ORIGINAL RESEARCH

Evaluation of systemic immune-inflammation index and systemic inflammation response index in the differentiation of acute Ischemic stroke and transient Ischemic attack

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Abstract

Objective

The aim of this study was to examine the levels of hematologic parameters in acute ischemic stroke (AIS) and transient ischemic attack (TIA) and to evaluate the use of Neutrophil/Lymphocyte ratio (NLR), Systemic Immune-Inflammation Index (SII), and systemic inflammation response index (SIRI) in the differentiation of AIS and TIA.

Materials and Methods

Data and hematological results of patients admitted to the emergency department and diagnosed with AIS and TIA were compared retrospectively.

Results

The study included 36 TIA patients (M/F = 15/21) with a mean age of 64.52 ± 15.597 years and 74 AIS patients (M/F = 35/39) with a mean age of 71.91 ± 13.86 years. Laboratory data showed that lymphocyte count ($p = 0.022$) and hemoglobin level ($p = 0.017$) were significantly higher in AIS patients. In addition, monocyte count ($p = 0.001$), neutrophil/lymphocyte ratio (NLR) ($p < 0.001$), CRP level ($p = 0.007$), and SII ($p = 0.001$) and SIRI values (< 0.001) were significantly increased in AIS patients compared to TIA patients.

Conclusion

The results obtained in the present study show that hematologic inflammatory parameters are increased in AIS. NLR, SII and SIRI may provide insight in the differential diagnosis of AIS and TIA.

Keywords: Acute ischemic stroke, Transient ischemic attack, Systemic Immune-Inflammation Index, Systemic inflammation response index, İnflammatory response, Hemorrhage

Introduction

Acute ischemic stroke (AIS) is the leading cause of mortality and morbidity worldwide, and is caused by an acute reduction or complete blockage of blood flow to a part or all of the brain[1]. Adhesion molecules, cytokines, chemokines, and white blood cells play a crucial role in the pathogenesis of tissue damage in cerebral infarction[2]. Transient ischemic attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia without any acute infarction[3]. Symptoms are related to dysfunction of a localized area of the brain and occur transiently as the arterial blockade resolves or as collateral circulation provides adequate perfusion to the ischemic area. Symptoms of TIA typically last less than 1 hour, although they are usually described as lasting less than 24 hours. A clear distinction between the diagnosis of TIA and AIS is crucial because AIS requires urgent treatment.

Automated complete blood count panels provide rapid access to hematological markers of inflammation. Many studies have shown that the levels of hematological parameters are altered in AIS[4,5]. The recently defined Systemic Immune-Inflammation Index (SII), which is calculated using the formula platelet count x neutrophil count/lymphocyte count[6], and the Systemic Inflammation Response Index (SIRI), which is calculated using the formula neutrophil count x monocyte count/lymphocyte count, are two new parameters that show the inflammatory response using data obtained from hematological parameters[7]. These parameters can also be examined in cancers[8,9] and inflammatory diseases[10,11]. Studies suggest that these ratios can be used to predict the phenomenon of no reflow after primary percutaneous coronary intervention[12] and indicate the severity of uveitis[13]. Increased SII indicates an increased neutrophil/monocyte ratio or decreased lymphocyte count and reflects a strong proinflammatory response mediated by neutrophils along with a lymphocyte-mediated anti-inflammatory response. Limited studies have been conducted on determining SII levels in AIS[14,15].

The aim of the present study was to determine the levels of hematological parameters in AIS and TIA and to evaluate the use of NLR, SII, and SIRI in distinguishing AIS from TIA.

Materials and Methods

The current retrospective study was initiated after obtaining approval from the local ethics committee. Patients aged 18 years and older who were admitted to the emergency department of a University hospital within a one-year period and diagnosed with AIS and TIA were included in the study.

Among the patients presenting to the emergency department with new onset neurological symptoms, those with ischemic

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infarct or vascular occlusion detected by cerebral computed tomography angiography and/or diffusion magnetic resonance imaging were diagnosed with AIS. Patients with neurological symptoms and normal diffusion magnetic resonance imaging results were diagnosed with TIA. Patients with active infection, chronic inflammatory disease, blood disease, cancer, previous history of ischemic stroke, hemorrhagic stroke, visit to the emergency department more than 8 hours after the onset of symptoms, Alzheimer's disease, and dementia were excluded. Patients aged 18 years and older who met the inclusion criteria participated in the study. Patient characteristics and laboratory data of the participants were retrieved from electronic databases.

