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The value of adropin levels in determining the severity of pediatric mild traumatic brain injury in the emergency department: A prospective study

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Abstract

Background & Objective: The presence of mild traumatic brain injury (mTBI) in paediatric patients poses significant challenges in terms of diagnosis, particularly with regard to determining which patients require neuroimaging procedures. Adropin, a peptide hormone with neuroprotective properties, has been proposed as a biomarker of brain injury. The present study examined the association between serum adropin levels and mTBI severity in children, with the classification of subjects based on clinical and radiological risk factors. *Methods:* In this prospective study, 56 paediatric patients (aged 0–18 years) with mTBI and 57 age-matched controls were enrolled. The mTBI patients were stratified into low-, intermediate-, and high-risk categories based on clinical presentation and computed tomography (CT) findings. Serum adropin was measured using an enzyme-linked immunosorbent assay (ELISA). Group comparisons were performed with one-way analysis of variance (ANOVA) and Bonferroni post hoc tests; receiver operating characteristic (ROC) analysis was used to determine cut-off values, sensitivity, and specificity. *Results:* A significant increase in mean serum adropin levels was observed in the mTBI group compared to the control group (4815.04 ± 2970.26 vs 1385.48 ± 290.50 pg/mL; $p < 0.001$). Within the mTBI cohort, adropin levels increased with risk status, reaching the highest levels in high-risk patients and in those with temporoparietal trauma. ROC analysis identified a cut-off of 1650.5 pg/mL to differentiate mTBI from controls (sensitivity 84%, specificity 82%) and 5520 pg/mL to distinguish high- from low-risk mTBI (sensitivity 85%, specificity 80%).
Conclusion: Serum adropin levels appear to reflect injury severity in mTBI and may aid risk stratification and imaging decisions. In order to confirm these findings and to define the role of adropin and related biomarkers, further research is required in the form of larger studies.

Keywords: Adropin protein, mild traumatic brain injury, pediatric emergency medicine

INTRODUCTION

Pediatric traumatic brain injury (TBI) is a major contributor to morbidity and mortality in children, manifesting across a spectrum of severity that demands tailored diagnostic and therapeutic strategies. The initial injury—occurring at the moment of impact—inflicts direct mechanical damage to brain tissues, affecting neurons, vascular structures, and glial cells. This primary insult is irreversible and precipitates a cascade of secondary injuries.[1-3] These secondary processes include excitotoxicity, oxidative stress, inflammatory responses, and disturbances in the blood-brain barrier, cerebral perfusion, and metabolic homeostasis.[1-4] Such mechanisms can exacerbate neuronal damage and lead to cell death, while simultaneously providing a critical window for therapeutic intervention. Therefore, elucidating the complex pathophysiological underpinnings of TBI is essential for the development of targeted treatments and the improvement of patient care.

The accurate classification of TBI severity in children is critical for determining appropriate treatment and prognostic outcomes. While the Glasgow Coma Scale (GCS) remains the standard tool for assessing TBI severity, its effectiveness is constrained by the inherent heterogeneity of injuries and variable outcomes.

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Alternative approaches that integrate evidence-based guidelines, advanced scoring systems, and innovative analytical techniques—including latent class analysis and machine learning—have demonstrated enhanced precision in both severity classification and outcome prediction.[5-8] Nonetheless, further research is required to address existing evidence gaps and refine these methodologies for improved clinical management.

Computed tomography (CT) imaging is the primary diagnostic modality for evaluating TBI severity, particularly for detecting intracranial hematomas, elevated intracranial pressure, and midline shifts. Nevertheless, its limited sensitivity in identifying subtle injuries—particularly in cases of mild TBI — and its interpretive variability highlights the necessity for adjunctive diagnostic approaches, such as circulating biomarkers.[9,10] Mild TBI (mTBI), which is frequently used synonymously with the term "concussion", is characterised as a disruption of brain function caused by an external force. This typically results in a brief alteration of consciousness, confusion, or amnesia, but without detectable abnormalities on standard neuroimaging techniques such as CT scans.[11] The American Congress of Rehabilitation Medicine has recently updated its diagnostic criteria for mild TBI, emphasising the significance of observable signs, such as loss of consciousness or amnesia, as well as acute symptoms and cognitive or balance impairments. The updated criteria also acknowledge the absence of reliable imaging or fluid biomarkers for diagnosis.[12] The majority of individuals with mild TBI recover within weeks; however, approximately 10–15% experience persistent symptoms known as post-concussive syndrome. Furthermore, repeated injuries have been demonstrated to increase the risk of chronic neurological conditions, such as chronic traumatic encephalopathy (CTE). Epidemiological data indicate that among children aged two years and older, the prevalence of mild blunt head trauma (GCS 14–15) ranges from 3% to 7% as confirmed by CT imaging with no apparent neurological deficits. Approximately 1% of these cases manifest clinically significant TBI, and an additional 0.1% to 0.6% may require surgical intervention.[13,14] A major clinical challenge is that patients initially classified with 'mild' TBI can experience persistent, debilitating symptoms, whereas some individuals with 'severe' TBI (GCS <8) may achieve unexpectedly favorable recoveries. Despite these observations, there is a dearth of high-quality research specifically examining mTBI severity. In recent years, biomarkers have emerged as a promising adjunct to conventional diagnostic methods for mTBI, offering potential in assessing injury severity and predicting outcomes.

