

THE DIFFERENCE IN D-DIMER VALUES BETWEEN PATIENTS WITH ACUTE ISCHEMIC STROKE WITH AND WITHOUT COVID-19 DISEASE

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Abstract

Background: Latest in the wake of the SARS-COV-2 pandemic, many studies point out the deranged hemostatic function in patients with acute ischemic stroke (AIS) due of the Covid-19; however, reports of high levels of D-dimers in cases of AIS and Covid-19 were not without conflicting findings. Aim: To explore the difference in D-dimer levels between patients with proven AIS and Covid-19 and AIS patients without Covid-19.

Material and methods: The present study was a descriptive as well as a comparative study. Due to the coronavirus pandemic – Covid-19, during the inclusion period, due to hospital protocol all patients with the clinical signs of an acute stroke that are hospitalized for diagnosis and treatment undergo native computed tomography of the brain, electrocardiography and laboratory work-up with complete blood count, metabolic panel, markers of hemostasis and testing for SARS-CoV-2 infection.

Results: Nine AIS patients with and twenty-four without Covid-19 met the inclusion criteria. Twenty-six patients with AIS (78.79%) had elevated D-dimer levels (>500 ngr/mL), among them eight patients (30.77%) had confirmed AIS/Covid-19. A not significantly higher D-dimer levels was found in positive for SARS-CoV-2 versus negative for SARS-CoV-2 (2850.25 [610-6530] ngr/mL versus 1430.67 [509-4090] ngr/mL, P = 0.138).

Conclusion: It is worth noting that the results suggest the associations between D-dimer levels and AIS and Covid-19 disease only, but in cases diagnosed simultaneously with both diseases (AIS/Covid-19) that suggest association was not significant. These results demonstrated that more attention is warranted when interpreting elevated D-dimer levels in AIS patients with and without Covid-19.

Keywords: ischemic stroke, Covid-19, D-dimer levels, comparative analysis

1. Introduction

Acute ischemic stroke (AIS) can occur from a wide array of possible etiologies. Initiation and progression of AIS involve disorders in the coagulation cascade, fibrinolysis system, inflammatory response, lipid metabolism, blood pressure homeostasis, and a hypercoagulability state [Spence et al, 2020]. The disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is named Coronavirus disease 2019 (Covid-19) by World Health Organization and is characterized by clinical manifestations ranging from asymptomatic and subclinical infection to severe hyperinflammatory syndrome and death [Cummings et al, 2020]. The covid-19 disease itself is a risk factor for stroke, and a systematic review and meta-analysis reported it occurred in 1.4% of Covid-19 infections [Nannoni et al, 2021]. Elevated levels of D-dimers have been reported in patients with AIS [Kataoka et al, 2000; Zi et al, 2014; Zhang et al, 2020], in patients with Covid-19 [Zhang et al, 2020], and in patients with AIS and Covid-19 [Nannoni et al, 2021; Yaghi et al, 2020]; however, reports of high levels in D-dimers in cases of AIS and Covid-19 are not without conflicting findings. Yaghi with colleagues [Yaghi et al, 2020] suggests that high levels of D-dimers are more common in patients with stroke and that hypercoagulability may be the basis of a large proportion of strokes in patients with SARS-CoV-2 infection. According to an international panel [Qureshi et al, 2020], COVID-19 patients who have a stroke were older and had hypertension and higher D-dimer levels. Latest in the wake of the SARS-COV-2 pandemic, many studies point out the deranged one unifying factor that seems to exist

among the association between AIS and SARS-CoV-2 infection is elevated D-dimer levels among SARS-CoV-2 infected patients experiencing AIS, suggesting activation of the coagulation and innate immune system [Yaghi et al, 2020]. Knowing that with the increase in hospital treatment of Covid-19 patients the number of hospitalized with stroke decreased in the neurology department of Clinical Hospital Tetovo [Bajpam, 2020] *the study aimed to prove the influence of D-dimer and its concentration in AIS in the presence or absence of SARS-COV-2 infection.*

