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Incidence and Laboratory Predictors of Acute Ischemic Stroke in COVID-19: A Cross-Sectional Study

Mehdi Torabi[1*], Sara Azizi shoul[1], Mina Ameri[1]

Department of Emergency Medicine, Kerman University of Medical Sciences, Kerman, Iran

* ***Corresponding author:*** Mehdi Torabi, Associate Professor of Emergency Medicine, Department of Emergency Medicine, Kerman University of Medical Sciences, Kerman, Iran. Email: mtorabi1390@yahoo.com

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Abstract

Background: The possibility of central nervous system (CNS) involvement following Coronavirus Disease 2019 (COVID-19) is rare. Laboratory tests may play a predictive role in the occurrence of stroke.

Objective: The objectives of this study were twofold: first, to investigate the incidence of acute stroke, and second, to examine the role of laboratory tests in predicting the occurrence of these events following infection.

Methods: This cross-sectional study was conducted over one year. The inclusion criteria were as follows: patients over 18 years of age with a positive multiple polymerase chain reaction (RT-PCR) test result or typical lung CT findings of confirmed cases of pneumonia due to COVID-19 and who had undergone a brain CT scan due to suspicion of brain damage. The patients were divided into two groups, with and without brain damage, and compared with each other. The chi-square test was employed to evaluate the correlation between the qualitative variables, while the Mann-Whitney U test and the Student's t-test were applied to analyze the quantitative variables. Subsequently, logistic regression analysis was conducted to examine the association between patient outcomes and the pertinent variables. A p-value of less than 0.05 was established as indicative of statistical significance. Data analysis was conducted using SPSS.

Results: Among the 6604 patients, 98 underwent brain CT scans, of which 9.18% had stroke. Notably, 0.55% of all patients had acute ischemic stroke, a proportion that was significantly higher in women than in men. A statistically significant difference was observed in blood glucose (BG) and activated partial thromboplastin time (aPTT) levels among patients with ischemic stroke compared to those without stroke ($p < 0.05$). In both univariate and multivariate analyses with logistic regression, the three variables gender, blood glucose, and aPTT were significantly associated with the incidence of ischemic stroke. The Area Under the Curve (AUC) values for BG and aPTT were determined to be 0.66 and 0.67, respectively.

Conclusion: The incidence of acute stroke following COVID-19 infection is not common. In female patients, decreased blood glucose and decreased aPTT were associated with an increased incidence of ischemic stroke following infection.

Keywords: Activated Partial Thromboplastin Time, Blood glucose, Covid-19, Stroke

1. Background

The outbreak of the novel coronavirus, officially designated as Coronavirus Disease 2019 (COVID-19), which first emerged in Wuhan, China, in 2019, has substantially strained healthcare systems across numerous nations. Although the virus primarily affects the respiratory system, it can also lead to complications involving other vital organs (1).

Coronaviruses are not primarily neurotropic viruses; their primary target is the respiratory epithelium. However, the target receptor for cell binding is the angiotensin-converting enzyme 2 (ACE 2) receptor, which is also found on glial cells in brain and spinal cord neurons. The virus can also activate the coagulation system and endothelial dysfunction, leading to arterial thrombosis and subsequent stroke. These mechanisms, in conjunction with hypoxic brain injury and immune-mediated damage to the central nervous system (CNS), are among the causative factors of the neurological complications associated with COVID-19. These neurological complications are more prevalent in patients with severe COVID-19, and stroke has been reported in 2.7 to 3.8% of cases (2-5).