Several proteins, including glial fibrillary acidic protein (GFAP), S100B, neuron-specific enolase (NSE), and ubiquitin C-terminal hydrolase-L1 (UCH-L1), have been identified as candidate biomarkers.[15,16] These proteins are indicative of neuronal and astrocytic injury, are detectable in cerebrospinal fluid and serum, and have been correlated with injury severity and clinical outcomes. Moreover, biomarkers have demonstrated the capacity to predict long-term outcomes and the development of secondary injuries; for example, S100B has been consistently associated with the prediction of both injury severity and outcomes in severe TBI cases.[17-19] Patients with head trauma exhibit significantly elevated adropin levels relative to healthy controls, suggesting that adropin may play a critical role in the physiological response to cranial injury and could serve as a potential biomarker for trauma severity. The current literature offers limited insight into the role of adropin as a TBI biomarker. Thus, further research is warranted to elucidate potential correlations between adropin levels and TBI outcomes.

Adropin is a peptide hormone that plays a significant role in maintaining metabolic and non-metabolic homeostasis.[20,21] Emerging evidence suggests that it has potential as a biomarker for central nervous system (CNS) disorders.[22,23] Adropin has been demonstrated to exert a protective effect in the context of neurological diseases, with a particular emphasis on those involving the cerebrovasculature. It is known that 2 potential receptors for adropin are identified: G protein-coupled receptor GPR19 and membrane-bound Notch1 ligand NB-3. As demonstrated in the accompanying figure, adropin exerts a multifaceted role in regulating the blood-brain barrier, encompassing stabilization, antioxidative effect, augmented brain perfusion, and neuromodulation. These effects are achieved through the synthesis of nitric oxide (NO) in endothelial cells, facilitated by the activation of endothelial nitric oxide synthetase (eNOS). Additionally, adropin has been shown to inhibit energy dysregulation in mitochondria by impeding the activity of pyruvate dehydrogenase kinase (PDK) (Figure 1).[23,24]

The primary objective of this study was to examine the relationship between adropin