Laboratory measurements

Creatinine (0.6–1.2 mg/dL), C-reactive protein (CRP, 0–0.5 mg/dL), urea (10–50 mg/dL), and glucose (75–115 mg/dL) levels were determined at the biochemistry laboratory of the University hospital using an Advia 2400 Chemistry system (Siemens Diagnostics, Tarrytown, NY, USA). Hematological parameters, including white blood cell count (WBC, 3.8–8.6 103/mm3), hemoglobin (11.1–17.1 mg/dL), hematocrit (HCT, 33%–57%), platelet (140–360 103/mm3), lymphocyte (1.3–3.5 10e3/μL), neutrophils (2.1–6.1 10e3/μL), monocytes (0–0.9 10e3/μL) and eosinophils (0–1.5 10e3/μL) were measured using the Advia 2120i automated analyzer (Siemens, Germany). Plasma prothrombin time (PTT, 10.5–15.5 s.), activated partial thromboplastin time (aPTT, 22–36 s.) and the international normalized ratio (INR, 0.8–1.2) were measured using the Sysmex CS5100 device (Sysmex, Japan).

Statistical analysis

Data were statistically analyzed using SPSS 21.0 (IBM Corporation, Armonk, NY, USA) package program. Kolmogorov-Smirnov and Shapiro-Wilk normality tests were used to evaluate whether continuous variables were normally distributed. Parametric numerical data are expressed as mean ± standard deviation, nonparametric and non-normally distributed numerical data are expressed as median (IQR: interquartile range), and qualitative data as percentage. Mann-Whitney U test was used to compare two independent groups. Chi-Square test (cross-tab) was used to compare categorical variables between groups. Receiver operating characteristic (ROC) curve analysis was carried out to determine whether AIS and TIA could be differentiated using SII. ROC curve analysis results are presented as % specificity, % sensitivity (area under the ROC curve [AUC], p value, 95% Confidence Interval [CI]). $P < 0.005$ was considered statistically significant in all analyses.

Results

The study included 36 TIA patients (Male/Female = 15/21) with a mean age of 64.52 ± 15.597 years and 74 AIS patients (Male/Female = 35/39) with a mean age of 71.91 ± 13.86 years. No significant difference could be identified in the gender distribution between the two groups ($p = 0.578$); however, AIS patients were found to be significantly older than the TIA patients ($p = 0.015$). Laboratory data showed that lymphocyte count ($p = 0.022$) and hemoglobin levels ($p = 0.017$) were significantly higher in the AIS patients. In addition, the monocyte count ($p = 0.001$), neutrophil/lymphocyte ratio (NLR) ($p < 0.001$), CRP levels ($p = 0.007$), and SII values ($P = 0.001$) were significantly higher in the AIS patients compared to the TIA patients. The laboratory parameters of the patients are shown in Table 1.

A ROC curve analysis was carried out to determine whether NLR, SII, and SIRI values could be used to distinguish between AIS and TIA patients. We observed a sensitivity of 58.11% and specificity of 80.56% when the cut off value of NLR was >2.60, a sensitivity of 44.59% and specificity of 94.44% when the cut-off value of SII was >935.78, and a sensitivity of 56.76% and specificity of 83.33% when the cut-off value of SIRI was >1.74 (Figure 1 and Table 2).

Discussion

In the present study, NLR, SII, and SIRI were found to be significantly higher in patients admitted to the emergency department and diagnosed with AIS, compared to patients diagnosed with TIA. The two main parameters in the pathophysiology of stroke are hemorrhage and ischemia. Hemorrhage is characterized by the presence of blood pressing on the brain parenchyma and adjacent parenchyma, while ischemia is characterized by an inadequate blood supply that fails to meet the oxygen and nutrient needs of the brain tissue[16]. Blockage of a cerebral artery and the resultant of lack of oxygen, glucose, and lipids can lead to necrosis of the cerebral parenchyma. Multiple mechanisms, including excitotoxicity, oxidative stress and inflammation can be implicated in ischemia-induced brain injury[2,17]. Macrophages, microglia, and neutrophils in the systemic circulation are affected by ischemia in the brain. It has been reported that neutrophils reach the brain parenchyma 30 minutes to several hours after ischemia-induced damage, peak in 3 days, and then gradually decrease.