Many predictive models have been developed to ascertain the prognosis of patients infected with the novel COVID-19. Among the demographic data, clinical symptoms, history of underlying diseases, and vital signs, laboratory factors have contributed significantly to predicting patient outcomes (6).In several trials, Xie et al. have indicated the prognostic role of lymphocytes and lactate dehydrogenase (LDH) in the outcome of patients hospitalized with COVID-19 (7). Lu et al. emphasized the predictive role of C-reactive protein (CRP) given the inflammatory nature of the disease, noting that this index can predict short-term mortality associated with the disease. They suggested that this index may serve as a valuable and appropriate tool for rapidly establishing a hierarchical management system for the disease to reduce the medical burden and mortality in highly endemic areas (8). Concurrently, Zhang et al. corroborated the findings of Macias-Muñoz et al., who previously identified high LDH, neutrophil-to-lymphocyte ratio, and direct bilirubin levels as independent predictors of 28-day mortality in adult patients hospitalized with COVD-19. The researchers further proposed that a prognostic scoring system, predicated on these variables, could serve as a valuable tool to assist physicians in monitoring and managing patients infected with COVID-19 (9). Concurrently, Macias-Muñoz et al. identified risk factors for mortality in hospitalized patients with COVD-19 through a retrospective study design, identifying lymphocyte, platelet, creatinine, D-dimer, troponin, and CRP counts as independent risk factors for death among patients (10).

The role of laboratory tests in predicting the outcome of patients with COVID-19 is indisputable. However, the prognostic value of these tests in patients with stroke conditions remains to be elucidated. The objectives of this study were twofold: firstly, to investigate the incidence of acute stroke in patients with COVID-19, and secondly, to examine the role of laboratory tests at the time of hospital admission in predicting acute stroke following COVID-19.

2.Objective

The objectives of this study were twofold: first, to investigate the incidence of acute stroke, and second, to examine the role of laboratory tests in predicting the occurrence of these events following infection.

3. Methods

Study Design and Setting

This study employs a descriptive-analytical cross-sectional design. The study population encompasses all patients diagnosed with COVID-19 and subsequently admitted to Afzalipour Academic Hospital, a referral center for internal and infectious diseases located in Kerman, southeastern Iran, during one year from April 12, 2020, to April 12, 2021. Enrollment in the study was conducted using a census method. Due to the retrospective nature of this study, individual consent from participants was not obtained, and all patient information remained confidential. All study methods were conducted in accordance with the relevant guidelines and regulations of the Declaration of Helsinki.

Study Population

The inclusion criteria encompassed all patients over the age of 18 who had been diagnosed with COVID-19 and had a positive multiple polymerase chain reaction (RT-PCR) test or characteristic lung Computed Tomography (CT) scan findings of the disease, as well as those with a brain CT scan performed with suspicion of brain lesions. Patients under 18 years of age suspected of having COVID-19 with negative RT-PCR test results and lung CT, incomplete and unaltered files in the hospital archive, and those without a brain CT scan performed were excluded from the study.

Data collection and variables

The research assistant collected data, which was recorded using a predetermined checklist. The study's variables encompassed patient age, gender, underlying disease, length of stay (LOS), laboratory tests administered at the time of hospital admission, and stroke as the study's primary outcome. A meticulous review of all files about patients diagnosed with COVID-19 who had positive RT-PCR tests or exhibited typical lung CT findings indicative of COVID-19 pneumonia was conducted. Patients with repetitive negative RT-PCR tests were also included in the study. Data from files of patients exhibiting neurological symptoms and for whom brain CT scans were performed were collected. The decision to perform a CT scan was made after a consultation with a neurologist and the neurologist's expert opinion. Subsequently, brain and chest CT scans were interpreted by a radiologist. Patients were divided into two groups, with and without brain damage, and compared with each other.

Outcome measurement

The outcome included patients diagnosed with COVID-19 with stroke.

Ethical approval

This study was reviewed by the Ethics Committee of Kerman University of Medical Sciences (IR.KMU.AH.REC.1403.040) and was granted ethical approval.

