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Risk factors for epilepsy following arterial ischemic stroke childhood: A retrospective cohort study

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ABSTRACT

Aim: PSE is reported more frequently in childhood than in adults. In this study, we aimed to investigate potential risk factors for the development of post-stroke epilepsy (PSE) in children with arterial ischemic stroke (AIS).
Material methods: The current retrospective cohort study included the medical records of 50 pediatric participants (aged 29 days to 18 years) diagnosed with AIS at a university hospital between January 2006 and December 2023. All information of the patients who were followed for at least two years for the development of PSE after AIS was entered into the hospital database and recorded in a pre-designed questionnaire. Acute symptomatic seizures were defined as seizures occurring within 7 days after stroke. Two or more late seizures occurring after the acute period (>7 days) were classified as PSE. The incidence of PSE and potential risk factors were investigated.
Results: After AIS, more than half of the patients (58 %) developed acute seizures and almost one-third (38 %) developed PSE. Risk factors associated with the development of PSE, very early seizures (within the first six hours), high stroke severity, cortical lesions, neurological deficits and low serum vitamin D levels were detected ($p = 0.05$, $p = 0.036$, $p = 0.011$, $p < 0.001$, $p < 0.001$, respectively).
Conclusion: Seizures within the first six hours, high stroke severity, and neurological deficits are important risk factors for the development of PSE in children. Knowing the potential risk factors of PSE may be helpful for clinicians to identify high-risk patients. It can also contribute to treatment decision-making and post-discharge follow-up planning.

1. Introduction

Epilepsy is one of the most prominent consequences of arterial ischemic stroke (AIS) in children. Recent research data reveals an incidence rate of PSE at 11.6 per 100,000 person-years. The related study indicated that the risk of PSE is highest in the first 6 months but remains high even two decades after diagnosis [1]. This should be taken into account in the follow-up of children affected by the stroke.

Previous studies show that the frequency of PSE in children is between 7 % to 41 % [2–8]. Certain factors, including acute symptomatic seizures, ischemic cortical involvement, and young age, have been consistently reported to be associated with an increased risk of PSE in children [2–8]. Additionally, additional clinical and radiological features may contribute to the development of PSE, including high stroke severity in the acute phase, status epilepticus, multifocal infarctions, anterior circulation zone involvement, and stroke recurrence [8,9]. Numerous risk factors for the development of PSE have been suggested, but methodological differences between studies (differences in definitions of post-stroke epilepsy, whether community or hospital-based, age ranges selected, length of follow-up, and outcome measures) have led to the emergence of some complex and contradictory risk factors. Therefore, understanding of risk factors for the development of PSE in children is limited.

In this study, we aimed to investigate the risk factors for the development of PSE in children diagnosed with AIS. Knowing the prognostic risk factors of PSE may benefit clinicians in treatment decision-making and post-discharge follow-up planning.

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2. Materials and methods

2.1. Study population

Children and adolescents aged 29 days to 18 years who confirmed the diagnosis of childhood AIS (one or more acute cerebral infarctions in the arterial distribution detected on magnetic resonance imaging (MRI) performed within the first week after the onset of neurological symptoms) were eligible participants for the study [10].

Previous stroke (perinatal and antenatal ischemic stroke), hypoxic-ischemic encephalopathy, global or border zone infarcts due to hypoxia or resuscitation, pre-stroke epilepsy diagnosis, sinovenous thrombosis, hemorrhagic stroke, primary intracranial hemorrhage, skull surgery, stroke associated with intracranial tumor, traumatic head and neck patients with injury, no follow-up for at least two years after stroke and missing data patients were excluded.

The data analyzed in our study is a retrospective cohort study containing clinical, laboratory and radiological information collected from 50 patients (aged 29 days–18 years) diagnosed with AIS at a tertiary university hospital between January 2006 and December 2023. The current research was approved by the related Ethics Committee of Inönü University (protocol no: 2023/4396). Since this study was designed as a retrospective cohort study, informed consent was not obtained from the participants.

2.1.1. Study data

Children diagnosed with AIS and meeting the inclusion criteria were included in the study. AIS diagnoses were confirmed by magnetic resonance neuroimaging. AlI patients were followed for at least two years. Clinical, laboratory and radiological information of patients with AIS were entered into the hospital database and recorded. Stroke age, gender, etiologies, complaints at presentation, focal and widespread neurological symptoms and findings, laboratory investigations that were carried out at admission with stroke (complete blood cell count, biochemical, infectious, metabolic, immunological tests and vitamin D levels), neuroimaging results, time of the first seizure, time of late seizures, development of neurologic deficit were reported. Brain MRI and magnetic resonance angiography (MRA) findings were recorded according to location (cortical, subcortical involvement), affected circulation (anterior, posterior), and involved artery.

Inflammatory biomarkers; neutrophil–lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), systemic immune-inflammation index (SII) and systemic inflammatory response index (SIRI) were calculated. SII and SIRI are new markers of the inflammatory and immune status of patients and can be easily calculated with routine blood tests. (Calculated as SII = Neutrophil x platelet / lymphocyte and SIRI = Neutrophil × monocytes / lymphocyte).