Neutrophils can cause brain damage because they can induce the generation and release of free oxygen radicals[18]. Unlike neutrophils and monocytes, some lymphocytes can play a protective role in the inflammatory response after AIS by regulating and inhibiting the local inflammatory response[19]. Lymphocyte (but not neutrophil) levels are known to be decreased after ischemic stroke. Thus, the neutrophil-to-lymphocyte ratio can increase after stroke and this has been found to be associated with higher mortality and infarct size[20,21]. Peripheral monocytes and neutrophils may function as a source of matrix metalloproteinase-9, which can cause symptomatic deterioration[22]. Tissue damage due to inflammation plays a fundamental role in the pathophysiology of AIS, whereas TIA is defined as a transient episode of ischemia-induced neurological dysfunction in the brain, spinal cord, or retina without acute infarction or tissue damage. We observed that inflammation parameters were higher in AIS compared to TIA.

Although their pathophysiology are highly distinct, AIS and TIA have a similar clinical presentation. The use of laboratory parameters in the differentiation of AIS and TIA in the emergency department has been examined previously. Gökhan S et al.[23] reported that NLR levels were significantly higher in deceased AIS and acute hemorrhagic stroke patients compared to the surviving patients. The same authors also reported that NLR levels were significantly lower in patients with TIA compared to patients with AIS and acute hemorrhagic stroke ($p < 0.001$)[23]. Hematologic inflammatory parameters in AIS can be used not only for the the diagnosis but also to predict outcomes after treatment. Supporting this, Lux et al.[24] evaluated 121 AIS patients and reported that NLR was correlated with infarct size and could be effective in predicting 3-month functional outcomes. In addition, Xu et al.[25] reported that a high platelet-to-lymphocyte ratio (PLR)

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Table 1: Basic data of patients with acute ischemic stroke and transient ischemic attack

	Transient Ischemic Attack	Acute Ischemic Stroke	P
N (F/M)	36 (15/21)	74 (35/39)	0,578
Age /year	64,52±15,59	71,91±13,86	0,015
White Blood Cell (10^3/mm^3)	7,32 (5,79- 8,83)	8,73 (7,04- 9,97)	0,150
Lymphocyte (10e3/µL)	2,13 (1,79- 2,80)	1,89 (1,29- 2,45)	0,022
Neutrophil (10e3/µL)	3,85 (3,51- 5,40)	5,54 (4,22- 7,28)	0,073
Monocytes (10e3/µL)	0,57 (0,47- 0,77)	0,66 (0,50- 0,85)	0,001
Eosinophil (10e3/µL)	0,18 (0,09- 0,26)	0,11 (0,04- 0,20)	0,431
Haemoglobin(mg/dL)	14,05 (12,93- 15,13)	13,40 (12,05- 14,60)	0,017
Haematocrit (%)	43,05 (40,03- 44,85)	41,85 (37,60- 44,60)	0,103
Platelet bv(10^3/mm3),	256,00 (217,25- 290,25)	260,00 (207,00- 309,50)	0,108
NLR	1,88 (1,50- 2,55)	2,93 (1,93- 4,98)	0,000
SII	485,52 (339,33- 681,19)	824,09 (444,87- 1347,13)	0,001
SIRI	1,24 (0,73-1,6)	1,81 (1,23-3,16)	<0,001
Glucose (mg/dL),	112,50 (98,25- 140,25)	117,50 (103,75- 145,25)	0,569
Urea (mg/dL)	38,00 (30,00- 42,75)	39,00 (33,50- 52,50)	0,144
Creatinine (mg/dL)	0,84 (0,73- 1,04)	0,94 (0,72- 1,12)	0,458
C-reactive protein (mg/dL)	3,30 (3,30- 8,35)	7,72 (3,90- 26,80)	0,007
Plasma prothrombin time (sec)	12,55 (11,73- 12,98)	12,70 (12,20- 13,65)	0,668
Activated Partial Thromboplastin Time (Sec)	23,50 (22,53- 26,78)	23,70 (21,98- 25,98)	0,163
International Normalized Ratio	1,03 (0,95- 1,06)	1,04 (0,99- 1,13)	0,366