Statistical analysis

Quantitative data with a normal distribution were presented as the mean ± standard deviation and a non-normal distribution as the median (interquartile range [IQR]). Qualitative variables were expressed as numbers (percentages). The chi-square test assessed the relationship between the dichotomous qualitative variable and other qualitative variables. In instances where data was non-normal, the Mann-Whitney U test was employed, while the Student's t-test was utilized in scenarios where data followed a parametric distribution. A p-value less than 0.05 was designated as statistically significant. Subsequently, univariate logistic regression was implemented to investigate the association between patient outcomes and the variables. The strength of the relationship between the variables and the patient outcome was subsequently assessed by calculating odds ratios (OR) and confidence intervals (CIs). Variables with p-values less than 0.2 were entered into the multivariate regression model. Finally, receiver operating curves (ROC) were plotted for the variables that had a significant relationship with the outcome, and at the optimal cut-off, the area under the curve (AUC), sensitivity, and specificity were calculated. The statistical analysis was conducted using SPSS software, version 27.0 (SPSS Inc., Chicago, IL, USA).

4. Results

During the one year under consideration, 6604 patients with confirmed cases of COVID-19, as indicated by positive RT-PCR tests or typical lung CT scans, were included in the study. Of these patients, 98 requested brain CT scans due to neurological symptoms and suspected brain damage and were thus enrolled in the study. The remaining patients were excluded from the study (Figure 1). Of the 98 patients who underwent brain CT scans, the results created two groups: one with brain involvement and one without. Nine patients (9.18%) had brain damage, and the radiologist reported that all of these cases were ischemic stroke. The most common underlying disease was diabetes (26.66%), followed by hypertension (13.33%). A statistically significant disparity was observed in the CNS involvement between female and male patients (p=0.002). Additionally, a notable difference in blood glucose (BG) levels at admission was identified between patients with and without ischemic stroke (p=0.004). Furthermore, a statistically significant discrepancy was observed between the two groups in activated partial thromboplastin time (aPTT) at admission (p=0.02). Furthermore, a borderline statistically significant difference was observed between the two groups of patients with and without ischemic stroke concerning laboratory tests, including WBC, PMN, BUN, LDH, and D-dimmer (Table 1).

Table 1. Patients' characteristics stratified by the presence of stroke based on spiral brain CT scan

Variables	Outcome, mean ±SD Patients experiencing a stroke	Patients not experiencing a stroke	P-value
Sex, n (%) Male Female	4(4.08) 5 (5.10)	52(53.06) 37(37.76)	0.002
Age	58.37±26.09	61.60±23.15	0.52
LOS[1]	8.59±7.46	9.60±6.23	0.46
WBC[2]	11.82±7.30	9.57±5.48	0.08
PMN[3]	80.52±11.03	75.97±13.11	0.07
Lymphocyte	13.53±9.73	16.54±12.39	0.18
NLR[4]	11.86±15.55	9.99±10.41	0.48
PLR[5]	24.65±20.15	20.46±20.41	0.31
Hemoglobin	13.15±2.59	13.20±3.27	0.93
Platelet	217.68±132.27	96.38±12.76	0.15
BUN	79.56±55.10	61.52±39.95	0.06
Creatinine	1.50±1.40	1.37±0.94	0.59
Blood sugar	210.24±169.83	125.86±66.22	0.004
PT[6]	14.95±3.61	14.57±3.92	0.62
INR[7]	1.19±0.35	1.21±0.41	0.83
aPTT[8]	38.29±17.17	31.64±6.70	0.02
LDH[9]	1187.73±1616.04	690.89±471.58	0.06
ESR[10]	42.12±30.82	36.68±34.76	0.42
CRP[11]	39.66±35.26	33.42±47.15	0.48
D-dimer	3.09±1.26	2.68±1.07	0.08
RDW[12]	15.84±3.49	15.57±3.15	0.68
MPV[13]	10.44±0.59	10.56±0.78	0.40
MPV/RDW	0.06±0.04	0.09±0.15	0.25

1Length of stay, 2White Bood Cel, 3Polymorphonuclear leukocyte, 4Neutrophil-Lymphocyte Ratio, 5Platelet-Lymphocyte Ratio,6 Prothrombin Time, 7International Normalized Ratio, 8 activated Partial Thromboplastin Time, 9Lactate Dehydrogenase, 10Erythrocyte Sedimentation Rate, 11C-Reactive Protein, 12Red Cell Distribution Width, 13Mean Platelet Volume