2.1.2. Definitions

The International League Against Epilepsy (ILAE) defines post-stroke acute seizures (PSS) as seizures occurring within 7 days of an stroke [11]. Acute seizures were grouped by the time of onset as ‘very early seizures’ (a primary seizure in the first six hours of stroke), a primary seizure between the 6–48 h of stroke, ‘early seizures’ (a primary seizure in the first 48 h of stroke) and a primary seizure between the 2nd and 7th days of stroke [5].

PSE is defined as two unprovoked seizures or a single seizure associated with an enduring condition that increases the chance of future seizures if the probability of further seizures is similar to the general recurrence risk (at least 60 %) after two unprovoked seizures, occurring over the next 10 years [12]. PSE includes late seizures occurring more than 7 days after an acute stroke [11]. All patients documented to have an untriggered seizure underwent a standard interictal EEG within the first 2 weeks after the seizure.

The neurologic deficit was defined as any neuropsychiatric sequelae and/or motor deficit documented at the end of the second year of stroke onset [5].

2.1.3. Criteria for clinical stroke severity and functional outcomes

Clinical stroke severity was assessed with the Pediatric National Institutes of Health Stroke Scale (PedNIHSS). It has been shown that the adult form of the scale (NIHSS) can predict initial stroke severity, infarct volume and neurological outcomes in adults. Its value in children is not yet known in this respect, but it has been important in terms of ensuring standardization in future studies. Mild stroke (PedNIHSS score ≤ 5) was defined as moderate/severe stroke (PedNIHSS score > 5) [13].

Functional results were evaluated with the Modified Rankin Scale (mRS) for children. After a stroke, those who score 1 and 2 on the mRS continue to live independently, while those who score 3 or more continue to live as dependents. It was defined as good outcome (mRS $<$ 3) and poor outcome (mRS ≥ 3) [14,15]. Patients were re-evaluated at discharge and at six months.

2.1.4. Statistical analysis

The features utilized in the current research were expressed with mean, standard deviation, median, minimum and maximum values, frequency and percentage. The Shapiro-Wilk test was employed to test normal distribution for quantitative features. The Mann-Whitney *U* test was utilized to test the significance between independent groups in terms of quantitative features and, Yates’ chi-square and Fisher’s exact tests were utilized for qualitative variables. Multiple stepwise logistic regression was employed to model between acute seizure and independent features. The ROC (Receiver Operating Characteristics) analysis was performed to define the cutoff for the quantitative features. The classification performance of the logistics regression mode and the cutoff value was evaluated by overall accuracy, sensitivity, specificity and AUC (Area under the Curve) metrics. $p \leq 0.05$ was accepted as statistical significance level. IBM SPSS Statistics 27 software was utilized in the analysis.

3. Results

3.1. Demographic, clinical and radiological characteristics of patients diagnosed with AIS

The average age of stroke of the 50 children diagnosed with AIS included in the study sample was 102.98 ± 69 (range: 5–205) months and 27 (54 %) were male. The most common stroke-related etiological risk factors for AIS patients were prothrombotic/hematological diseases 21 (42 %), followed by cardiac diseases 14 (28 %), arteriopathies 9 (18 %), infections 4 (8 %) and malignancies 2 (4 %) followed (Table 1).

When the brain MRI of patients diagnosed with AIS was examined, it was seen that the cortical region was involved in 34 (68 %) of the acute infarcts, the subcortical region was involved in 14 (28 %) and the infratentorial region was involved in 2 (4 %). In 4 (8 %) cases with hemorrhagic transformation, there were small petechiae and no hematoma. Of the acute infarcts, 25 (50 %) showed left lateralization, 17 (34 %) had right lateralization, and 8 (16 %) showed bilateral lateralization. 38 patients (76 %) had focal ischemic lesions, and 12 (24 %) had multifocal ischemic lesions. The anterior circulation was involved in 36 (72 %) of the infarcts, the posterior circulation was involved in 8 (16 %), and the anterior and posterior circulations were involved together in 6 (12 %) (Table 1). In brain MRA, there were pathologies such as stenosis, thinned flow, aneurysmatic expansion, and contour irregularity, mostly in 34 (68 %) Middle Cerebral Artery segments. All patients with abnormal MRA underwent follow-up imaging and were shown to have normalized vascular imaging. Of the patients diagnosed with AIS, 20 (40 %) received only anticoagulant, 12 (24 %) received only antiplatelet, and 18 (36 %) received anticoagulant and antiplatelet. No patient received thrombolytic therapy.

Table 1
Comparison of clinical features and AIS presentation between AIS groups with and without post-stroke acute seizures.

