doi: 10.53446/actamednicomedia.1599482

Acta Medica Nicomedia

Cilt: 8 Sayı: 2 Haziran 2025 / Vol: 8 Issue: 2 June 2025
https://dergipark.org.tr/tr/pub/actamednicomedia

Research Article | Araştırma Makalesi

ISCHEMIA-MODIFIED ALBUMIN MAY NOT BE A RELIABLE BIOMARKER IN CHILDREN WITH ACUTE RHEUMATIC FEVER

AKUT ROMATİZMAL ATEŞİ OLAN ÇOCUKLARDA İSKEMİ MODİFİYE ALBÜMİN GÜVENİLİR BİR BİYOBELİRTEÇ OLMAYABİLİR

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ABSTRACT

Objective: Acute rheumatic fever (ARF) poses significant health challenges in low- and middle- income countries, particularly due to its potential to cause severe cardiac complications. This study investigated the role of ischemia-modified albumin (IMA) as a biomarker for inflammation in children diagnosed with ARF.

Methods: The study included 25 ARF patients and a control group of 25 healthy children and was conducted between January 2019 and May 2020 at a regional hospital. Clinical assessments and echocardiographic evaluations were performed, in addition to serum IMA level measurements at diagnosis and post-treatment.

Results: The findings indicated that while acute phase reactants such as C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) were elevated in the ARF patients, the IMA levels were not significantly different from those in the control group, both at diagnosis and post-treatment. Specifically, the IMA levels were lower at diagnosis (0.62 ± 0.73 ng/mL) compared to post-treatment (1.18 ± 0.94 ng/mL), with no consistent correlation with the CRP, although a negative correlation with the ESR was observed.

Conclusion: These findings suggest that IMA may not be a reliable biomarker for diagnosing and monitoring ARF in children, challenging previous claims about its utility in this patient group. Further research is necessary to explore the effects of other factors on IMA levels in this population.

Keywords: Acute rheumatic fever, ischemia-modified albumin, enzyme-linked immunosorbent assay

ÖZ

Amaç: Akut romatizmal ateş (ARA), gelişmekte olan ülkelerde sık görülen ve ciddi kardiyak komplikasyonlara yol açabilen önemli bir sağlık problemidir . Bu çalışmada, ARA tanısı alan çocuklarda inflamasyon belirteci olarak iskemi modifiye albüminin (IMA) rolü araştırılmıştır.

Yöntem: Çalışmaya 25 ARA hastası ve 25 sağlıklı çocuktan oluşan kontrol grubu dahil edilmiştir. Ocak 2019 ile Mayıs 2020 tarihleri arasında bölgesel bir hastanede yürütülmüştür. Klinik değerlendirmeler, ekokardiyografik incelemeler yapılmış; tanı anında ve tedavi sonrası serum IMA düzeyleri ölçülmüştür.

Bulgular: Bulgular, ARA hastalarında C-reaktif protein (CRP) ve eritrosit sedimantasyon hızı (ESR) gibi akut faz reaktanlarının yüksek olduğunu göstermiştir. Ancak, IMA düzeyleri hem tanı anında hem de tedavi sonrasında kontrol grubu ile anlamlı farklılık göstermemiştir. Tanı anındaki IMA düzeyleri (0.62 ± 0.73 ng/mL), tedavi sonrasına göre (1.18 ± 0.94 ng/mL) daha düşük olmakla birlikte CRP ile anlamlı bir korelasyon göstermemiştir; ancak ESR ile negatif korelasyon izlenmiştir.

