. ABC/2 is a simple and reliable technique using A=maximum diameter of hemorrhage (in cm), B=width to A and C=the number of slices multiplied by slice thickness. This accurate method allows physicians to assess the intracerebral hemorrhage volume and predict patient outcomes in a short time.

Statistical analysis

Statistical analyses were done using IBM SPSS software, version 25.0 (SPSS, Inc., Chicago, IL, USA). Categorical variables were reported as frequencies and percentages, while continuous variables were summarized using means and standard deviations. Continuous variables were compared between COVID-19 and non-COVID-19 groups using the independent t test or Mann-Whitney U test. The categorical variables were analyzed using the chi-square or Fisher exact test. Univariate linear and logistic regression was used to investigate the relationship between COVID-19, demographic and clinical factors with ACHV, and mortality in TBI patients. All variables with a $P<0.25$ in the univariate models were entered into the multiple linear and logistic models. The significance level in all tests was set at $P<0.05$ and the tests were considered two domains.

Results

Demographic features, including age, gender, smoking status, and comorbidities, were evenly balanced between the two study groups ($P>0.05$). The reason for head trauma in most of the studied samples (92.2%) was road accidents. There was no significant statistical relationship between trauma mechanisms and COVID-19. The most common types of brain lesions were subdural hematoma (SDH) (51.6%), epidural hematoma (EDH) (50.0%), intracranial hemorrhage (ICH) (20.3%), contusion (16.4%) and subarachnoid hemorrhage (SAH) (10.2%). Among different types of brain lesions, SDH had a significant relationship with contracting COVID-19 in patients with TBI ($P=0.043$). The frequency of SDH lesions in people with COVID-19 was considerably lower than in people without COVID-19 (36.4% vs 56.8%). Among patients, 13(10.2%) were on anticoagulants, with no significant differences between the groups. Most patients underwent surgery; no significant differences were observed between the two groups (Table 1).The mean Glasgow Coma Scale (GCS) of hospitalized patients with COVID-19 (8.1±3.3) was not significantly different from that of patients without COVID-19 (8.5±3.6) ($P=0.528$). Of 128 admitted patients, 66(51.6 %) had mild, 41(32.0 %) moderate and 21(16.4%) severe head injuries. There was no significant statistical difference between the two groups in this aspect. There was no statistically significant difference in the ACHV between the two groups (21.4±16.3 vs 21.3±18.3; $P=0.758$). Fifty-four patients (42.2%) died, with 15(45.4%) in the COVID-19 group and 39(41.1%) in the other. There was no statistically significant difference in this outcome between the two groups. Other clinical outcomes examined in both study groups showed no significant differences. The results are presented in Table 2.

Table 3 shows no statistically significant difference in ACHV between COVID-19 and non-COVID-19, separated by smoking and anticoagulant use. Only anticoagulant use was significantly associated with ACHV in COVID-19 patients. Among the COVID-19 patients, those who anticoagulant users experienced a higher ACHV than those who did not use medication ($P=0.015$).

The univariate linear regression model showed no significant relationship between COVID-19 and ACHV ($P=0.983$). However, age, comorbidity, EDH, ICH, contusion, and anticoagulant use were all significantly related to ACHV. The multivariate linear regression model revealed that brain lesions, including SDH, EDH, ICH, and contusions, were significantly related to ACHV (Table 4).

The findings in Table 5 show that COVID-19 had no significant association with TBI patient mortality ($P=0.695$). Age, comorbidity, ICH, contusion, SAH and anticoagulant use were all significantly related to mor-

Table 1. Comparing TBI patients with and without COVID-19 in terms of demographic, trauma mechanism and type of bleeding

Factors		Mean±SD/No. (%)			P
		Total (n=128)	COVID-19		
			Positive (n=33)	Negative (n=95)	
Age (y)		41.1±18.4	40.7±17.8	41.2±18.7	0.897†
Female		43(33.6)	8(24.2)	35(36.8)	0.187‡
Smoking		30(23.4)	10(30.3)	20(21.1)	0.280‡
Comorbidity		24(18.8)	6(18.2)	18(18.9)	0.923‡
Hypertension		18(75.0)	4(66.7)	14(77.8)	0.618‡
Hyperlipidemia		13(54.2)	4(66.7)	9(50.0)	0.649‡
Diabetic		5(20.8)	2(33.3)	3(16.7)	0.568‡
Trauma mechanism	Road accidents	118(92.2)	29(87.9)	89(93.7)	0.280‡
	Falling down	10(7.8)	4(12.1)	6(6.3)	
SDH		66(51.6)	12(36.4)	54(56.8)	0.043‡
EDH		64(50.0)	21(63.6)	43(45.3)	0.069‡
ICH		26(20.3)	8(24.2)	18(18.9)	0.515‡
Contusion		21(16.4)	4(12.1)	17(17.9)	0.440‡
SAH		13(10.2)	5(15.1)	8(8.4)	0.318‡
Anticoagulant use		13(10.2)	3(9.1)	10(10.5)	0.999‡
Type of treatment	Surgical	75(58.6)	21(63.6)	54(56.8)	0.495‡
	Conservative	53(41.4)	12(36.4)	41(43.2)	

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Abbreviations: SDH: Subdural hematoma; EDH: Epidural hematoma; ICH: Intracranial hemorrhage; SAH: Subarachnoid hemorrhage.