Types	Variables*	Categories	Acute seizure		Total ($n = 50$)	Chi-square statistics	p
			No ($n = 21$)	Yes ($n = 29$)			
Clinical characteristics	Sex	Female	9a (42.9 %)	14a (48.3 %)	23 (46.0 %)	0.008	0.927[2]
		Male	12a (57.1 %)	15a (51.7 %)	27 (54.0 %)		
	Etiology	Hematologic	11a (57.9 %)	10a (32.3 %)	21 (42.0 %)	5.821	0.342[1]
		Cardiac	3a (15.8 %)	11a (35.5 %)	14 (28.0 %)		
		Arteriopathy	3a (15.8 %)	6a (19.4 %)	9 (18.0 %)		
		Infection	1a (5.3 %)	3a (9.7 %)	4 (8.0 %)		
		Malignancy	1a (5.3 %)	1a (3.2 %)	2 (4.0 %)		
	Focal Symptom	Hemiparesis	11a (52.4 %)	15a (51.7 %)	26 (52.0 %)	7.971	**0.028**[1]
		Monoparesis	1a (4.8 %)	0a (0.0 %)	1 (2.0 %)		
		Paresthesia	5a (23.8 %)	1a (3.4 %)	6 (12.0 %)		
		Hemiparesis and facial paralysis	4a (19.0 %)	13b (44.8 %)	17 (34.0 %)		
	Diffuse Symptom	Impaired consciousness	1a (4.8 %)	14b (48.3 %)	15 (30.0 %)	11.049	**0.007**[1]
		Headache	9a (42.9 %)	7a (24.1 %)	16 (32.0 %)		
		Dizziness	1a (4.8 %)	1a (3.4 %)	2 (4.0 %)		
		No diffuse symptoms	10a (47.6 %)	7a (24.1 %)	17 (34.0 %)		
	Stroke severity (PedNIHSS)	Mild stroke (≤5)	5a (23.8 %)	5a (17.2 %)	10 (20.0 %)	–	0.723[3]
		Moderate and severe (>5)	16a (76.2 %)	24a (82.8 %)	40 (80.0 %)		
	Neurological deficit	No	15a (71.4 %)6a	7b (24.1 %)	22 (44.0 %)	9.216	**0.002**[2]
		Yes	(28.6 %)	22b (75.9 %)	28 (56.0 %)		
	Functional outcomes (mRS discharge)	Good outcome (<3)Poor outcome (≥3)	5a (50.00 %) 16a (28.6 %)	5a (24.1 %) 24a (75.9 %)	10 (44.0 %) 40 (56.0 %)	–	0.723[3]
	Functional outcome (mRS after 6 months)	Good outcome (<3)Poor outcome (≥3)	15a (71.4 %)6a (28.6 %)	21a (72.4 %) 8a (27.6 %)	36 (72.0 %) 14 (28.0 %)	0.000	0.999[2]
MRI characteristics	Laterality	Right hemisphere	4a (19.0 %)	13a (44.8 %)	17 (34.0 %)	4.459	0.107[1]
		Left hemisphere	14a (66.7 %)	11a (37.9 %)	25 (50.0 %)		
		Bilateral hemisphere	3a (14.3 %)	5a (17.2 %)	8 (16.0 %)		
	Stroke number	Unifocal	17a (81.0 %)	21a (72.4 %)	38 (76.0 %)	0.131	0.717[2]
		Multifocal	4a (19.0 %)	8a (27.6 %)	12 (24.0 %)		
	Stroke circulation territory	Anterior (ACA + MCA)	14a (66.7 %)	22a (75.9 %)	36 (72.0 %)	1.708	0.536[1]
		Posterior (PCA)	5a (23.8 %)	3a (10.3 %)	8 (16.0 %)		
		Anterior and posterior	2a (9.5 %)	4a (13.8 %)	6 (12.0 %)		
	Affected brain area	Frontal	3a (14.3 %)	1a (3.4 %)	4 (8.0 %)	5.935	0.606[1]
		Parietal	1a (4.8 %)	4a (13.8 %)	5 (10.0 %)		
		Temporal	4a (19.0 %)	7a (24.1 %)	11 (22.0 %)		
		Occipital	5a (23.8 %)	4a (13.8 %)	9 (18.0 %)		
		Basal ganglia	6a (28.6 %)	10a (34.5 %)	16 (32.0 %)		
		Thalamus	1a (4.8 %)	2a (6.9 %)	3 (6.0 %)		
		Cerebellum	1a (4.8 %)	0a (0.0 %)	1 (2.0 %)		
		Brainstem	0a (0.0 %)	1a (3.4 %)	1 (2.0 %)		
	Hemorrhagic transformation	Into the infarct	0a (0.0 %)	4a (13.8 %)	4 (8.0 %)	–	0.999[3]
		No hemorrhage	21a (100.0 %)	25a (86.2 %)	46 (92.0 %)		
	Cortical involvement	No	10a (47.6 %)	6a (20.7 %)	16 (32.0 %)	2.916	0.088[2]
		Yes	11a (52.4 %)	23a (79.3 %)	34 (68.0 %)		
	MRI Angiography	Middle Cerebral Artery	12a (57.1 %)	22a (75.9 %)	34 (68.0 %)	3.871	0.483[1]
		Anterior Cerebral Artery	1a (4.8 %)	1a (3.4 %)	2 (4.0 %)		
		Internal Carotid Artery	5a (23.8 %)	4a (13.8 %)	9 (18.0 %)		
		Posterior Cerebral Artery	3a (14.3 %)	1a (3.4 %)	4 (8.0 %)		
		Brachiocephalic Artery	0a (0.0 %)	1a (3.4 %)	1 (2.0 %)		
	Total		21 (100.0 %)	29 (100.0 %)	50 (100.00 %)		