To ascertain the intensity of the association of demographic information and laboratory tests with patient outcomes, logistic regression with OR and 95% CI was employed. The OR for ischemic stroke in women was 3.61 times that of men, which was statistically significant (OR: 3.61, CI 95%: 1.54-8.45, p-value=0.003). Furthermore, a statistically significant inverse correlation was observed between BG levels and ischemic stroke (OR: 0.99, CI 95%0.98-0.99, p-value=0.003). This indicates that for every unit decrease in BG, the likelihood of stroke in patients with COVID-19 increases by 1%. A similar inverse association was observed between aPTT and ischemic stroke (OR: 0.93, CI 95%0.88-0.98, p-value=0.01), indicating that for every unit decrease in aPTT, the risk of ischemic stroke increased significantly by 7 times. In addition, a borderline statistically significant difference was observed between the two groups of patients with and without stroke to laboratory tests, including WBC, PMN, and BUN (p-value=0.05-0.1). However, no statistically significant relationship was observed between the two groups in terms of laboratory tests, including age, LOS, lymphocytes, NLR, PLR, hemoglobin, platelet, creatinine, PT, INR, ESR, CRP, D-dimer, RDW, MPV, and MPV/RDW ratio (p-value > 0.1) (Table 2).

Table 2. Univariate logistic regression association with stroke in Covid-19 patients

Variables	Odds Ratio	CI95%	P-value
Sex	3.61	1.54-8.45	0.003
Age	1.00	0.98-1.02	0.51
LOS[1]	1.02	0.96-1.08	0.46
WBC[2]	0.94	0.88-1.01	0.09
PMN[3]	0.96	0.93-1.00	0.07
Lymphocyte	1.02	0.98-1.06	0.19
NLR[4]	0.98	0.95-1.02	0.48
PLR[5]	0.99	0.97-1.01	0.31
Hemoglobin	1.00	0.87-1.15	0.93
Platelet	0.99	0.99-1.00	0.13
BUN	0.99	0.98-1.00	0.07
Creatinine	0.90	0.64-1.28	0.59
Bood sugar	0.99	0.98-0.99	0.003
PT[6]	0.97	0.87-1.08	0.62
INR[7]	1.11	0.39-1.20	0.83
aPTT[8]	0.93	0.88-0.98	0.01
LDH[9]	0.99	0.99-1.00	0.06
ESR[10]	0.99	0.98-1.00	0.42
CRP[11]	0.99	0.98-1.00	0.47
D-dimer	0.70	0.45-1.09	0.12
RDW[12]	0.97	0.86-1.10	0.68
MPV[13]	1.28	0.71-2.28	0.39
MPV/RDW	44.17	0.03-59726.90	0.30

[1]Length of stay, [2]White Bood Cel, [3]Polymorphonuclear leukocyte, [4]Neutrophil-Lymphocyte Ratio, [5]Platelet-Lymphocyte Ratio,[6] Prothrombin Time, [7]International Normalized Ratio, [8] activated Partial Thromboplastin Time, [9]Lactate Dehydrogenase, [10]Erythrocyte Sedimentation Rate, [11]C-Reactive Protein, [12]Red Cell Distribution Width, [13]Mean Platelet Volume

Subsequently, variables with p-values less than 0.2 were entered into the multivariate model using the backward elimination method. This analysis revealed a statistically significant relationship between the three variables of gender, BG, and aPTT with ischemic stroke (Table 3).

Table 3. Multivariate logistic regression association with stroke in Covid-19 patients

Variables	Odds Ratio	CI95%	P-value
Sex	2.97	1.06-8.34	0.03
Bood sugar	0.99	0.98-0.99	0.004
aPTT*	0.92	0.87-0.99	0.02

*activated Partial Thromboplastin Time

Finally, ROC curves were drawn separately to ascertain the predictive role of BG and aPTT in stroke incidence. The AUC was determined to be 0.66 for BG and 0.67 for aPTT (Figures 2 and 3). The sensitivity, specificity, and AUC for the two variables of BG and aPTT at the best cut-off for stroke prediction were calculated and are presented in (Table 4).