†The Independent t-test; ‡The Pearson chi-square test, ‡The Fisher exact test.

tality. Multivariate analysis indicated that older age, presence of ICH and contusions were significantly associated with mortality.

Discussion

Covid-19, a global pandemic, can affect several different systems in the body. Not only have there been reports of its effects on the hematological and neurological system [13, 14], but it also causes disorders in the function and self-regulation of cerebral vessels, followed by their rupture [16]. In this study, we examined the amount of bleeding and the clinical consequences between the two groups of with and without COVID-19 patients suffering from concussions and compared to check whether COVID-19 had a significant effect on the bleeding volume or their clinical outcome based on demographic characteristics.

Road accidents were the primary underlying phenomenon of trauma in our study, while in a similar study done by Lara-Reyna et al. in the later period of COVID-19, the major mechanism of head injury was reported to be falling. However, no significant correlation was discovered between patients' clinical outcomes and COVID-19 infection in both groups [25].

Regarding the underlying disease, most subjects did not suffer from any underlying conditions. However, high blood pressure and hyperlipidemia were the most

Table 2. Comparing TBI patients with and without COVID-19 according to tbi features and clinical outcomes

Factors		Mean±SD/No. (%)			P
		Total (n=128)	COVID-19		
			Positive (n=33)	Negative (n=95)	
GCS		8.4±3.5	8.1±3.3	8.5±3.6	0.528†
Mild	13-15	66(51.6)	19(57.6)	47(49.5)	
Moderate	9-12	41(32.0)	10(30.3)	31(32.6)	0.653‡
Severe	3-8	21(16.4)	4(12.1)	17(17.9)	
ACHV		21.3±17.8	21.4±16.3	21.3±18.3	0.758†
Impaired consciousness		70(54.7)	21(63.6)	49(51.6)	0.231‡
Neurological deficit		29(22.7)	9(27.3)	20(21.0)	0.462‡
Outcome	Death	54(42.2)	15(45.4)	39(41.1)	
	Disability	58(45.3)	16(48.5)	42(44.2)	0.601‡
	Recovery	16(12.5)	2(6.1)	14(14.7)	
ICU-LOS		2.8±1.7	2.9±1.3	2.7±1.8	0.530†
Hospital-LOS		5.2±4.0	5.4±3.4	5.2±4.2	0.169†

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Abbreviations: TBI: Traumatic brain injury; GCS: Glasgow coma score; ACHV: Average cerebral hemorrhage volume; ICU-LOS: Intensive care unit length of stay; LOS: Length of stay.

†The Mann-Whitney U test; ‡The Pearson chi-square test.

prevalent among the underlying diseases, but there was no difference between the two investigated groups.

There was no significant difference in smoking between the COVID-19 and non-COVID-19 groups. Another study also found no significant relationship between smoking and COVID-19 disease [26].

Also, no significant disparity was discovered in the average bleeding volume between the two mentioned groups.

The most prevalent type of brain lesion in our study was SDH, unlike other studies in which the largest subgroup caused by trauma was ICH [27]. Nevertheless, in our study, the frequency of SDH in the group with COVID-19 was noticeably lower than non-COVID-19.

The ACHV also had no significant difference between the two groups; in most patients, the bleeding volume was less than 20 mL. The hypothesis behind our study was that COVID-19 can increase the bleeding volume in the group with concussion injuries who suffer from COVID-19 due to its effect on hematological elements. However, there was no difference in bleeding in infected and non-infected patients. Nevertheless, among the group of COVID-19 patients, subjects who took anticoagulant medication experienced a higher average volume of bleeding than those who did not use medication. That outcome could result from a potential synergism formed between anticoagulant drugs and COVID-19 [4, 28, 29]. Since the effect of COVID-19 in reducing the platelet count and increasing PT and as leukopenia has been reported, it is probable that coupled with the use of anticoagulants, it can augment the platelets reduction and prolong PT, which leads to an increase in the frequency and volume of bleeding and has been witnessed in people who use anticoagulants such as aspirin. This point can strengthen the hypothesis of a synergistic effect of COVID-19 and the anticoagulant effect.

Several studies have revealed that patients with intracerebral bleeding risk factors are more prone to bleeding and its progression [4]. Among the mentioned risk factors are a high level of D-dimer, a low level of plate-

Table 3. Comparing ACHV in TBI patients with and without COVID-19 according to smoking and anticoagulant drug use

Variables		COVID-19		P
		Positive (n=33)	Negative (n=95)	
		ACHV		
Smoking	Yes	25.8±21.6	17.7±15.1	0.248†
	No	19.5±13.6	22.3±19.1	0.860†
P		0.603†	0.355†	
Anticoagulant use	Yes	44.3±11.0	30.6±24.3	0.112†
	No	19.1±15.1	20.2±17.3	0.992†
P		0.015†	0.117†	

ACHV: The average cerebral hemorrhage volume; TBI: Traumatic brain injury.