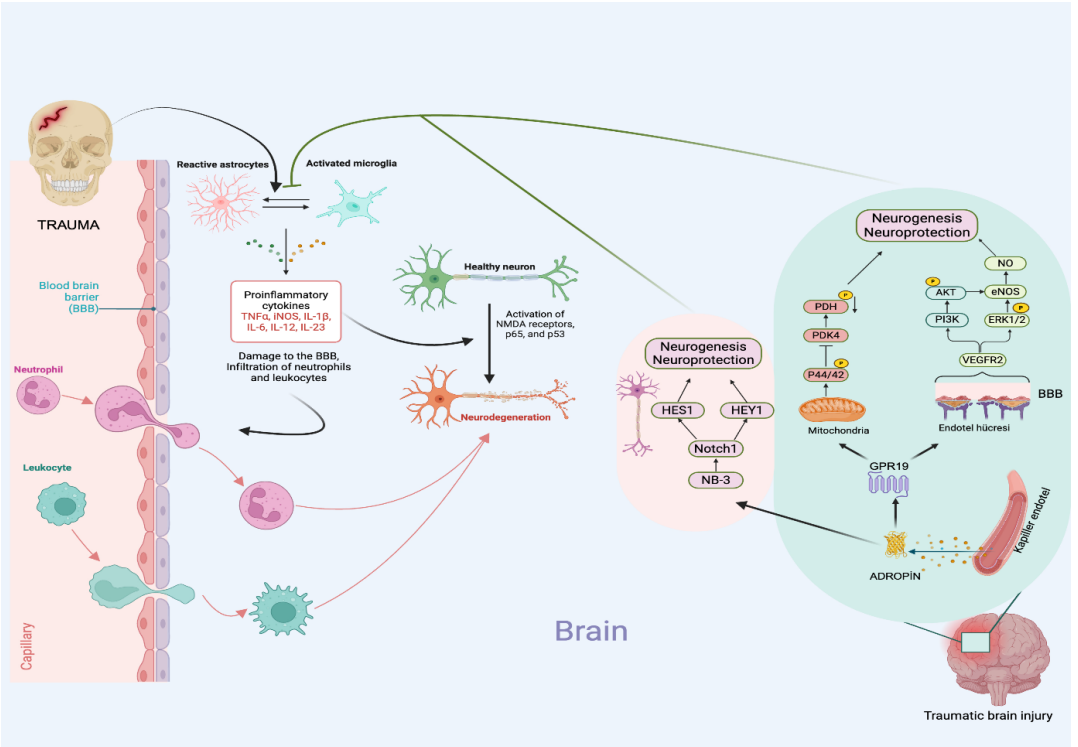

Figure 1. Neuroprotective pathways that are induced by the presence of adropin (Created in https://BioRender.com)[25]

levels and the severity of mTBI, as determined by clinical presentation and brain CT scans. In paediatric TBI, adropin levels have been observed to be positively correlated with trauma severity as determined by CT imaging. Elevated adropin levels have been shown to reflect increased severity of trauma. The findings of this study will facilitate the identification and follow-up of children with low-risk mTBI who do not require cranial CT scans.

METHODS

Design of study

A total of 56 patients aged between 0 and 18 years old, who had been referred to the emergency department at Erzurum City Hospital in Turkey with a diagnosis of mTBI between December 2021 and June 2023, were included in this observational prospective study. The predominant trauma mechanisms were falls (n=38), bicycle accidents (n=4), traffic accidents occurring both inside (n=6) and outside (n=3) the vehicle, sports injuries (n=1), impact to the head on a heater core (n=3), and impact to the head by stones during an earthquake (n=1).

The study incorporated patients who were admitted within 24 hours of sustaining a trauma. Patients with mTBI were classified into three distinct subgroups based on their clinical and radiological characteristics, designated as low-, intermediate-, and high-risk. Patients who were asymptomatic and exhibited normal neurological examination findings were classified as belonging to the low-risk group. Patients who had lost consciousness for a period of less than a few seconds, patients who had experienced short-term post-traumatic seizures, apathy and restlessness that had resolved immediately, children aged five years and older with amnesia, patients who had sustained a significant mechanism of trauma and nonfrontal subgaleal haematoma, and children aged less than three months who had been exposed to minor trauma were included in the medium-risk group. Patients exhibiting parieto-temporal subgaleal haematoma, recurrent vomiting, altered consciousness (irritability or somnolence), loss of consciousness exceeding a few seconds, headache unresponsive to analgesia and skull base or palpable bone fracture were classified as high risk.[13,26,27]

The control group comprised 57 patients aged between 0 and 18 years who attended the outpatient clinic for the purposes of undergoing

health checks and comprehensive health examinations.

The G Power 3.1.9.7 (Franz Faul, Germany) programme was utilized to calculate the effect size (d:0.809) based on the data obtained from the study conducted by Yu *et al*. The calculation was performed with 95% power and a 5% margin of error, indicating a minimum total sample size of 82 (41 in each group). The study was designed with 50 patients in each group to allow for potential attrition and to ensure the inclusion of a sufficient number of participants for the analysis.[28]

Methods of measurement

Five milliliter blood samples were transferred into plastic tubes with gel separator for adropin level measurements (ELISA). The tubes were then subjected to a centrifugation process at 4500 rpm at +4°C for a duration of five minutes. The serum thus obtained was stored in Eppendorf® tubes at -80 ˚C until required. The analysis was conducted in accordance with the ELISA method, employing kits procured from ELABSCIENCE Laboratories Inc. (Houston, Texas, USA), in strict adherence to the manufacturer's instructions. As the serum samples were diluted 10-fold, the results were multiplied by 10 and expressed as pg/mL.

Exclusion criteria include the following: Patients who presented with a delay of more than 24 hours following the trauma, and who had chronic neurological, hepatic, and/or renal disease, and who were taking medication for a pre-existing condition, and who had other systemic traumas associated with TBI, and who had communication or language problems, and for whom adequate trauma data was not provided, or who refused to participate in the study.