Table4. AUC[1], the best cut-off, sensitivity, and specificity of laboratory tests for predicting stroke in Covid-19 patients

	AUC	Cut-off	Sensitivity	Specificity
Bood sugar	0.66	104.5	70.7%	54.4%
aPTT[2]	0.67	30.5	68.3%	52.6%

[1]Area under curve, [2]activated Partial Thromboplastin Time

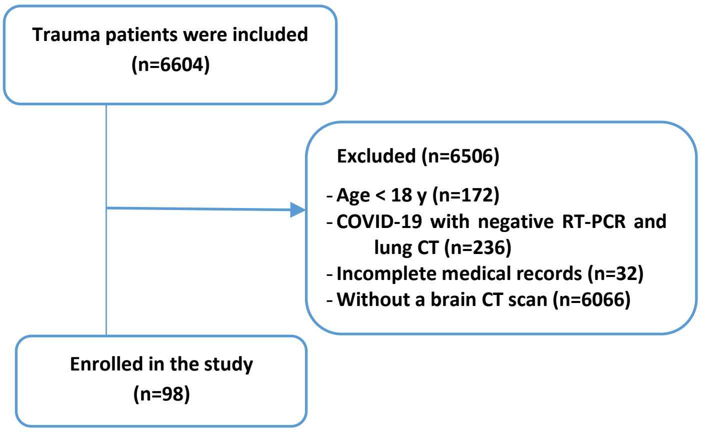

Figure. 1 Flow chart showing enrollment of patients

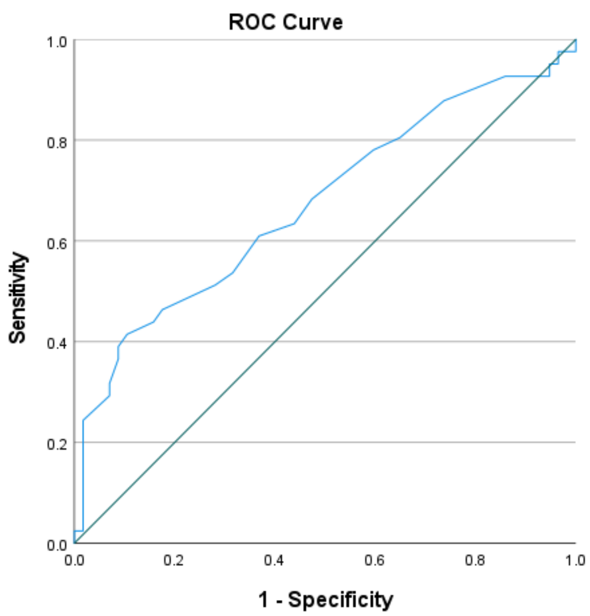

Figure 2. ROC curve of blood sugar for predicting stroke in Covid-19 patients

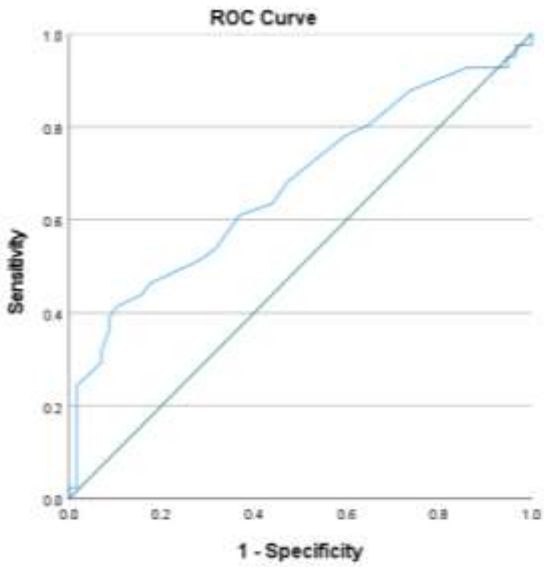

Figure 3. ROC curve of aPTT for predicting stroke in Covid-19 patients

5. Discussion

In the present study, the incidence of acute and new-onset stroke in patients with COVID-19 who were suspected of CNS involvement was 9.18%, while the incidence of these events in one year among all approximately 0.55, of which all were ischemic lesions. The underlying diseases in most of these patients with COVID-19 were diabetes and, subsequently, hypertension.