Each letter denotes a subset of AIS categories whose column proportions do not differ significantly from each other at the 0.05 level.
The statistically significant difference is expressed in bold.
AIS, arterial ischemic stroke; MRI, magnetic resonance image; PedNIHSS, Pediatric National Institutes of Health Stroke Scale; mRS, Modified Rankin Scale; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.
* Variables are expressed as frequency (percent).
[1] Pearson chi-square (exact)
[2] Continuity correction
[3] Fisher's exact test

3.2. Characteristics of patients who developed PSS

Approximately half of the stroke patients 29 (58 %) developed PSS. The average age of these patients was 93.97 ± 63.4 months (range: 5–194 months) and 15 (55.6 %) were male. The age of patients diagnosed with PSS was younger than patients without seizures, but no statistical difference was found between the groups in terms of age and gender ($p > 0.05$) (Table 2). According to PSS subgroups, very early seizures occurred in 14 (48.3 %) patients, seizures within 6–48 h in 11 (37.9 %), early seizures in 25 (86.2 %) and between 2 and 7 days

Table 2
Comparison of demographic data and laboratory parameters between AIS groups with and without post-stroke acute seizures.

Variables*	Acute seizure		Total ($n = 50$)	p**
	No ($n = 21$)	Yes ($n = 29$)		
Stroke age (month)	115.43 ± 75.88 | | 144 (13–205)	93.97 ± 63.4 | 65 (5–194)	102.98 ± 69 | 90.5 (5–205)	0.275
Neutrophil (10^9/L)	4.06 ± 2.17 | 4.3 (0.03–9.3)	4.89 ± 3.3 | 4.2 (0.08–15.3)	4.54 ± 2.88 | 4.25 (0.03–15.3)	0.455
Lymphocyte (10^9/L)	3.71 ± 2.11 | 3.2 (1.8–10.56)	3.41 ± 2.15 | 2.9 (0.3–8.16)	3.54 ± 2.12 | 2.95 (0.3–10.56)	0.485
Monocyte (10^9/L)	0.79 ± 0.4 | 0.7 (0.4–2.1)	0.77 ± 0.52 | 0.6 (0.06–2.1)	0.78 ± 0.47 | 0.6 (0.06–2.1)	0.292
Platelet (10^9/L)	308.9 ± 87.83 | 308 (81–505)	313.17 ± 139.95 | 307 (44–839)	311.38 ± 119.77 | 307.5 (44–839)	0.836
NLR	1.32 ± 0.81 | 1.44 (0.01–2.91)	2.29 ± 2.83 | 1.33 (0.18–13)	1.88 ± 2.26 | 1.37 (0.01–13)	0.569
PLR	98.21 ± 39.93 | 98.16 (32.39–161.33)	131.46 ± 104.21 | 97.06 (34.19–446.28)	117.49 ± 84.45 | 97.61 (32.39–446.28)	0.694
SIRI	1.05 ± 0.92 | 1.07 (0.01–4.07)	2.03 ± 3.68 | 0.91 (0.02–15.59)	1.62 ± 2.89 | 0.93 (0.01–15.59)	0.644
SII	414.33 ± 271.98 | 377.22 (1.41–1074.74)	756.61 ± 1016.81 | 311.38 (11.73–4329)	612.85 ± 806.3 | 344.3 (1.41–4329)	0.609
Vitamin D (ng/mL)	30.95 ± 12.17 | 32.2 (7.32–51.2)	18.3 ± 13.35 | 12.1 (4–52)	23.61 ± 14.21 | 23.1 (4–52)	**0.002**

The statistically significant difference is expressed in bold.
AIS, arterial ischemic stroke; NLR, Neutrophil-Lymphocyte Ratio; PLR, Platelet-Lymphocyte Ratio; SIRI, Systemic Inflammation Response Index; SII, Systemic Immune-Inflammation Index.
* Variables are expressed as mean ± std. deviation | median (minimum–maximum).
** Mann-Whitney U test.

seizures in 4 (13.8 %).

Serious clinical symptoms, including loss of consciousness (diffuse symptom), hemiparesis and facial paralysis (focal finding), were detected significantly more frequently in patients with PSS than in those without seizures ($p = 0.007$, $p = 0.028$, respectively) (Table 1). In the analysis of the variables leading to the development of PSS the development of neurological deficits was found to be associated with potential risk factors ($p = 0.002$) (Table 1). Vitamin D levels were significantly lower in patients who developed PSS ($p = 0.002$) (Table 2).