NLR: Neutrophil/Lymphocyte ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic inflammation response index (SIRI)

Table 2: ROC analysis data for the use of NLR, SII, and SIRI for differentiating TIA and AIS

	Cut Off	AUC	95% CI	Sensitivity (%)	Specificity (%)	P
NLR	>2,60	0,708	0,614 - 0,791	58,11	80,56	< 0,001
SII	>935,78	0,694	0,599- 0,779	% 44,59	94,44	< 0,001
SIRI	>1,74	0,722	0,629 - 0,803	56,76	83,33	<0,0001

AUC: Area under the ROC curve, CI: Confidence Interval NLR: Neutrophil/Lymphocyte ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic inflammation response index (SIRI)

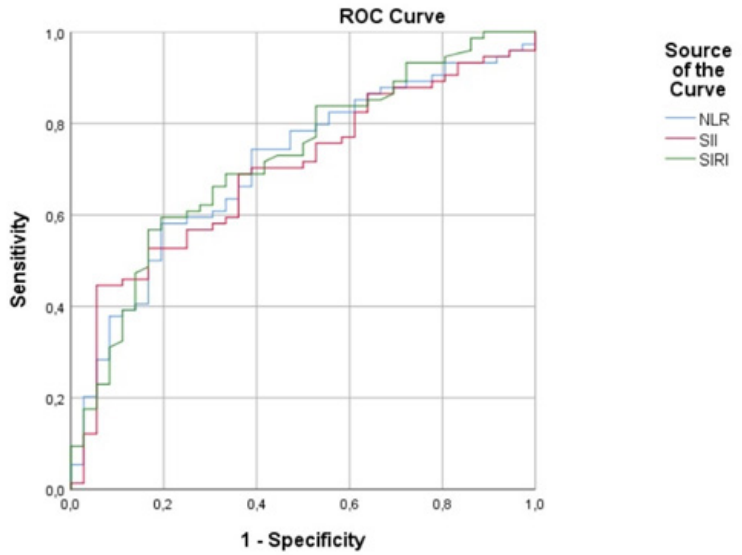

Figure 1: ROC plot of NLR, SII and SIRI values for the discrimination between TIA and AIS.

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may be associated with poor prognosis and worse 3-month mortality after intravenous thrombolysis treatment in AIS patients. Gong P et al.[26]. reported that NLR and PLR could predict early neurological deterioration after thrombolysis, while NLR was associated with early neurological recovery after thrombolysis. Yun S et al.[27] reported that elevated SIRI and SII index may be independent predictive factors for poor prognosis after bleeding in patients with subarachnoid hemorrhage. Similarly, Yang et al.[28] reported that a higher SII value was associated with a higher risk of hemorrhagic transformation in hemorrhagic stroke patients. Supporting these studies, we observed in the current study that SII and SIRI values were significantly higher in AIS patients compared to TIA patients. Additionally, the NLR, SII, and SIRI values had specificities of 80.56%, 94.44%, and 83.33%, respectively, in differentiating between AIS and TIA.

Evaluation of the hematological inflammatory parameters detected in the early stages and the clinical presentation of the patients may help in differentiating between TIA and AIS patients. This may also encourage early initiation of treatment in the AIS patients and to direct the patient to a stroke center with more advanced imaging facilities.

The results obtained in the present study show that hematologic inflammatory parameters are increased in AIS. NLR, SII, and SIRI values may provide insight into the differential diagnosis of AIS and TIA.

Limitations

The primary limitations of the study are its retrospective design and dependence on verbal and estimated statements of the patients or their relatives in determining the time of onset of symptoms.

Acknowledgements

Declarations

Ethics approval and consent to participate: Informed consent was obtained from all participants. This study was approved by the Ethics Committee of University (HRÜ/22.17.23)

Author contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests

Authors state no conflict of interest.

Data availability statement

Data available on request from the authors. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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