Female patients with low blood glucose and low aPTT levels exhibited an elevated incidence of ischemic stroke following the onset of the disease.

While the primary target organ of the virus is the respiratory system, the virus can potentially affect other vital organs, including the brain, causing significant damage. Therefore, it is imperative to consider the occurrence of stroke in these patients. Ischemic stroke, a recognized neurological complication of the disease, is associated with high mortality and disability (11). The pathophysiology of ischemic stroke is multifactorial, involving three leading causes: endothelial damage, hyperviscosity, vascular stasis, and conditions that cause hyper coagulopathy (12-15). The spike protein of the SARS-CoV-2 virus has been observed to bind strongly to the human ACE-2 receptor, potentially inducing endothelial cell apoptosis and neuronal damage (16). Furthermore, hypoxemia has been associated with increased blood viscosity and the activation of hypoxia-related genes, which can mediate coagulation and fibrinolysis, ultimately leading to thrombotic events (17). Patients with COVID-19 who have stroke have a poorer outcome compared with patients without stroke (18,19).

Hypertension has been identified as a significant contributing factor to stroke in severe cases of Coronavirus Disease 2019 (20-22). A meta-analysis conducted by Luo et al. in 2022 on 26,691 patients with the disease revealed a prevalence of ischemic stroke of 2%. The prevalence of hypertension and diabetes in these patients was reported to be 66% and 40%, respectively (23). Avola et al. reported four patients with COVID-19 who were over 73 years of age and presented with stroke early in their illness (24). In another study, Mao et al. showed that 5.7% of patients with severe infection developed delayed cerebrovascular disease (25). Li et al. reported an incidence of stroke in severe cases of 5%, citing comorbidities including hypertension, diabetes, coronary artery disease, and previous cerebrovascular disease (26). Oxley et al. reported five cases of large-vessel stroke in patients under 50 years of age with severe COVID-19. Two of the patients had no medical history or risk factors for stroke, one had hyperlipidemia and hypertension, one had undiagnosed diabetes, and the fifth had diabetes and a history of previous stroke (27). Beyrouti et al. reported six patients with acute ischemic stroke and large-vessel occlusion due to COVID-19. Three patients exhibited multi-regional infarction, two patients experienced concurrent venous thrombosis, and two patients had ischemic stroke despite undergoing anticoagulant therapy (28). Janes et al. reported a stroke incidence rate of 1.5% in patients with COVID-19. The study identified independent risk factors for stroke in patients with COVID-19, including disease severity and ischemic heart disease, as well as obesity. However, diabetes was not identified as a risk factor for stroke following COVID-19. In patients with COVID-19, 32.1% of strokes were likely caused by infection-related coagulation, while 67.9% were likely caused by viral infection (29). It was observed that among 98 COVID-19 patients suspected of having brain damage, 9.18% and 6604 COVID-19 patients, 0.55% developed acute stroke during the disease, all of which were ischemic lesions. In terms of underlying diseases, the most common underlying disease was diabetes (26.66%), followed by hypertension (13.33%).

Gender plays a significant role in ischemic stroke, and stroke severity and outcome in women differ from men. Primary outcomes in women are associated with higher in-hospital mortality, longer LOS, and greater disability (30, 31). Our study showed that women with COVID-19 who develop acute stroke during their illness have more than twice the risk of developing acute ischemic stroke compared with men.