Sonuç: Elde edilen bulgular, IMA'nın çocukluk çağı ARA tanı ve izleminde güvenilir bir biyobelirteç olmayabileceğini göstermekte; bu parametrenin bu hasta grubundaki kullanımına ilişkin önceki bulguları sorgulatmaktadır. IMA düzeylerini etkileyebilecek diğer faktörlerin ortaya konması için ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Akut romatizmal ateş, iskemi modifiye albümin, enzim bağlantılı immünosorbent test

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Submitted/Başvuru: 10.12.2024 • **Accepted/Kabul:** 18.04.2025 • **Published Online/Online Yayın:** 30.06.2025

Introduction

Acute rheumatic fever (ARF) is one of the most prevalent and serious cardiac diseases in developing countries. It is characterized by damage to the heart, joints, brain, and skin, and results due to an autoimmune response in susceptible individuals following group A streptococcal (GAS) pharyngitis. Cardiac involvement, primarily manifesting as pancarditis, predominantly presents with valvulitis. The prognosis for ARF depends on the occurrence of recurrence and the severity of cardiac involvement. Chronic rheumatic heart disease is a potential consequence of cardiac involvement, and accounts for 25%–45% of cardiovascular diseases in adults and remains a leading cause of heart failure in developing countries [1].

Detecting inflammation markers is important for early diagnosis, preventing missed cases, and distinguishing true GAS pharyngitis from carriers in high-risk populations. Consequently, biomarkers indicative of inflammation may facilitate early diagnosis and potentially improve long-term clinical outcomes.

The role of albumin in the human body has been well established for decades. However, it was later discovered that albumin undergoes conformational changes under various conditions such as hypoxia, acidosis, ischemia, and oxidative stress [2]. Ischemia-modified albumin (IMA) is a variant of albumin produced due to the degradation of its N-terminal region caused by tissue ischemia, hypoxia, or oxidative stress, leading to a diminished metal-binding capacity. Elevated circulating levels of IMA have been identified in ischemia, hypoxia, acidosis, and oxidative stress [3]. Despite some research conducted on IMA in ARF [4,5], its application in routine diagnosis and disease monitoring remains unclear. Hence, the aim of this study was to assess the potential role of IMA as an inflammation biomarker in children with ARF.

Methods

The study was conducted at Ministry of Health Van Regional Education and Research Hospital between January 2019 and May 2020. Patients and their parents were informed about the study and the additional blood sample collection. The local ethics committee approved the study, and informed consent was obtained from all the participants.

Children diagnosed with ARF in the pediatric cardiology department of our institution were included in the ARF group, while healthy children who presented to the pediatric cardiology department with symptoms like murmur, palpitation, and non-specific chest pain constituted the control group. Children with known congenital or acquired cardiac disease, any chronic diseases, and morbidity, and those receiving specific medication were excluded from the study.

Demographic information and a detailed history were obtained from all the participants. Following a thorough physical examination, each participant underwent electrocardiography and echocardiography. An erythrocyte sedimentation rate (ESR) above 30 mm/h and a CRP level exceeding 3 mg/dL were considered as elevated [6]. Anti-streptolysin O (ASO) levels were deemed high if they exceeded the age-specific upper limit, and serum albumin values below 35 g/L were categorized low [7–9].

Two experienced pediatric cardiologists performed a detailed echocardiographic evaluation using a Vivid 7 Pro echocardiography device (GE Vingmed Ultrasound AS, Horten, Norway) with a 3–6 M Hz transducer. Doppler and morphological findings were used in the diagnosis of rheumatic valvulitis in accordance with the 2015 Revised Jones Criteria [6].

Carditis was described as mild in the presence of trivial-to-mild valvar disease; moderate when there were valve lesions without signs or symptoms of heart failure and normal left ventricular function; and severe when there was severe valvar disease or moderate-to-severe valvar lesion with signs of heart failure [10]. Patients with mild carditis were treated with naproxen sodium, while those with moderate-to-severe carditis received oral prednisolone [11].

In addition to routine laboratory tests used for diagnosing and managing ARF, extra blood samples for IMA analysis were collected from all the ARF group participants at the time of diagnosis and post-treatment. Blood samples for IMA analysis were also collected from the control group. To ensure unbiased analysis, a nurse assigned a code to each blood sample, and neither the pediatric cardiologists nor the biochemists were aware of whether the sample belonged to the study or control group.