For all cohort, multiple stepwise logistic regression analysis (MSLRA) was performed to predict acute seizure. The predictors used in the relevant model were selected according to their statistical significance levels (≤ 0.05) in univariate tests. Although all significant predictors were included in the model, the stepwise analysis identified only two predictors (Vitamin D and neurological deficit) as significant. Hosmer and Lemeshow (HL) test indicated a significant goodness of fit model which was established with neurological deficit and vitamin D variables. According to the results of MSLRA, the coefficients of neurological deficit and vitamin D variables were determined to be statistically significant ($p = 0.002$, OR = 12.68; $p = 0.003$, OR = 0.91) (Table 5). According to the results, the development of the neurological deficits was associated with an approximately 12.68-fold increase in the development of PSS. Each 1-unit increase in vitamin D level was associated with an approximately 0.91-fold decrease in the development of PSS (Table 5). Receiver operating characteristic (ROC) Analysis results for Vitamin D are shown in Table 6 and Fig. 1.

3.3. Characteristics of patients who developed PSE

Almost one-third of stroke patients 19 (38 %) developed PSE. The mean age of patients with PSE was 90.74 ± 63.41 (range: 5–192 months, median 63 months). Loss of consciousness (diffuse symptom), hemiparesis and facial paralysis (focal finding) were significantly more common in patients who developed PSE ($p = 0.041$, $p = 0.005$, respectively) (Table 3). In the analysis of variables leading to the development of PSE, cortical involvement, stroke severity and the development of neurological deficits may be associated with potential risk factors ($p = 0.011$, $p = 0.036$, $p < 0.001$, respectively) (Table 3). PSE developed in 12 of 14 patients (85.7 %) who developed acute seizures within the first 6 h after stroke ($p = 0.05$). Vitamin D levels were statistically significantly lower in patients who developed PSE ($p < 0.001$) (Table 4). All participants with PSE were treated with anti-seizure medication (ASM). 12 (63.2 %) of the patients used one drug, 5 (26.3 %) used two drugs, and 2 (10.5 %) used three ASMs.

4. Discussion

This study shows that very early seizures within the first six hours after stroke, high stroke severity, cortical ischemia, development of neurological deficits and low serum vitamin D levels may be risk factors associated with the development of PSE.

PSS was detected in more than half of the patients (58 %) and PSE in approximately one-third (38 %). Our incidence of PSE is consistent with previous observational studies of pediatric patients hospitalized for stroke (27–41 %) [5,6,8]. In a study, the risk of developing PSE in pediatric AIS patients was found to be 11.9 % after 5 years and 26.4 % after 30 years [1]. A large population-based cohort study compared adult and childhood seizure rates in the setting of acute stroke. This study showed that children are 18 times more likely than adults to have a seizure within 24 h of stroke symptoms [16]. It has been reported that the likelihood of seizures increases at younger ages at the onset of stroke or within the first seven days (acute period) (5). Additionally, in a *meta*-analysis, younger age was associated with an increased risk of PSE [17]. The higher seizure rates in children than in adults are likely due to the immaturity of neural networks leading to imbalances in excitatory and inhibitory amino acids [18,19]. This situation may lead to increased susceptibility to seizures. It has also been suggested that there are different mechanisms in developing and mature brains due to ontogenic differences in the number, distribution and affinity of excitatory amino acid receptors involved in epileptogenesis [19].

In this study, consistent with the literature, very early seizures seen within the first six hours after stroke, high stroke severity, cortical involvement and neurological deficit development were associated with an increased risk of PSE [2,8]. A previous study showed that very early seizures increased the risk of developing PSE in children sixfold [5]. Acute seizures that develop during and/or in the first hours of a stroke may contribute to the development of PSE by causing worsening of neurodegeneration due to stroke and ischemia. The literature has shown that acute symptomatic seizures increase the risk of PSE by 9-fold [2]. In addition, it has been determined that long-term and recurrent acute seizures cause a 5-fold increase in the risk of PSE for every 10 min of seizure duration. It has been shown that the number of recurrent acute seizures is greater than 10, increasing the risk of PSE by approximately 30-fold [4]. In particular, status epilepticus has been shown to be associated with a higher risk of PSE [9]. The current study showed that higher stroke severity was associated with an increased risk of PSE, consistent with the literature [17,20–22]. It is not yet clear whether seizures in children are more likely to alert the clinician to a possible underlying problem and thus diagnose stroke more quickly. Future studies examining symptoms and time of presentation should be considered to identify risk factors for PSE [16]. Cortical involvement is the best-known risk factor for early post-stroke seizures and PSE, as shown in previous studies [5,8,9,17]. Cortical ischemia results in

Table 3
Comparison of clinical features between AIS groups with and without post-stroke epilepsy.