Thirteen samples were excluded from the study on the grounds of severe hemolysis. Of these, six were from the patient group and seven from the control group.

Statistical analysis

The data were recorded and analyzed on SPSS version 20.0 for Windows software (SPSS Inc., IL, USA). Descriptive data were expressed as numbers and percentages for categorical variables and mean ± standard deviation for numerical variables. The normality of the distribution was assessed in two ways: firstly, visually, using histograms and probability plots; and secondly, analytically, using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Groups were compared using Student's t-test for two-group comparisons or one-way analysis of variance (ANOVA) with Bonferroni's honestly significant difference (HSD) post hoc test for comparisons between three to four groups. A statistical analysis of gender distribution differences between the groups was performed using the chi-square test ($\chi 2$). The sensitivity, specificity, area under the curve (AUC), and cut-off value of serum adropin were calculated using the ROC curve, which indicates the predictive power of a given method. P values below 0.05 were considered to be statistically significant.

RESULTS

The mean age of patients in the study was 7.94 ± 3.73 years, while the mean age of controls was 7.52 ± 4.19 years. A non-significant difference was observed between the two groups with respect to age ($p = 0.598$) and gender distributions ($p = 0.542$). The patient group consisted of 19 females and 31 males while the control group consisted of 22 females and 28 males. When the patients presented to the emergency department, physical examination revealed subgaleal haematoma (n=29), scalp laceration (n=13), skull fracture (n=9), strabismus (n=1) and soft tissue damage (n=2). In eleven patients, no findings were found. While six patients described recurrent nausea and vomiting, the other symptoms were headache (n=9), syncope (n=1), amnesia (n=6), double vision(n=1), and otorrhagia (n=2). 29 patients had no reports of any problems. The mean serum adropin concentration was found to be 4815.04 ± 2970.26 pg/mL, which was significantly higher than the mean concentration observed in the control group, which was 1385.48 ± 290.50 pg/mL ($p <0.001$).

The serum adropin levels of the three groups, which have been constituted based on the risk of severe head trauma, are shown in Table 1. Of particular note are the elevated adropin levels observed in patients within the high-risk category.

Serum adropin levels were found to be significantly higher in the intermediate- and high-risk groups compared to the healthy controls ($p<0.001$ for both). Conversely, although serum adropin levels were higher in the low-risk trauma group compared to the control group, the difference was not statistically significant ($p = 1.0$) (Figure 2).

The patient group was also categorised according to the region of the head affected by the trauma: maxillofrontal (n = 12), temporoparietal

Table 1: Serum adropin levels of patients according to trauma risk classification

	High risk (n =20)	Intermediate risk (n =18)	Low risk (n =12)
Adropin (pg/mL)	7050.95 ± 2992.49	4527.39 ± 1317.54	1520.0 ± 282.93
Statistics			
Group 1 vs. group 2 vs. group 3[a]	p < 0.001	p < 0.001	p < 0.001
Group 1 vs. Group 2[a]	p = 0.01	p = 0.01	
Group 1 vs. Group 3[a]	p < 0.001		p < 0.001
Group 2 vs. Group 3[a]		p = 0.001	p = 0.001

The values are presented as the mean ± standard deviation. Group 1: High risk, Group 2: Intermediate risk, Group 3:Low risk and a: One-way ANOVA

(n = 10), occipital (n = 16), or none (n = 12). As demonstrated in Table 2, the highest serum adropin levels were observed in patients with temporoparietal trauma. Conversely, patients without trauma-related signs and symptoms exhibited lower serum adropin levels. Statistically significant differences were determined in adropin levels among the various trauma regions (see Table 2).

ROC curve analysis was applied to ascertain the diagnostic sensitivity and specificity of serum adropin levels in patients with TBI. Utilising a cut-off value of 1650.5 pg/mL, serum adropin levels demonstrated a sensitivity of 84% and a specificity of 82% in differentiating head trauma cases from healthy individuals (AUC = 0.902, p <0.001, 95% CI = 0.841-0.964) (see Figure 3).

The cut-off value of 5520 pg/mL for serum adropin levels was utilised to differentiate between high-risk and low-risk trauma patients. This resulted in sensitivity and specificity levels of 85% and 80%, respectively (AUC=0.870, p<0.001, 95% confidence interval (0.748-0.992)) (Figure 4).

The serum adropin test has been demonstrated to be a highly effective method of differentiating between high-risk trauma patients and low-risk patients with a high degree of sensitivity and specificity.