Venous blood samples for the IMA analysis were centrifuged for 15 min at 1000 × *g* at 2–8 °C after clotting at room temperature for 2 h. The serum was collected and stored at −80 °C until the day that it would be assayed. The concentration of serum IMA was analyzed via micro enzyme-linked immunosorbent assay (ELISA) using commercial kits (Wuhan Elabscience Biotechnology Co. Ltd., Wuhan, Hubei, China; Lot No. CRQXD8EW17 and MF4LTGELGA, respectively) and in accordance with the manufacturer's instructions.

Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). The mean ± standard deviation (SD) and frequency were used to express the descriptive statistics. The Independent Sample's t test was used for comparison of the groups. The Paired Sample's T test was used to compare the pre- and post-treatment findings in the patient group. One-way analysis of variance was used for comparison of the subgroups. Pearson's correlation analysis was used for the correlation analysis. The confidence interval was given as 95% and statistical significance was set at $p < 0.05$.

Results

The study included 50 participants, comprising 25 children diagnosed with ARF in the ARF group, and a control group of 25 healthy children. The mean ages of the ARF and control groups were 9.8 ± 2.3 and 10.6 ± 2.6 years, respectively (p = 0.167). In the ARF group, 11 (44%) patients were female compared to 14 (56%) in the control group, with no significant difference in the sex distribution between the groups (p = 0.572).

The clinical and laboratory findings of the ARF group based on the diagnostic criteria are summarized in Table 1. None of the patients had Sydenham chorea, subcutaneous nodules, or erythema nodosum.

Table 1. Findings of the ARF group based on the diagnostic criteria

	n (%)
Carditis	21 (84%)
Mild	12 (48%)
Moderate	7 (28%)
Severe	2 (8%)
Arthritis	20 (80%)
Fever	18 (72%)
Elevated ESR and/or CRP	25 (100%)
Elevated ASO titers	17 (68%)
Positive throat culture for group A β-hemolytic streptococcus	11 (44%)
Low albumin level	9 (36%)
First degree AV block	14 (56%)

ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, ASO: anti-streptolysin O

The mean ESR and CRP levels in the ARF group were significantly higher at the time of diagnosis compared to the post-treatment level (p = 0.000). In the ARF group, the albumin concentration was 36.5 ± 3.2 g/L, compared to 43 ± 1.99 g/dL in the control group. There was a statistically significant difference in albumin levels between the ARF and control groups (p < 0.001).

The mean IMA level in the ARF group at the time of diagnosis (0.62 ± 0.73 ng/mL) was significantly lower than the mean post-treatment level (1.18 ± 0.94 ng/mL) (p = 0.010). When compared with the control group, the mean IMA levels of both groups were similar at the time of diagnosis and post-treatment.

Additionally, the IMA level was found to be negatively correlated with the ESR at the time of diagnosis (p = 0.014, correlation coefficient = -0.487), whereas no correlation was observed between the IMA and CRP levels.

Table 2. Comparison of the mean serum IMA levels of the ARF and control groups

	ARF Group (n = 25)	Control Group (n = 25)	p-value
IMA			
Pre-treatment (mean ± SD)	0.62 ± 0.73	1.15 ± 1.21	0.063
Post-treatment (mean ± SD)	1.18 ± 0.94	1.15 ± 1.21	0.930
P-value	**0.010**	-	

T test, IMA is expressed as ng/mL

Discussion

This study examined the role of IMA as an inflammatory marker in the diagnosis and monitoring of ARF. According to the findings, while acute phase reactants such as CRP and ESR are typically elevated, IMA levels may not be significantly increased in children with ARF. This suggests that IMA may not serve as a reliable biomarker for diagnosing or monitoring ARF in the pediatric population.

The initial manifestation of ARF typically occurs between the ages of 5 and 14 years, and the current investigation included patients within this age group [12]. The findings herein align with previous research on this population. ARF occurs with similar prevalence in both males and females [12]. In the present analysis, while there was a slightly higher prevalence among the males, the difference between the sexes was not statistically significant. Consistent with prior findings, the prevalence of carditis, fever, and arthritis/polyarthralgia was 100%, 72%, and 80%, respectively [6,13].

