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

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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

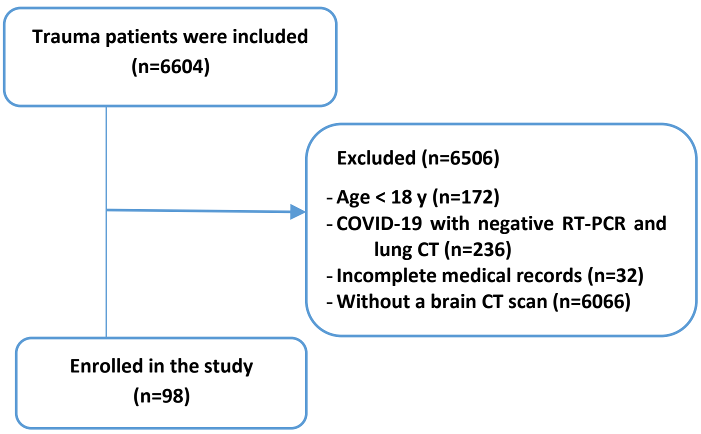

Figure. 1 Flow chart showing enrollment of patients

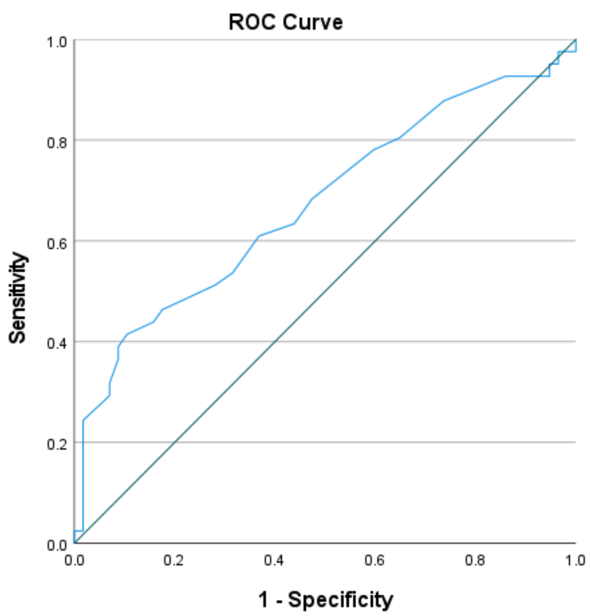

Figure 2. ROC curve of blood sugar for predicting stroke in Covid-19 patients

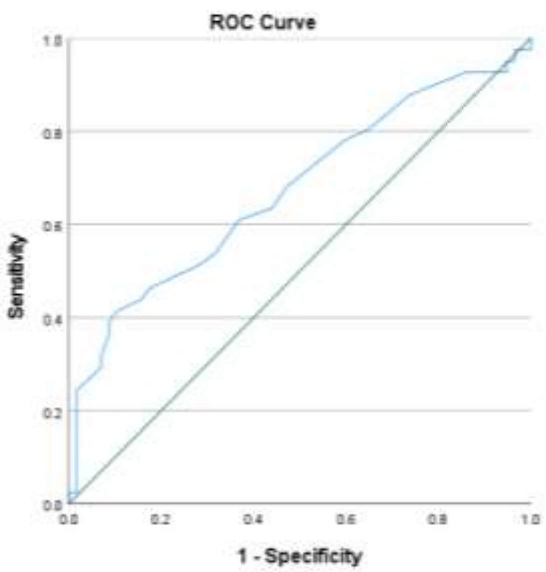

Figure 3. ROC curve of aPTT for predicting stroke in Covid-19 patients

3. 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.

4. 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.