2. Material and methods

2.1. Study design and participants

The neurology department is prioritized in diagnosing and treating neurological illness in Clinical Hospital Tetovo in Tetovo, a city in the northwest of North Republic of Macedonia, with a population of more than 200 thousand people where the first case of neurological symptoms with SARS-CoV-2 infection was detected in 2020 [Bajpam, 2020]. Therefore, this study is the first description of the difference in levels of D-dimer measured in admission in AIS patients with and without Covid-19 disease. The investigation comprised all consecutive patients with the clinical signs of an acute stroke according to the World Health Organization criteria [Hatano, 1976] without known cerebrovascular incidents and symptoms of an acute respiratory infection in anamnesis who were admitted to the neurology department between July 1, 2020, and July 31, 2021. A total of forty first-ever hospitalized ischemic stroke patients over a year were involved, however, thirty-three patients met the inclusion criteria for the study, and their records analyzed that is 25% of the total of hospitalized patients for 12 months. Due to the coronavirus pandemic – Covid 19 during the inclusion period, per hospital protocol all patients with the clinical signs of an acute stroke that are hospitalized for diagnosis and treatment undergo native computed tomography (CT) of the brain, electrocardiography, and laboratory work-up with complete blood count, metabolic panel and markers of hemostasis and testing for SARS-CoV-2 infection in the first 12 hours of admission.

2.2 Eligibility criteria

Eligibility inclusion criteria were the patients aged 18-90 years; admitted to hospital within the last 3 days; without either fever ($\geq 37.5^{\circ}\text{C}$); cough or sore throat; with a diagnosed AIS based on neurological examination and computed tomography findings without a history of previous stroke and/or Covid 19 disease in a personal history but in hospital tested for SARS-CoV-2 infection and during admission were analyzed their concentrations of D-dimer. Patients with previous stroke or patients who lack results of laboratory examination, without hospital tested for SARS-CoV-2 infection and D-dimer testing upon admission were excluded.

2.3 Study sample and data extraction

Data were extracted by the author and the present study was a descriptive as well as a comparative study. In this study, samples were enrolled and analyzed collected routinely on admission demographic and clinical data, laboratory parameters, computed tomography imaging findings, and medical records of elective hospitalized patients with confirmed AIS. The blood samples for laboratory tests were collected on admission. The laboratory method for D-dimer assay was not described in the written report from the Center for Transfusion Medicine Tetovo, D-dimer reference range (0-500 ngr/mL). The case ascertainment for AIS is done by clinical and neurological examination and the diagnosis of AIS is confirmed by a CT scan of the head. Also, routinely at admission, all patients were physically examined for Covid 19 related symptoms

and their vital signs (e.g., temperature, blood pressure, pulse rate, oxygen saturation, and respiratory rate) were recorded. The nasopharyngeal swab was taken in an isolated hospital room and tested in a public health laboratory that is accredited for testing for SARS-CoV-2. The diagnosis of Covid 19 was determined with a least one positive result of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay for SARS-CoV-2. Based on RT-PCR test results, assessed patients with confirmed AIS were grouped into two groups (group 1, patients without Covid 19; group 2, patients with Covid 19). All asymptomatic patients who tested positive for SARS-CoV-2 on RT-PCR were isolated and treated in designated Covid-19 centers at the hospital. As doesn't require additional sampling of blood (as the analyses are in the hospital protocol) and the records of each hospitalized patient were checked for confirmation of the diagnosis of AIS, defined as a diagnosis of AIS with or without Covid-19 on discharge, and the informed consent was not required.

2.4 Statistical analyses

Statistical analysis was performed using SPSS 17.0. Group comparisons were made using the T-test to determine if there is a significant difference between the means of the two groups. Demographic and laboratory data were expressed as mean \pm SD. $P = 0.05$ was considered statistically significant. D-dimer was defined as a categorical variable in the analysis, and levels of ≤ 500 ngr/mL and ≥ 500 ngr/mL were chosen.

3. Results

Initially, for the specified period were included 40 patients with confirmed AIS (69.76 ± 8.549 ; 49-86 years), 22 females (68.227 ± 8.417 ; 49-83 years), 18 males (71.667 ± 8.561 ; 55-86 years), $p = 0.963$ $t = -1.274$ $df = 38$]. From them, seven patients (71.57 ± 5.740 ; 65-79 years), 4 females (73.75 ± 6.021 ; 66-79 years), 3 male (68.67 ± 4.725 ; 65-74 years) were without finding for test for the SARS-CoV-2 and were excluded from the study. This analysis included a total of 33 patients with confirmed AIS divided into two groups (twenty-four into group 1, patients without Covid-19; nine into group 2, patients with Covid-19) with a mean age of 69.39 years (SD = 9.059; 49-86 years). Overall, 18 (54.55%) patients were female (67.00 ± 8.506 ; 49-83 years), and 15 (45.45%) patients were male (72.27 ± 9.138 ; 55-86 years). There was no significant difference between the age and sex distribution of the two groups. Patients with confirmed AIS with and without Covid-19 were similar concerning to age (72.00 ± 8.352 and 68.42 ± 9.287 years, respectively) and gender (female/male: 5/13 and 4/11, respectively). The descriptive statistics of the patient sample is represented in Table 1.