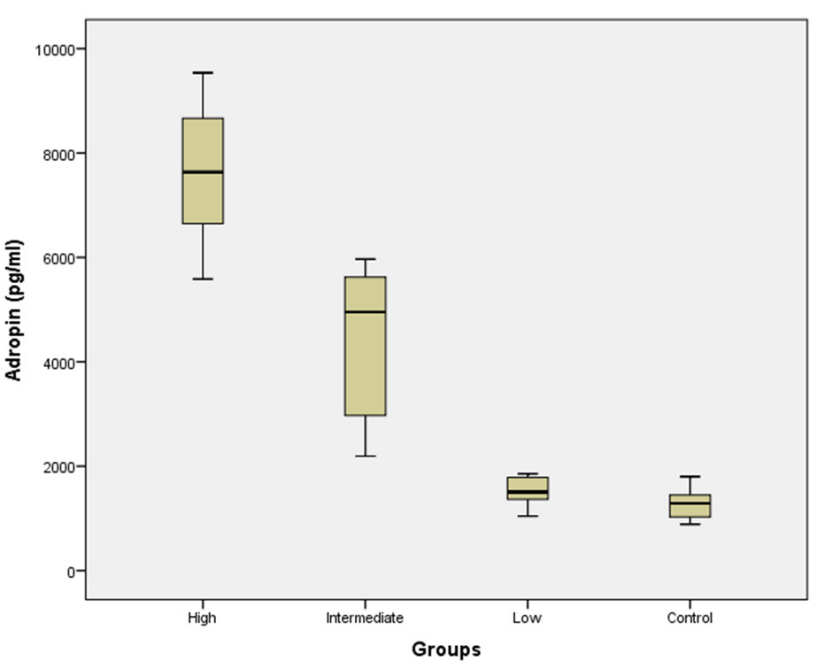

Figure 2. Adropin levels according to trauma severity risk groups

Table 2: Trauma region-associated adropin levels

	Maxillofacial (n=12)	Temporoparietal (n=10)	Occipital (n=16)	None (n=12)
Adropin (pg/mL) ± STD	3117.13 ± 1097.03	10464 ± 3038.66	6208.76 ± 956.17	1470.13 ± 309.53
Statistics				
1 vs. 2 vs. 3 vs 4[a]	p < 0.001	p < 0.001	p < 0.001	p < 0.001
1 vs. 2[a]	p < 0.001	p < 0.001		
1 vs. 3[a]	p < 0.001		p < 0.001	
1vs 4[a]	p=0.034			p=0.034
2 vs. 3[a]		p < 0.001	p < 0.001	
2 vs. 4[a]		p < 0.001		p < 0.001
3 vs. 4[a]			p < 0.001	p < 0.001

1: Maxillofacial region, 2:Temporoparietal region, 3: Occipital region, 4:None, a:One-way ANOVA

DISCUSSION

CT scanning is a critical diagnostic tool for children with head trauma; however, it presents several drawbacks. These include exposure to ionizing radiation, the absence of immediate oversight by emergency physicians, the need for sedation—particularly in younger children—and extended stays in the emergency department due to image extraction and reporting processes. Consequently, CT imaging should be reserved for selected cases. In this context, the incorporation of biomarkers could enhance patient triage, management, and follow-up, while simultaneously reducing unnecessary costs. In the context of Turkish healthcare, the financial burden associated with undergoing a CT brain scan (excluding the cost of sedation for children) is approximately 25 to 50 USD. In contrast, the cost of measuring adropin in a single sample is approximately 6 to 7 USD. Consequently, the financial outlay required for a single biomarker determination (adropin) is 4 to 8 times less than that of a CT brain scan.[29] Evidence indicates that the quantification of serum biomarkers not only reinforces established clinical decision rules but also improves diagnostic efficiency and minimizes radiation exposure.[30]

A comprehensive approach to mTBI necessitates consideration of injury severity, underlying mechanisms, and both clinical and pathophysiological findings. In the present study, injury severity was classified based on patients' clinical presentations and imaging characteristics.[31] Notably, low adropin levels were observed in the low-risk group that did not require CT imaging. Therefore, reduced adropin levels may serve as a valuable indicator for determining whether children with mTBI require observation in the emergency department.

A preliminary study examined the relationship between a panel of 16 biomarkers and TBI severity, uncovering a potential link with microvascular impairment. However, it is important to note that adropin was not included in this biomarker panel.[32] In the present study, elevated adropin levels were identified in the high-risk TBI group.