References

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020; 28;395(10229):1054-62. https://doi.org/10.1016/S0140-6736(20)30566-3 PMid:32171076
2. Gąsecka A, Borovac JA, Guerreiro RA, Giustozzi M, Parker W, Caldeira D, Chiva-Blanch G. Thrombotic complications in patients with COVID-19: pathophysiological mechanisms, diagnosis, and treatment. Cardiovascular drugs and therapy. 2021;35:215-29. https://doi.org/10.1007/s10557-020-07084-9 PMid:33074525 PMCid:PMC7569200
3. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, Kucher N, Studt JD, Sacco C, Bertuzzi A, Sandri MT. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thrombosis research. 2020; 1;191:9-14. https://doi.org/10.1016/j.thromres.2020.04.024 PMid:32353746 PMCid:PMC7177070
4. Ahmad I, Rathore FA. Neurological manifestations and complications of COVID-19: A literature review. Journal of Clinical Neuroscience. 2020; 1;77:8-12 https://doi.org/10.1016/j.jocn.2020.05.017PMid: 32409215 PMCid:PMC7200361
5. Al-Ani F, Chehade S, Lazo-Langner A. Thrombosis risk associated with COVID-19 infection. A scoping review. Thrombosis research. 2020; 1;192:152-60. https://doi.org/10.1016/j.thromres.2020.05.039 PMid:32485418 PMCid:PMC7255332
6. Antunez Muinos PJ, Lopez Otero D, Amat-Santos IJ, Lopez Pais J, Aparisi A, Cacho Antonio CE, Catalá P, Gonzalez Ferrero T, Cabezón G, Otero Garcia O, Gil JF. The COVID-19 lab score: an accurate dynamic tool to predict in-hospital outcomes in COVID-19 patients. Scientific Reports. 2021; 30;11(1):9361. https://doi.org/10.1038/s41598-021-88679-6PMid:33931677 PMCid:PMC8087839
7. Xie J, Hungerford D, Chen H, Abrams ST, Li S, Wang G, Wang Y, Kang H, Bonnett L, Zheng R, Li X. Development and external validation of a prognostic multivariable model on admission for hospitalized patients with COVID-19. MedRxiv. 2020, 30:2020-03. https://doi.org/10.1101/2020.03.28.20045997
8. Lu J, Hu S, Fan R, Liu Z, Yin X, Wang Q, Lv Q, Cai Z, Li H, Hu Y, Han Y. ACP risk grade: a simple mortality index for patients with confirmed or suspected severe acute respiratory syndrome coronavirus 2 disease (COVID-19) during the early stage of outbreak in Wuhan, China. MedRxiv. 2020; 23:2020-02. https://doi.org/10.2139/ssrn.3543603
9. Zhang S, Guo M, Duan L, Wu F, Hu G, Wang Z, Huang Q, Liao T, Xu J, Ma Y, Lv Z. Development and validation of a risk factor-based system to predict short-term survival in adult hospitalized patients with COVID-19: a multi-center, retrospective, cohort study. Critical Care. 2020

;24:1-3. https://doi.org/10.1186/s13054-020-03123-xPMid:32678040 PMCid:PMC7364297