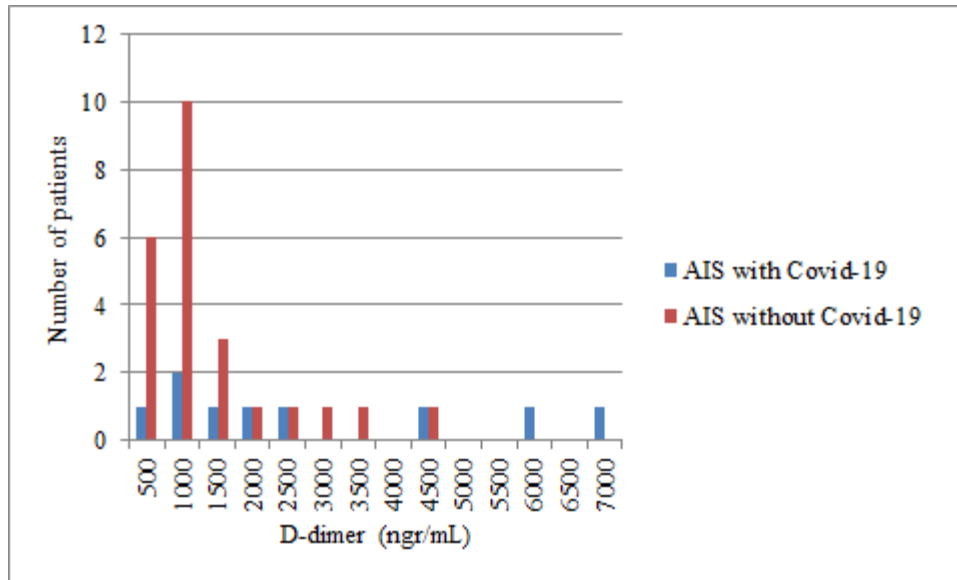
Table 1: Demographic characteristic of the sample*

		Patients with confirmed AIS and with Covid-19	Patients with confirmed AIS and without Covid-19	P
		(n = 9)	(n = 24)	
Age (mean, SD)	All	72.00 \pm 8.352	68.42 \pm 9.287	0.303
	F	67.80 \pm 7.294	66.69 \pm 9.187	0.795
	M	77.25 \pm 6.994	70.45 \pm 9.417	0.173
Gender (n, %)	F	5 (55.56)	13 (54.17)	
	M	4 (44.44)	11 (45.83)	0.303

*Comparisons between AIS patients with and without Covid-19: n, number; AIS, acute ischemic stroke

As follows, the group of male patients with confirmed AIS and Covid-19 was somewhat older (77.25 years versus 70.45 years) than male patients with confirmed AIS and without Covid-19 ($P = 0.173$). Also, the group of female patients with confirmed AIS and Covid-19 was somewhat older (67.80 years versus 66.69

years) than female patients with confirmed AIS and without Covid-19 ($P = 0.795$). The highest D-dimer elevation upon admission was recorded in only two patients with confirmed AIS/Covid-19 disease who were in critical clinical conditions. The distribution of relative frequency of AIS diagnosis by D-dimer range based on RT-PCR test results (patients with and without Covid-19) is shown in Figure 1.



*AIS, acute ischemic stroke

Figure 1: Relative frequency of AIS* diagnosis by D-dimer range (ngr/mL) based on RT-PCR test results (patients with and without Covid-19)

In both study groups the value of mean D-dimer level was measured (Table 2).