IMA is a biomarker that has been extensively studied in cardiovascular diseases, particularly in ischemic heart diseases [14,15]. Ischemic conditions may lead to the generation of free radicals, and the release of free metal ions and acidosis. These free radicals result in albumin with reduced metal-binding capacity. Beyond cardiovascular disease, IMA has also been investigated in chronic non-cardiac diseases that may lead to increased oxidative stress or chronic inflammation [16].

Some studies have shown a positive correlation between IMA and acute phase reactants [5,4,17]. The IMA values reported in these studies on ARF are given in Table 3. Other research has found significantly higher IMA levels in patients with ARF compared to the control groups. In the current study, in contrast, it was found to be lower compared to the control group. Nevertheless, upon looking at the values, there was no substantial difference in the IMA levels compared to previous studies.

In the present study, the IMA levels were measured using ELISA. Unlike the technique for measuring cobalt-binding capacity in the albumin cobalt binding (ACB) test, the results were obtained using specific antibody in ELISA. Çalışkan et al. reported that the measurement of IMA levels using ELISA was not a reliable method for diagnosing mesenteric ischemia [18]. In the study of Sbarouni, which evaluated IMA levels using the ACB test, no statistically significant increase was found in patients

with dilated cardiomyopathy compared to the healthy group [19]. Roy et al. reported that IMA levels decreased after an exercise test in patients with peripheral vascular disease [20]. It has been suggested that this decline may be due to the interference of metabolites released from skeletal muscle during exercise with IMA measurement. Furthermore, molecules and complexes generated due to a compromised immune response in ARF may affect the result of IMA levels, potentially impacting its reliability as a biomarker in this condition.

Table 3. Comparison of the IMA values of children with ARF in different studies

	IMA Values
Dawn et al [(17)*]	0.42 ± 0.05 ABSU
Toker et al [(4)*]	0.55 (0.44 - 1.13) ABSU
Karataş et al [(5)*]	0.54 ± 0.12 ABSU
The current study	0.62 ± 0.73 ng/mL

*ACB test, ABSU- absorbance units,

Toker et al. found that IMA levels were elevated during the acute phase before therapy and subsequently diminished following treatment. Conversely, according to the findings of the current study, the level of IMA, which was reduced pre-treatment, increased post-treatment. It may be speculated that this may have resulted from the confounding influence of the administered medications. There is a need for further research on how medications influence IMA levels, as no studies have been conducted on this topic to date.

Moreover, the albumin concentration serves as the primary predictor of IMA levels [22]. Variations in albumin concentrations may explain the differences in IMA levels observed across studies. Additionally, extremely high or low albumin levels could have led to falsely low IMA readings [21]. Supporting this, the study of Gaze et al. demonstrated a negative correlation between IMA levels and albumin levels below 34 g/L [22].

The current study had several limitations that should be considered. First, it was conducted at a single center. Furthermore, there was a relatively small sample size, which may have affected the generalizability of the findings. However, despite this limitation, this is the only study to have reported lower IMA levels in ARF, as previous studies have demonstrated elevated levels. This emphasizes the necessity for further studies with larger cohorts to better understand this variation and its therapeutic implications. Moreover, serial measurements of IMA rather than measurements at the time of diagnosis and post-treatment would yield more reliable data. Additionally, it is necessary to acknowledge that IMA levels may produce different findings based on the measuring technique employed, such as ELISA or the ACB test, which may possibly account for the differences reported among the research. Therefore, more research that directly compares these two methods is required in order to assess their reliability.

In conclusion, this study aimed to investigate the role of IMA in pediatric patients with ARF. The findings suggest a negative correlation between the IMA level and ARF. However, to better assess the reliability of IMA in the diagnosis and monitoring of ARF and elucidate the mechanisms influencing IMA levels, additional multicenter studies with larger sample sizes and different techniques are needed.

Ethical Approval

The study was approved by the ethics committee of Ministry of Health Van Regional Education and Research Hospital (2018/14).

Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

YND: Writing – Original draft; MR: Writing; ZE: Investigation; MOB: Methodology; SE: Supervision

Financial Support

This research received no specific grant from any funding agency, commercial or not-for-profit sector.

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