A comprehensive review of the existing literature on mTBI was undertaken to determine whether any studies had previously compared biomarker levels with the anatomical regions affected by trauma. This investigation revealed that adropin levels were highest in patients who sustained trauma to the temporoparietal region and were categorized as high-risk, whereas lower levels were observed in the maxillofrontal trauma group, and the lowest levels were found in asymptomatic patients. The present study, however, is not without limitations. Notably, a larger sample size would have enhanced the robustness of the findings, and the variability in the time interval between trauma and presentation to the emergency department precluded the optimization of post-traumatic blood sampling timing. Moreover, the potential impact of undiagnosed pre-existing conditions on serum biomarker levels cannot be ruled out.

In conclusion, the management of pediatric mTBI demands precise classification given the

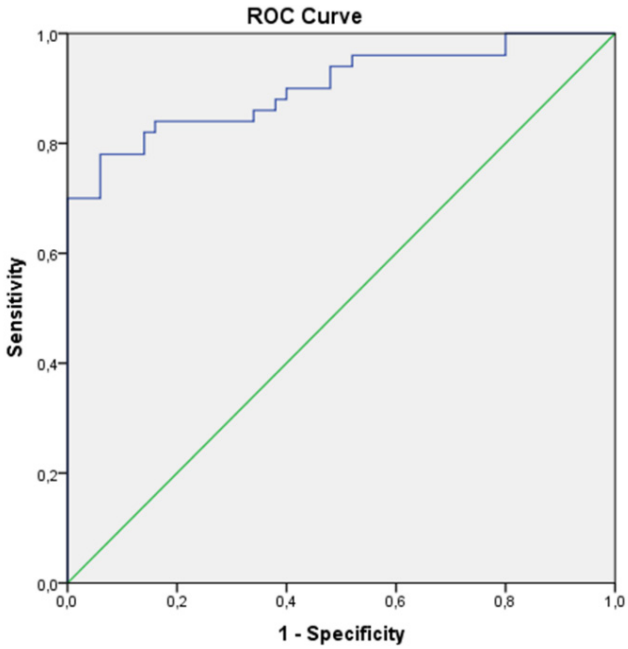

Figure 3. ROC curve analysis showing the diagnostic sensitivity and specificity of serum adropin levels in patients with minor head trauma

condition's complexity and the broad spectrum of severity levels. This study aimed to examine adropin levels in children with mTBI, with findings that may hold substantial prognostic value for moderate and severe head injuries. However, further research is essential to validate these results and clarify their clinical significance. It is imperative that standardized methodologies be adopted and that larger-scale studies be conducted to confirm the utility of biomarkers in pediatric mTBI. A thorough understanding of the pathophysiology and ongoing debates

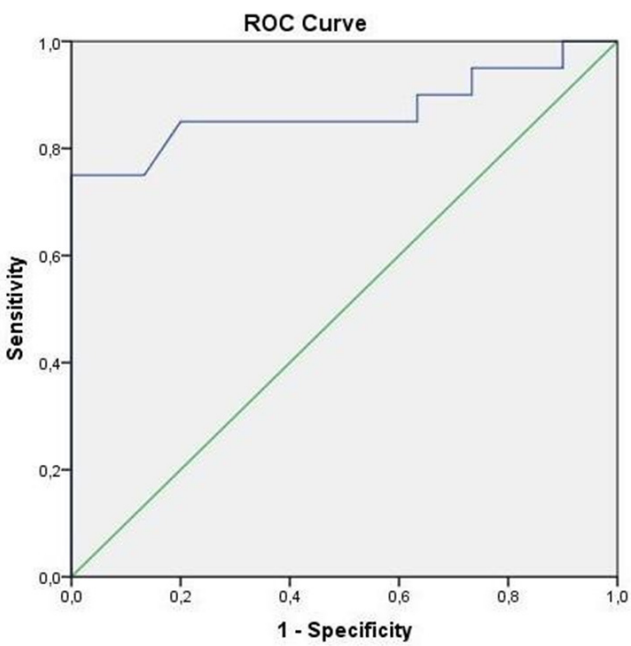

Figure 4. ROC curve analysis showing the diagnostic sensitivity and specificity of serum adropin levels in patients with high-risk and low-risk mtbı patients

surrounding mTBI classification could ultimately lead to improved clinical practices and outcomes for affected children.

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DISCLOSURE

Ethics: Approval for the study was granted by the Atatürk University clinical research ethics committee (Decision no. 2021/04).

Data availability: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Financial support: None. There is no financial support to cover the costs associated with the Adropin kit.

Conflict of interest: None

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