10. Macias-Muñoz L, Wijngaard R, González-de la Presa B, Bedini JL, Morales-Ruiz M, Jiménez W. Value of clinical laboratory test for early prediction of mortality in patients with COVID-19: the BGM score. Journal of circulating biomarkers. 2021;10:1. https://doi.org/10.33393/jcb.2021.2194PMid:33717357 PMCid:PMC7890680
11. Norouzi-Barough L, Asgari Khosroshahi A, Gorji A, Zafari F, Shahverdi Shahraki M, Shirian S. COVID-19-induced stroke and the potential of using mesenchymal stem cells-derived extracellular vesicles in the regulation of neuroinflammation. Cellular and Molecular Neurobiology. 2023;43(1):37-46. https://doi.org/10.1007/s10571-021-01169-1 PMid:35025001 PMCid:PMC8755896
12. Sadeghmousavi S, Rezaei N. COVID-19 infection and stroke risk. Reviews in the Neurosciences. 2021;32(3):341-9. https://doi.org/10.1515/revneuro-2020-0066 PMid:33580645
13. . Wang W, Sun Q, Bao Y, Liang M, Meng Q, Chen H, Li J, Wang H, Li H, Shi Y, Li Z. Analysis of risk factors for thromboembolic events in 88 patients with COVID-19 pneumonia in Wuhan, China: a retrospective descriptive report. Medical science monitor: international medical journal of experimental and clinical research. 2021;27:e929708-1. https://doi.org/10.12659/MSM.929708
14. Han H, Yang L, Liu R, Liu F, Wu KL, Li J, Liu XH, Zhu CL. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clinical Chemistry and Laboratory Medicine (CCLM). 2020;58(7):1116-20. https://doi.org/10.1515/cclm-2020-0188 PMid:32172226
15. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, Chen H, Ding X, Zhao H, Zhang H, Wang C. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. New England Journal of Medicine. 2020;382(17):e38. https://doi.org/10.1056/NEJMc2007575 PMCid:PMC7161262
16. Pranata R, Huang I, Lim MA, Wahjoepramono EJ, July J. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19-systematic review, meta-analysis, and meta-regression. Journal of stroke and cerebrovascular diseases. 2020 ; 29(8):104949. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104949 PMCid:PMC7221373
17. Gupta N, Zhao YY, Evans CE. The stimulation of thrombosis by hypoxia. Thrombosis research. 2019;181:77-83. https://doi.org/10.1016/j.thromres.2019.07.013 PMid:31376606
18. Qin C, Zhou L, Hu Z, Yang S, Zhang S, Chen M, Yu H, Tian DS, Wang W. Clinical characteristics and outcomes of COVID-19 patients with a history of stroke in Wuhan, China. Stroke. 2020;51(7):2219-23. https://doi.org/10.1161/STROKEAHA.120.030365 PMid:32466735 PMCid:PMC7282412
19. Ji XY, Ma Y, Shi NN, Liang N, Chen RB, Liu SH, Shi S, Wu GH, Li JK, Chen H, Wang JW. Clinical characteristics and treatment outcome of COVID-19 patients with stroke in China: A multi-center retrospective study. Phytomedicine. 2021;81:153433. https://doi.org/10.1016/j.phymed.2020.153433 PMid:33373925 PMCid:PMC7836955
20. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?. The Lancet respiratory medicine. 2020;8(4):e21. https://doi.org/10.1016/S2213-2600(20)30116-8 PMid:32171062
21. Kreutz R, Algharably EA, Azizi M, Dobrowolski P, Guzik T, Januszewicz A, Persu A, Prejbisz A, Riemer TG, Wang JG, Burnier M. Hypertension, the renin-angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID-19: European Society of Hypertension COVID-19 Task Force Review of Evidence. Cardiovascular research. 2020;116(10):1688-99. https://doi.org/10.1093/cvr/cvaa097 PMid:32293003 PMCid:PMC7184480
22. Lippi G, Wong J, Henry BM. Hypertension and its severity or mortality in Coronavirus Disease 2019 (COVID-19): a pooled analysis. Pol Arch Intern Med. 2020;130(4):304-9. https://doi.org/10.20452/pamw.15272 PMid:32231171
23. Luo W, Liu X, Bao K, Huang C. Ischemic stroke associated with COVID-19: a systematic review and meta-analysis. Journal of Neurology. 2022:1-0.
24. Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S, Glaser A, Elsayegh D. COVID-19 presenting as stroke. Brain, behavior, and immunity. 2020;87:115-9. https://doi.org/10.1016/j.bbi.2020.04.077 PMid:32360439 PMCid:PMC7187846
25. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X. Neurologic manifestations of hospitalized patients with