Table 2: D-dimer value in AIS patients with and without Covid-19

Patients with confirmed AIS and	Descriptive Statistic (D-dimer ngr/mL)			P* - Level
	N	Mean	SD	
with COVID-19	9	2580.22	2.342.184	t = -1.749
without COVID-19	24	1771.88	964.964	p = 0.114

*Independent Samples T-Test

The results indicates that the D-dimer levels (mean) were no significantly ($P = 0.114$) higher in AIS patients with Covid-19 as compared to AIS patients without Covid-19 (2580.22 [420-6530] ngr/mL versus 1771.88 [270-4090] ngr/mL, respectively). Based on D-dimer reference rang (0-500 ngr/mL), patients were grouped into two groups (group 1, patients with normal D-dimer (<500 ngr/mL); group 2, patients with elevated D-dimer values (>500 ngr/mL). Seven of thirty-three (21.21%) assessed patients with confirmed AIS had normal D-dimer levels and only one patient with confirmed AIS with normal D-dimer level was positive for SARS-CoV-2. In group 2, patients with elevated D-dimer values (>500 ngr/mL), twenty-six of thirty-three patients (78.79%) had elevated D-dimer values. From them, eight patients (30.77%) with AIS were positive for SARS-CoV-2 and eighteen patients (69.23%) with AIS were negative for SARS-CoV-2. The comparison of their mean values in D-dimer is shown in Table 3.

Table 3: D-dimer value (>500 ngr/mL) in AIS patients with and without Covid-19

Patients with confirmed AIS and	Descriptive Statistic (D-dimer ngr/mL)			P* - Level
	N	Mean	SD	
with COVID-19	8	2850.25	2349.37	t =-1.646
without COVID-19	18	1430.67	986.47	p = 0.138

**Independent Samples T-Test*

According to the mean D-dimer levels shown in Table 3, the mean D-dimer levels were higher in patients with proven AIS and Covid-19 compared with AIS patients without Covid-19 on hospital stay. However, there is a not significant difference between the means of two groups (1430.67 [509-4090] ngr/mL, P = 0.138 into group 1, patients without Covid-19; 2850.25 [610-6530] ngr/mL into group 2, patients with Covid-19).

4. Discussion

Ischemic stroke and Covid-19 are complex disorders with different etiology [Cummings et al, 2020; Nannoni et al, 2021]. These two distinct diseases have an overlapping feature, such as hypercoagulability [Yaghi et al, 2020]. Our findings were consistent with the results of a previous prospective study that showed that D-dimer levels were elevated in the acute phase of AIS compared with a healthy control population [Zi et al, 2014.]. Elevated D-dimer levels have been reported in a limited number of studies involved in both AIS and Covid-19 patients [Qureshi et al, 2020]. As demonstrated in this study, like AIS patients with Covid-19, the D-dimer levels of most AIS patients without Covid-19 were also elevated. Interestingly, it was worth mentioning that in this study, 21.21% of patients with AIS had lower D-dimer levels (under normal range, 0-500 ngr/mL), among them only one was with positive SARS-CoV-2 test results. D-dimer levels were higher in patients with proven AIS and Covid-19 disease compared with AIS patients without Covid-19 disease, like telling a study [Yaghi et al, 2020]. The diagnostic value of D-dimer levels for thrombus formation in Covid-19 patients is unclear although supported by the concept of coronavirus infection of endothelial cells and hypercoagulability [Varga et al, 2020] or other factors besides a thrombo-inflammatory condition [Jackson et al, 2019], who is responsible for activation of the coagulation system in patients with Covid-19 disease. According to Spence et al., a number of mechanisms are involved in the occurrence of stroke in Covid-19 disease [Spence et al, 2020], and between them is include a hypercoagulability state. It seems likely that anticoagulation will play a substantial role in the management of stroke in Covid-19 disease. The generalized prothrombotic state has been seen in some patients with Covid-19 with activation of the coagulation pathway and elevated D-dimer and fibrinogen being common features [Nannoni et al, 2021]. Yaghi with colleagues [Yaghi et al, 2020] suggests that high levels of D-dimers are more common in patients with stroke and that hypercoagulability may be the basis of a large proportion of strokes in patients with COVID-19 disease. Several studies reported that patients admitted to the hospital with Covid-19 disease experienced thrombotic complications involving the heart, brain, and peripheral vascular system and which mainly led to myocardial infarction, ischemic stroke, and venous thromboembolism [Bikdeli et al, 2020]. Patients with severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection may develop associated arterial and venous thrombotic complications [Piazza et al, 2020]. In a study [Zhang et al, 2020], all critically ill Covid-19 patients recorded elevated levels of markers of hypercoagulability such as D-dimer. Something similar, in this study, only two patients with confirmed AIS/Covid-19 diseases were in critical clinical conditions, and in them were found the highest D-dimer level elevation upon admission.