As previously stated, diabetes is a risk factor for stroke, and this is also true in patients with the novel COVID-19 (32-45). In addition to the deleterious role of hypoglycemia, it should be noted that COVID-19 can be an independent risk factor for ischemic stroke, especially in cases of severe disease, due to increased inflammation, coagulopathy, and pro-inflammatory pathogenic mechanisms that activate a prothrombotic state (46,47). Conversely, older diabetics who develop stroke are at increased risk for hypoglycemia (48). Furthermore, cognitive and functional impairments have been demonstrated to be strongly associated with an elevated risk of severe hypoglycemia (49). Consequently, patients diagnosed with COVID-19 are likely to have a higher risk of stroke compared to those not infected with the disease (50). Therefore, the role of blood glucose in patients with COVID-19 as a predisposing factor for ischemic stroke cannot be overstated. This study demonstrated that patients with hypoglycemia at the time of admission may exhibit a higher incidence of ischemic stroke, with a 10-fold increase in the risk of ischemic stroke for every 10 units decrease in BG.

In addition to the established role of baseline blood glucose as a risk factor for stroke in patients with COVID-19, it is imperative to acknowledge the heightened risk of both coagulopathy and thrombotic events in these patients (51). Qiu et al. substantiated the association of coagulopathy with severe COVID-19 in their study. They observed that coagulation functions are impaired in patients with COVID-19 and that an excessive coagulation state in patients may result in a heightened risk of stroke (52).In a review article emphasizing the hypercoagulable role of the COVID-19 virus, coagulation laboratory tests that may serve a predictive role for thrombotic events were examined, but the results of different studies were not consistent (53). CUI et al. introduced the role of aPTT and D-dimer as suitable factors to identify high-risk groups for thromboembolic events (54). Fraissé et al. noted that patients at higher risk of thrombotic events had lower PT and higher D-dimer compared to patients without these events (55). Statsenko et al. described the role of aPTT as highly effective in predicting the severity of COVID-19 disease. In their study, they demonstrated that patients admitted to the ICU with lower aPTT had a higher mortality risk compared to patients discharged from the hospital. They reported an area under the curve (AUC) of 0.64 with a cut-off of 39.9 at admission, with a sensitivity of 51% and a specificity of 73%, as the prognostic role of aPTT in these patients (56). In contrast, this study revealed that for every one-unit decrease in aPTT during admission of patients with COVID-19, the mortality risk of these patients who had acute stroke increased by 8%. Furthermore, this study obtained an area under the curve (AUC) of 0.67 with a cut-off of 30.5 for aPTT at admission, yielding a sensitivity of 68.3% and a specificity of 52.6% that further studies in this area are needed to confirm this.

Limitations

The present study was subject to several limitations. The single-center design of the study was a salient limitation; however, this constraint was mitigated by the fact that the hospital in question played a pivotal role in treating patients with COVID-19 during the outbreak. It was designated as the provincial referral hospital and consequently admitted many patients. The severity of COVID-19 infection (mild, moderate, severe, intensive care unit admission) was not included. The study's inability to thoroughly examine patients' clinical symptoms and its exclusive focus on diagnostic tests were additional limitations. The study's limited sample size and failure to yield significant outcomes represent additional limitations. Moreover, the inability to examine the prognostic significance of other inflammatory factors, such as interleukins, further constrained the study's scope. Due to the extensive array of laboratory tests and prognostic studies conducted on COVID-19, it was not feasible to include all of them in this analysis.

6. Conclusion

The incidence of acute stroke in patients with COVID-19 is relatively uncommon, occurring in 0.55% of all patients and 9.81% of patients with CNS symptoms, most frequently in diabetic and hypertensive patients. Female patients with low blood glucose and low aPTT levels at the time of hospital admission were associated with an increased incidence of ischemic stroke following COVID-19.

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Availability of data and materials: The dataset presented in the study is available on request from the corresponding author during submission or after its publication.

Conflicts of interests: The authors declared no potential conflicts of interest.

Consent for publication: Not applicable.

Ethics approval and consent to participate: The Kerman University of Medical Sciences ethics committee approved the study protocol with the number of IR.KMU.AH.REC.1403.040, which complies with the declaration of Helsinki.

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Author contributions: Study concept, design, and supervision: M.T, S.AS, M.A. Acquisition of data: M.A. Analysis and interpretation of data: M.T. Drafting of the manuscript, technical and material support: M.T, S.AS, M.A.

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