Types	Variables*	Categories	Epilepsy		Total (n = 29)	Chi-square statistics	p
			No (n = 10)	Yes (n = 19)			
Clinical characteristics	Sex	Female	6a (60.0 %)	8a (42.1 %)	14 (48.3 %)	–	0.45[3]
		Male	4a (40.0 %)	11a (57.9 %)	15 (51.7 %)		
	Etiology	Arteriopathy	2a (20.0 %)	9a (47.4 %)	11 (37.9 %)	4.052	0.408[1]
		Cardiac	0a (0.0 %)	1a (5.3 %)	1 (3.4 %)		
		Hematologic	5a (50.0 %)	5a (26.3 %)	10 (34.5 %)		
		Malignancy	0a (0.0 %)	1a (5.3 %)	1 (3.4 %)		
		Other etiologies	3a (30.0 %)	3a (15.8 %)	6 (20.7 %)		
	Focal Symptom	Hemiparesis	9a (90.0 %)	6b (31.6 %)	15 (51.7 %)	8.979	**0.005**[1]
		Monoparesis	0a (0.0 %)	1a (5.3 %)	1 (3.4 %)		
		Hemiparesis and facial paralysis	1a (10.0 %)	12b (63.2 %)	13 (44.8 %)		
	Diffuse Symptom	Impaired consciousness	2a (20.0 %)	12b (63.2 %)	14 (48.3 %)	7.501	**0.041**[1]
		Headache	5a (50.0 %)	2b (10.5 %)	7 (24.1 %)		
		Dizziness	0a (0.0 %)	1a (5.3 %)	1 (3.4 %)		
		No diffuse symptom	3a (30.0 %)	4a (21.1 %)	7 (24.1 %)		
Acute symptomatic seizures subgroups	Very early seizures	No	8a (80.0 %)	7b (36.8 %)	15 (51.7 %)	–	**0.05**[3]
		Yes	2a (20.0 %)	12b (63.2 %)	14 (48.3 %)		
	Seizures within 6-48th	No	4a (40.0 %)	14a (73.7 %)	18 (62.1 %)	–	0.114[3]
		Yes	6a (60.0 %)	5a (26.3 %)	11 (37.9 %)		
	Early seizures	No	2a (20.0 %)	2a (10.5 %)	4 (13.8 %)	–	0.592[3]
		Yes	8a (80.0 %)	17a (89.5 %)	25 (86.2 %)		
	Late seizures	No	8a (80.0 %)	17a (89.5 %)	25 (86.2 %)	–	0.592[3]
		Yes	2a (20.0 %)	2a (10.5 %)	4 (13.8 %)		
	Stroke severity (PedNIHSS)	Mild stroke (≤5)Moderate stroke (>5)	4a (40.0 %) 6a (60.0 %)	1b (5.3 %) 18b (94.7 %)	5 (17.2 %) 24 (82.8 %)	–	**0.036**[3]
	Neurological deficit	No	7a (70.0 %)	0a (0.0 %)	7 (24.1 %)	–	**<0.001**[3]
		Yes	3a (30.0 %)	19a (100.0 %)	22 (75.9 %)		
	Functional outcomes (mRS discharge)	Good outcome (≤3)Poor outcome (≥3)	4a (40.0 %) 6a (60.0 %)	1b (5.3 %) 18b (94.7 %)	5 (17.2 %) 24 (82.8 %)	–	**0.036**[3]
	Functional outcomes (mRS after 6 months)	Good outcome (≤3)Poor outcome (>3)	9a (90.0 %) 1a (10.0 %)	12a (63.2 %) 7a (36.8 %)	21 (72.4 %) 8 (27.6 %)	–	0.201[3]
MRI characteristics	Stroke number	Unifocal	8a (80.0 %)	13a (68.4 %)	21 (72.4 %)	–	0.675[3]
		Multifocal	2a (20.0 %)	6a (31.6 %)	8 (27.6 %)		
	Stroke circulation territory	Anterior	9a (90.0 %)	13a (68.4 %)	22 (75.9 %)	2.14	0.457[1]
		Posterior	0a (0.0 %)	3a (15.8 %)	3 (10.3 %)		
		Anterior and posterior	1a (10.0 %)	3a (15.8 %)	4 (13.8 %)		
	Affected brain area	Frontal	1a (10.0 %)	0a (0.0 %)	1 (3.4 %)	7.69	0.272[1]
		Parietal	0a (0.0 %)	4a (21.1 %)	4 (13.8 %)		
		Temporal	4a (40.0 %)	3a (15.8 %)	7 (24.1 %)		
		Occipital	2a (20.0 %)	2a (10.5 %)	4 (13.8 %)		
		Basal ganglia	2a (20.0 %)	8a (42.1 %)	10 (34.5 %)		
		Thalamus	1a (10.0 %)	1a (5.3 %)	2 (6.9 %)		
		Brainstem	0a (0.0 %)	1a (5.3 %)	1 (3.4 %)		
	Hemorrhagic transformation	Into the infarct	1a (0.0 %)	3a (20.0 %)	4 (13.8 %)	–	0.999[3]
		No hemorrhage	9a (100.0 %)	16a (80.0 %)	25 (86.2 %)		
	Cortical involvement	No	5a (50.0 %)	1b (5.3 %)	6 (20.7 %)	–	**0.011**[3]
		Yes	5a (50.0 %)	18b (94.7 %)	23 (79.3 %)		
	MRI Angiography	Middle Cerebral Artery	9a (90.0 %)	13a (68.4 %)	22 (75.9 %)	2.14	0.904[1]
		Anterior Cerebral Artery	0a (0.0 %)	1a (5.3 %)	1 (3.4 %)		
		Internal Carotid Artery	1a (10.0 %)	3a (15.8 %)	4 (13.8 %)		
		Posterior Cerebral Artery	0a (0.0 %)	1a (5.3 %)	1 (3.4 %)		
		Brachiocephalic Artery	0a (0.0 %)	1a (5.3 %)	1 (3.4 %)		
	Total		**10 (100.0 %)**	**19 (100.0 %)**	**29 (100.0 %)**		