coronavirus disease 2019 in Wuhan, China. JAMA neurology. 2020;77(6):683-90. https://doi.org/10.1001/jamaneurol.2020.1127 PMid:32275288 PMCid:PMC7149362
26. Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y, Wang D, Mao L, Jin H, Hu B. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Stroke and vascular neurology. 2020;5(3). https://doi.org/10.1136/svn-2020-000431 PMid:32616524 PMCid:PMC7371480
27. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, De Leacy RA, Shigematsu T, Ladner TR, Yaeger KA, Skliut M. Large-vessel stroke as a presenting feature of Covid-19 in the young. New England Journal of Medicine. 2020;382(20):e60. https://doi.org/10.1056/NEJMc2009787 PMid:32343504 PMCid:PMC7207073
28. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, Humphries F, Jäger HR, Losseff NA, Perry RJ, Shah S. Characteristics of ischaemic stroke associated with COVID-19. Journal of Neurology, Neurosurgery & Psychiatry. 2020;91(8):889-91. https://doi.org/10.1136/jnnp-2020-323586 PMid:32354768 PMCid:PMC7231545
29. Janes F, Sozio E, Gigli GL, Ripoli A, Sbrana F, Kuris F, Nesi L, Semenzin T, Bertolino G, Deana C, Bagatto D. Ischemic strokes in COVID-19: risk factors, obesity paradox, and distinction between trigger and causal association. Frontiers in Neurology. 2023;14:1222009. https://doi.org/10.3389/fneur.2023.1222009 PMid:37592943 PMCid:PMC10428626
30. Guo J, Guan TJ, Liu YL, Chao BH, Wang LD. Gender-specific factors of ischemic stroke among atrial fibrillation patients. Zhonghua yu Fang yi xue za zhi [Chinese Journal of Preventive Medicine]. 2019;53(11):1136-40.
31. Hu J, Lin JH, Jiménez MC, Manson JE, Hankinson SE, Rexrode KM. Plasma estradiol and testosterone levels and ischemic stroke in postmenopausal women. Stroke. 2020;51(4):1297-300. https://doi.org/10.1161/STROKEAHA.119.028588 PMid:32078496 PMCid:PMC7159036
32. Magdy Beshbishy A, Oti VB, Hussein DE, Rehan IF, Adeyemi OS, Rivero-Perez N, Zaragoza-Bastida A, Shah MA, Abouelezz K, Hetta HF, Cruz-Martins N. Factors behind the higher COVID-19 risk in diabetes: a critical review. Frontiers in Public Health. 2021;9:591982. https://doi.org/10.3389/fpubh.2021.591982 PMid:34307267 PMCid:PMC8292635
33. Aziz F, Aberer F, Bräuer A, Ciardi C, Clodi M, Fasching P, Karolyi M, Kautzky-Willer A, Klammer C, Malle O, Pawelka E. COVID-19 in-hospital mortality in people with diabetes is driven by comorbidities and age-propensity score-matched analysis of Austrian national public health institute data. Viruses. 2021;13(12):2401. https://doi.org/10.3390/v13122401 PMid:34960670 PMCid:PMC8705658
34. Gogu AE, Motoc AG, Stroe AZ, Docu Axelerad A, Docu Axelerad D, Pârv F, Munteanu G, Dan F, Jianu DC. Clinical spectrum and neuroimagistic features in hospitalized patients with neurological disorders and concomitant coronavirus-19 infection. Brain Sciences. 2021; 11(9):1138. https://doi.org/10.3390/brainsci11091138 PMid:34573160 PMCid:PMC8466125
35. Gupta RD, Atri A, Mondal S, Bhattacharjee A, Garai R, Hazra AK, Choudhury B, Dutta DS, Lodh M, Ganguly A. Characterizing progressive beta-cell recovery after new-onset DKA in COVID-19 provoked A-β+ KPD (ketosis-prone diabetes): A prospective study from Eastern India. Journal of Diabetes and its Complications. 2022;36(3):108100. https://doi.org/10.1016/j.jdiacomp.2021.108100PMid:34916147 PMCid:PMC8656268
36. Mondal S, DasGupta R, Lodh M, Gorai R, Choudhury B, Hazra AK, Ganguly A. Predictors of new-onset diabetic ketoacidosis in patients with moderate to severe COVID-19 receiving parenteral glucocorticoids: A prospective single-center study among Indian type 2 diabetes patients. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2021;15(3):795-801. https://doi.org/10.1016/j.dsx.2021.03.022 PMid:33839639 PMCid:PMC8004476
37. Jacobi J, Bircher N, Krinsley J, Agus M, Braithwaite SS, Deutschman C, Freire AX, Geehan D, Kohl B, Nasraway SA, Rigby M. Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. Critical care medicine. 2012 ; 40(12):3251-76. https://doi.org/10.1097/CCM.0b013e3182653269 PMid:23164767
38. Wang S, Ma P, Zhang S, Song S, Wang Z, Ma Y, Xu J, Wu F, Duan L, Yin Z, Luo H. Fasting blood glucose at admission is an independent predictor for 28-day mortality in patients with COVID-19 without previous diagnosis of diabetes: a multi-center retrospective study. Diabetologia. 2020;63(10):2102-11. https://doi.org/10.1007/s00125-020-05209-1 PMid:32647915 PMCid:PMC7347402
39. Fadini GP, Morieri ML, Boscari F, Fioretto P, Maran A, Busetto L, Bonora BM, Selmin E, Arcidiacono G, Pinelli S, Farnia F. Newly-diagnosed diabetes and admission hyperglycemia predict COVID-19 severity by aggravating respiratory