†The Mann-Whitney U test.

Table 4. Univariate and multivariate model for association between COVID-19 and ACHV

Factors	Univariate		Multivariate	
	B (95% CI)	P	B (95% CI)	P
COVID-19 (yes/no)	0.08 (-7.06,7.21)	0.983	-	-
Age (y)	0.17 (0.00,0.33)	0.051	-	-
Sex (female/male)	3.31 (-3.27,9.89)	0.321	-	-
Smoking (no/yes)	1.18 (-6.19,8.54)	0.752	-	-
Comorbidity (no/yes)	-8.00 (-15.87,-0.12)	0.047	-	-
Trauma mechanism (falling down/road accidents)	9.29 (-2.23,20.81)	0.113	-	-
SDH (yes/no)	-4.01 (-10.22,2.20)	0.203	9.33 (1.58-17.08)	0.019
EDH (yes/no)	7.55 (1.45,13.65)	0.016	18.47 (10.59,26.35)	<0.001
ICH (yes/no)	23.66 (17.12,30.20)	<0.001	24.33 (18.22,30.45)	<0.001
Contusion (yes/no)	11.22 (3.02-19.41)	0.008	9.62 (2.91-16.33)	0.005
SAH (yes/no)	3.56 (-6.75,13.88)	0.495	-	-
Anticoagulant use (no/yes)	-13.84 (-23.88,-3.80)	0.007	-	-
Type of treatment (conservative/surgical)	-4.31 (-10.60,1.98)	0.178	-	-

Abbreviations: ACHV: The average volume of cerebral hemorrhage; SDH: Subdural hematoma; EDH: Epidural hematoma; ICH: Intracranial hemorrhage; SAH: Subarachnoid hemorrhage.

Model: Linear regression model; age, comorbidity, trauma mechanism, SDH, EDH, ICH, contusion, anticoagulant use and type of treatment entered the multivariate model (P<0.250).

Table 5. Univariate and multivariate model for association between COVID-19 and mortality

Factors	Univariate		Multivariate	
	OR (95%CI)	P	OR (95%CI)	P
COVID-19 (yes/no)	1.20 (0.54-2.66)	0.659	-	-
Age (y)	1.04 (1.02-1.06)	<0.001	1.03 (1.01-1.06)	0.016
Sex (female/male)	1.13 (0.54-2.37)	0.745	-	-
Smoking (yes/no)	1.06 (0.47-2.43)	0.885	-	-
Comorbidity (yes/no)	2.78 (1.11-6.95)	0.029	-	-
Trauma mechanism (road accidents/falling)	0.46 (0.12-1.71)	0.244	-	-
SDH (yes/no)	1.71 (0.84-3.48)	0.138	-	-
EDH (yes/no)	0.60 (0.29-1.21)	0.153	-	-
ICH (yes/no)	28.80 (6.40-129.60)	<0.001	20.83 (4.34-100.04)	<0.001
Contusion (yes/no)	11.83 (3.27-42.83)	<0.001	15.26 (3.70-62.95)	<0.001
SAH (yes/no)	5.38 (1.40-20.62)	0.014	-	-
Anticoagulant use (yes/no)	9.21 (1.95-43.53)	0.005	-	-
Type of treatment (surgical/conservative)	0.92 (0.45-1.87)	0.816	-	-

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Abbreviations: SDH: Subdural hematoma; EDH: Epidural hematoma; ICH: Intracranial hemorrhage; SAH: Subarachnoid hemorrhage.

Model: Logistic regression model; age, comorbidity, trauma mechanism, SDH, EDH, ICH, contusion, SAH and anticoagulant use entered the multivariate model(P<0.250).

lets, a high level of white blood cells, and an increase in PT [30]. Coagulation disorders increase the lesion size and the risk of progression after TBI, as the progression rate of intracerebral hemorrhage after TBI is commonly increased with coagulation disorders, and it has been suggested that higher levels of international normalized ratio and D-dimer and lower counts of platelets increase the size and intensifies the progression rate of the hemorrhage [4].

Conclusion

The study shows that TBI patients with COVID-19 on anticoagulants had higher ACHV levels than infected patients not on the therapy. However, among non-COVID patients, anticoagulants did not affect ACHV levels. This finding suggests that COVID-19 exacerbates coagulation abnormalities through an additive, synergistic effect, marking it as a key risk factor for worsening such conditions.

Ethical Considerations

Compliance with ethical guidelines

All study procedures were in compliance with the Ethical Guidelines of the 2013 Declaration of Helsinki. The study was approved by the Ethics Committee of Guilan University of Medical Sciences (Code: IR.GUMS.REC.1400.424).

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Authors contributions

Conceptualization: Farnaz Mahdavi, Sima Fallah-Arzpeima, Zoheir Reihanian and Nooshin Zaresharifi; Methodology: Khatereh Asadi, Roghaye Zare and Mohammad Ali Yazdanipour; Investigation and resources: Farnaz Mahdavi, Sima Fallah-Arzpeima, Zoheir Reiha-

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Conflict of interest

The authors declared no conflict of interest.

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