Each letter denotes a subset of epilepsy categories whose column proportions do not differ significantly from each other at the 0.05 level.
The statistically significant difference is expressed in bold.
AIS, arterial ischemic stroke; MRI, magnetic resonance image; PedNIHSS, Pediatric National Institutes of Health Stroke Scale; mRS, Modified Rankin Scale.
*Variables are expressed as frequency (percent).
[1]Pearson chi-square (exact)
[2]Continuity correction
[3]Fisher's exact test

Table 4
Comparison of laboratory parameters between AIS groups with and without post-stroke epilepsy.

Variables*	Epilepsy		Total ($n = 29$)	p*
	No ($n = 10$)	Yes ($n = 19$)		
Stroke age (month)	100.1 ± 66.32 | 103.5 (12–194)	90.74 ± 63.41 | 63 (5–192)	102.98 ± 69 | 90.5 (5–205)	0.804[2]
Neutrophil (10^9/L)	4.75 ± 2.81 | 4.45 (0.9–10.4)	4.97 ± 3.6 | 3.9 (0.08–15.3)	4.89 ± 3.3 | 4.2 (0.08–15.3)	0.982[2]
Lymphocyte (10^9/L)	3.99 ± 2.17 | 3.8 (0.8–7.36)	3.11 ± 2.13 | 2.8 (0.3–8.16)	3.41 ± 2.15 | 2.9 (0.3–8.16)	0.266[2]
Monocyte (10^9/L)	0.72 ± 0.35 | 0.59 (0.4–1.4)	0.8 ± 0.6 | 0.6 (0.06–2.1)	0.77 ± 0.52 | 0.6 (0.06–2.1)	0.91[2]
Platelet (10^9/L)	386.5 ± 182.28 | 346.5 (155–839)	274.58 ± 96.42 | 288 (44–440)	313.17 ± 139.95 | 307 (44–839)	0.062[2]
NLR	2.45 ± 3.85 | 1.32 (0.18–13)	2.21 ± 2.25 | 1.33 (0.27–8.43)	2.29 ± 2.83 | 1.33 (0.18–13)	0.542[2]
PLR	149.74 ± 151.09 | 85.52 (39.13–446.28)	121.83 ± 72.09 | 106.98 (34.19–271.67)	131.46 ± 104.21 | 97.06 (34.19–446.28)	0.804[2]
SIRI	1.43 ± 1.57 | 0.88 (0.08–5.2)	2.34 ± 4.42 | 0.91 (0.02–15.59)	2.03 ± 3.68 | 0.91 (0.02–15.59)	0.839[2]
SII	1017.64 ± 1490.52 | 387.23 (48.85–4329)	619.22 ± 663.09 | 311.38 (11.73–2587.57)	756.61 ± 1016.81 | 311.38 (11.73–4329)	0.875[2]
Vitamin D (ng/mL)	33.73 ± 11.15 | 31.45 (16.7–52)	10.18 ± 3.64 | 9.4 (4–19.09)	18.3 ± 13.35 | 12.1 (4–52)	**<0.001**[1]

The statistically significant difference is expressed in bold.
AIS, arterial ischemic stroke; NLR, Neutrophil-Lymphocyte Ratio; PLR, Platelet-Lymphocyte Ratio; SIRI, Systemic Inflammation Response Index; SII, Systemic Immune-Inflammation Index.
* Variables are expressed as mean ± std. deviation | median (minimum–maximum).
[1] Independent samples *t*-test
[2] Mann-Whitney *U* test.

Table 5
The findings of MSLRA to identify variables predicting AIS for the whole cohort.

Model significance and goodness of fit statistics			The statistics of the model's coefficients				Classification performance metrics with 95 % CI	
Hosmer & Lemeshow test			**Variable**	***β***	***p***	**OR (95 % CI)**	**Metric**	**Value (95 % CI)**
			Neurological Deficit (Yes)	2.54	**0.002**	12.683 (2.527–63.669)	**Overall accuracy**	76 % (61.83 % – 86.94 %)
χ^2	***df***	***p***	**Vitamin D**	−0.088	**0.003**	0.916 (0.864–0.971)	**Sensitivity**	79.31 % (60.28 % – 92.01 %)
14.827	8	0.063	**Constant**	2.543	**0.005**	12.718	**Specificity**	71.43 % (47.82 % – 88.72 %)

β, Coefficient; *df*, Degree of freedom; CI, Confidence Interval; OR, Odds Ratio.
The statistically significant difference for variables is expressed in bold.
MSLRA, multiple stepwise logistic regression analysis.

Table 6
The ROC analysis results for vitamin D in patients with AIS (all cohort).

Variable	Cut-off value	Metrics with 95 % CI			p
		AUC	Sensitivity	Specificity	
Vitamin D	≤16.67	0.995 (0.871–1.000)	0.947 (0.740–0.999)	1.000 (0.692–1.000)	**<0.001**

AUC, Area under curve; CI, Confidence interval.

increased extracellular glutamate levels from the damaged neuron and an increased risk of secondary neuron damage due to excitotoxicity [23]. In particular, major cortical damage has been shown to significantly increase the risk of developing PSE [24].