deterioration. Diabetes research and clinical practice. 2020;168:108374. https://doi.org/10.1016/j.diabres.2020.108374 PMid:32805345 PMCid:PMC7428425

40. Mondal S, DasGupta R, Lodh M, Garai R, Choudhury B, Hazra AK, Mondal A, Ganguly A. Stress hyperglycemia ratio, rather than admission blood glucose, predicts in-hospital mortality and adverse outcomes in moderate-to-severe COVID-19 patients, irrespective of pre-existing glycemic status. Diabetes Research and Clinical Practice. 2022;190:109974. https://doi.org/10.1016/j.diabres.2022.109974 PMid:35809688 PMCid:PMC9259189
41. Wang J, Chen J. Infection with COVID-19 is a risk factor for poor prognosis in patients with intracranial hemorrhage: a prospective observational cohort study. Medicine. 2023; 102(45):e35716. https://doi.org/10.1097/MD.0000000000035716PMid:37960736 PMCid:PMC10637543
42. Shi Y, Zheng Z, Wang P, Wu Y, Liu Y, Liu J. Development and validation of a predicted nomogram for mortality of COVID-19: a multi-center retrospective cohort study of 4,711 cases in multiethnic. Frontiers in Medicine. 2023;10:1136129. https://doi.org/10.3389/fmed.2023.1136129 PMid:37724179 PMCid:PMC10505438
43. Borzì V, Frasson S, Gussoni G, Di Lillo M, Gerloni R, Augello G, Gulli G, Ceriello A, Solerte B, Bonizzoni E, Fontanella A. Risk factors for hypoglycemia in patients with type 2 diabetes, hospitalized in internal medicine wards: findings from the FADOI-DIAMOND study. Diabetes Research and Clinical Practice. 2016;115:24-30. https://doi.org/10.1016/j.diabres.2016.01.020 PMid:27242119
44. Norris T, Razieh C, Yates T, Zaccardi F, Gillies CL, Chudasama YV, Rowlands A, Davies MJ, McCann GP, Banerjee A, Docherty AB. Admission blood glucose level and its association with cardiovascular and renal complications in patients hospitalized with COVID-19. Diabetes Care. 2022;45(5):1132-40. https://doi.org/10.2337/dc21-1709 PMid:35275994 PMCid:PMC9174963
45. Yu TM, Lin CL, Chang SN, Sung FC, Kao CH. Increased risk of stroke in patients with chronic kidney disease after recurrent hypoglycemia. Neurology. 2014;83(8):686-94. https://doi.org/10.1212/WNL.0000000000000711 PMid:25031280
46. Katz JM, Libman RB, Wang JJ, Filippi CG, Sanelli P, Zlochower A, Gribko M, Pacia SV, Kuzniecky RI, Najjar S, Azhar S. COVID-19 severity and stroke: correlation of imaging and laboratory markers. American Journal of Neuroradiology. 2021;42(2):257-61. https://doi.org/10.3174/ajnr.A6920 PMid:33122216 PMCid:PMC7872163
47. Moin AS, Al-Qaissi A, Sathyapalan T, Atkin SL, Butler AE. Platelet protein-related abnormalities in response to acute hypoglycemia in type 2 diabetes. Frontiers in Endocrinology. 2021;12:651009. https://doi.org/10.3389/fendo.2021.651009 PMid:33859620 PMCid:PMC8043308