5. Conclusion

Nowadays, a great challenge in neurology is the hospitalization of a patient with acute ischemic stroke and Covid-19 disease and finding a way or method for prediction and diagnosis of this problem and thus timely placement is very important. Most of the included patients with confirmed AIS and with D-dimer elevation in this study were negative for Covid-19 disease. It is worth noting that the results suggest associations between D-dimer levels and AIS and Covid-19 disease only, but in cases diagnosed simultaneously with both diseases (AIS/Covid-19) that suggests the association statistically was not significant. These results demonstrated that more attention is warranted when interpreting elevated D-dimer levels in AIS patients with and without Covid-19 disease. Due to the small number of patients with confirmed AIS/Covid-19 diseases, it is difficult to tell from these data if D-dimer elevation is related to AIS/Covid-19 diseases and as result cannot support the application of D-dimer in AIS/Covid-19 diseases not just as a diagnostic tool for thrombosis before CT scans of the brain are performed. A larger randomized controlled clinical trial of D-dimer level appears to be warranted to validate these important findings.

Author Agreement

This article is the author's original work, hasn't received prior publication, and isn't under consideration for publication elsewhere.

References

- [1]. Bikdeli B, Madhavan MV, Jimenez D, et al. 2020. Covid-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. *J Am Coll Cardiol*, 75(23), 2950-2973.
- [2]. Bajram Kamberi. 2020. Прв случај на невролошки симптоми со COVID-19 инфекција: приказ на случај. *Vox Medici*, 109, 41-47 (<http://www.lkm.org.mk/VoxMedici/109.pdf>).
- [3]. Cummings MJ., Baldwin MR., Abrams D., Jacobson SD., Mayer BJ., Baloughu EM., et al. 2020. Epidemiology, clinical course, and outcome of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet*, 395 (10239), 1763-70.
- [4]. Hatano S. 1976. *Bull World Health Organ*, 54(5), 541-543.
- [5]. Jackson SP., Darbousset R., Schoenwaelder SM. 2019. Thrombo inflammation: challenges of therapeutically targeting coagulation and other host defense mechanisms. *Blood*, 133, 906-918.
- [6]. Kataoka S., Hirose G., Hori A., Shirakawa T., Saigan T. 2000. Activation of thrombosis and fibrinolysis following brain infarction. *J Neurol Sci*, 181(1-2), 82-88.
- [7]. Nannoni S., de Groot R., Bell S., et al. 2021. Stroke in Covid-19: a systematic review and meta-analysis. *Int J Stroke*, 16, 137-149.
- [8]. Piazza G, Campia U, Hurvitza S, et al. 2020. Registry of arterial and venous thromboembolic complications in patients with Covid-19. *J Am Coll Cardiol*, 76(18), 2060-2072.
- [9]. Qureshi AI., Abd-Allah F., Al-Senani F., Aytac E., Borhani-Haghighi A., Ciccone A., et al. 2020. Management of acute ischemic stroke in patients with COVID-19 infection: report of an international panel. *Am J Emerg Med*, 38(7), 1548.e5-1548.e7.
- [10]. Spence JD., de Freitas GR., Pettigrew LC., Ay H., Liebeskind DS., Kase CS., Del Brutto OH., Hankey GJ., Venketasubramanian N. 2020. Mechanisms of Stroke in COVID-19. *Cerebrovasc Dis*, 49, 451-458.
- [11]. Varga Z, Flammer AJ, Steiger P et al. 2020. Endothelial cell infection and endotheliitis in Covid-19. *Lancet*, 395, 1417-1418.
- [12]. Yaghi S., Ishida K., Torres J., Grory BM., Raz E., Humbert K., et al. 2020. SARS2-CoV-2 and stroke in a New York healthcare system. *Stroke*, 51(17), 2002-2011.
- [13]. Zi WJ, Shuai J. 2014. Plasma D-dimer levels are associated with stroke subtypes and infarction volume in patients with acute ischemic stroke. *PLoS One*, 9(1), e86465.
- [14]. Zhang Y, Cao W, Jiang W, et al. 2020. Profile of natural anticoagulant, coagulant factor and antiphospholipid antibody in critically ill Covid-19 patients. *J Thromb Thrombolysis*, 50(3), 580-586.