In the current study, vitamin D levels were found to be low in stroke patients. Additionally, a decrease in vitamin D levels was associated with an increased risk of developing PSE. As a novel finding, it was shown that each unit increase in vitamin D concentration was associated with an approximately 0.91-fold decrease in the development of PSE. A recent study identified low vitamin D levels as a risk factor for PSE. It has also been reported that low vitamin D levels may play a role in the development of PSE [5]. It has been reported in the literature that vitamin D regulates calcium homeostasis, can reduce neuron death through L-type voltage-dependent calcium channels in the brain, and has neuroprotective and immunomodulatory effects [25,26]. A *meta*-analysis showed that the risk of stroke increases as vitamin D levels decrease. This study reported that vitamin D intake may reduce the risk of stroke due to the inverse dose–response relationship between vitamin D intake and stroke risk [27]. Experimental studies show that vitamin D levels decrease in acute periods after brain injury. It is also thought that the decrease in vitamin D levels in plasma may be due to increased turnover in vitamin D receptor gene expression in the brain and increased vitamin D need after epileptogenic damage [26,28]. It has been reported that the decrease in vitamin D and its metabolites may be related to the severity of epileptogenic damage [28]. In our study, vitamin D levels measured after stroke were found to be low, similar to several previous studies [5,27]. In the current study, decreased vitamin D levels were observed in patients who developed PSE, however, when the available information in the related literature is evaluated, it is predicted that this may not indicate a causality. In this context, decreased vitamin D levels after stroke may be one of the candidate risk factors associated with PSE.

4.1. Limitations

First, since data collection began nearly two decades ago, the duration and number of recurrences of early acute seizures of many patients have been missing from records. Second, the emergence of seizures and non-convulsive epileptic states, especially in children after infancy, is likely to be overlooked due to the lack of standardized protocols for continuous EEG monitoring. Finally, some univariate significant findings were found, but these lost statistical significance when potentially associated factors were included in the main multiple logistic regression model. This is thought to be due to the relatively small sample size collected due to the low incidence of childhood stroke. Another important point is that since the anatomical and clinical attributes of

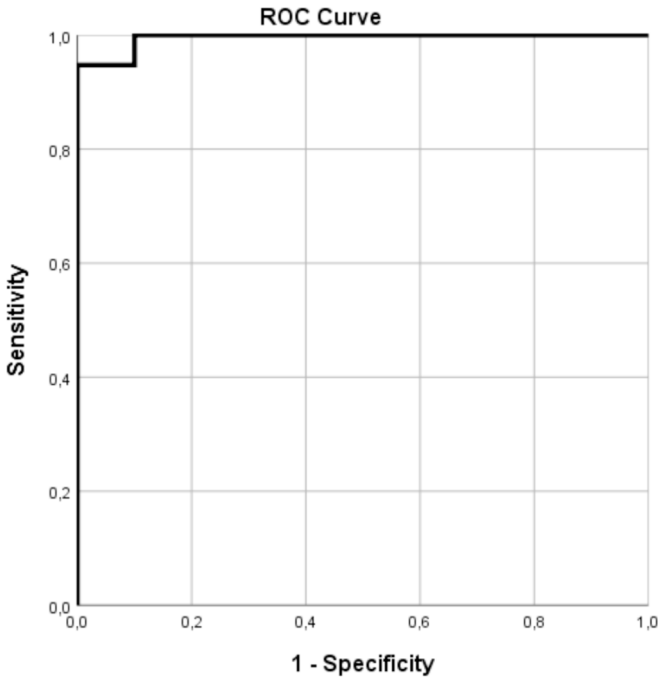

Fig. 1. ROC analysis results for vitamin D in patients with arterial ischemic stroke (all cohort).

stroke are related, the relationship between risk factors for post-stroke outcomes should be taken into account in further studies.

5. Conclusion

Acute seizures following AIS may affect long-term prognosis, so further studies are needed to identify risk factors associated with the development of PSE. Optimal patient management, especially seizure prevention and neuroprotective treatments, can only be developed through detailed studies.

Author contribution

Gül Yücel was responsible for data collection, analysis and drafting of the study and writing the main text of the article. Ahmet Kadir Arslan was responsible for the statistical analysis of the article, interpretation of data, and creation of tables and figures. Gül Yücel, Ahmet Kadir Arslan, Bilge Özgör and Serdal Güngör contributed to the management or administration of the trial. All authors read and approved the final version to be published.

Ethical considerations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee. The approval of the Ethical Committee of Inönü University was obtained (ethics approval no.: 2023/4396). Written informed consent was not obtained from the participants due to the retrospective nature of the study.

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Gül Yücel: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ahmet Kadir Arslan:** Writing – review & editing, Visualization, Validation, Software, Formal analysis, Data curation, Conceptualization. **Bilge Özgör:** Writing – review & editing. **Serdal Güngör:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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