48. Akirov A, Amitai O, Masri-Iraqi H, Diker-Cohen T, Shochat T, Eizenberg Y, Shimon I. Predictors of hypoglycemia in hospitalized patients with diabetes mellitus. Internal and emergency medicine. 2018;13:343-50. https://doi.org/10.1007/s11739-018-1787-0 PMid:29340912
49. Lee AK, Lee CJ, Huang ES, Sharrett AR, Coresh J, Selvin E. Risk factors for severe hypoglycemia in black and white adults with diabetes: the Atherosclerosis Risk in Communities (ARIC) study. Diabetes Care. 2017;40(12):1661-7. https://doi.org/10.2337/dc17-0819 PMid:28928117 PMCid:PMC5711330
50. Kapoor R, Timsina LR, Gupta N, Kaur H, Vidger AJ, Pollander AM, Jacobi J, Khare S, Rahman O. Maintaining blood glucose levels in range (70-150 mg/dL) is difficult in COVID-19 compared to non-COVID-19 ICU patients-a retrospective analysis. Journal of Clinical Medicine. 2020 ;9(11):3635. https://doi.org/10.3390/jcm9113635 PMid:33198177 PMCid:PMC7697842
51. Klok FA, Kruip MJ, Van der Meer NJ, Arbous MS, Gommers DA, Kant KM, Kaptein FH, van Paassen J, Stals MA, Huisman MV, Endeman H. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thrombosis research. 2020 July 1;191:148-50. https://doi.org/10.1016/j.thromres.2020.04.041 PMid:32381264 PMCid:PMC7192101
52. Qiu F, Wu Y, Zhang A, Xie G, Cao H, Du M, Jiang H, Li S, Ding M. Changes of coagulation function and risk of stroke in patients with COVID-19. Brain and Behavior. 2021;11(6):e02185. https://doi.org/10.1002/brb3.2185 PMid:33998177 PMCid:PMC8209810
53. Warkentin TE, Kaatz S. COVID-19 versus HIT hypercoagulability. Thrombosis research. 2020;196:38-51. https://doi.org/10.1016/j.thromres.2020.08.017PMid:32841919 PMCid:PMC7416717
54. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe

novel coronavirus pneumonia. Journal of Thrombosis and Haemostasis. 2020;18(6):1421-4. https://doi.org/10.1111/jth.14830 PMid:32271988 PMCid:PMC7262324

55. Fraissé M, Logre E, Pajot O, Mentec H, Plantefève G, Contou D. Thrombotic and hemorrhagic events in critically ill COVID-19 patients: a French monocenter retrospective study. Critical Care. 2020;24:1-4. https://doi.org/10.1186/s13054-020-03361-z https://doi.org/10.1186/s13054-020-03025-y PMid:32487122 PMCid:PMC7265664

56. Statsenko Y, Al Zahmi F, Habuza T, Neidl-Van Gorkom K, Zaki N. Prediction of COVID-19 severity using laboratory findings on admission: informative values, thresholds, ML model performance. BMJ open. 2021; 1;11(2):e044500. https://doi.org/10.1136/bmjopen-2020-044500 PMid:33637550 PMCid:PMC7918887