

Diagnostic Yield of Laboratory-driven Referrals in Pediatric Rheumatology: Clinical Characteristics and Outcomes

Çocuk Romatolojisinde Laboratuvar Temelli Yönlendirmelerin Tanısal Değeri ve Klinik Sonuçları

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Abstract

Objective: Referrals to pediatric rheumatology clinics encompass a broad range of clinical scenarios, including cases prompted by abnormal laboratory findings in the absence of clear clinical suspicion for rheumatic disease. This study aimed to evaluate the clinical characteristics and diagnostic outcomes of children referred for abnormal laboratory results.

Methods: This retrospective study included pediatric patients evaluated at the pediatric rheumatology clinic of our institution between April 2025 and February 2026 who were referred for abnormal laboratory results without definite clinical suspicion of rheumatic disease. Demographic features, referral indications, laboratory findings, clinical characteristics, and final diagnoses were recorded. Patients with previously established rheumatic disease were excluded. Statistical comparisons were performed between patients with and without rheumatologic diagnoses.

Results: A total of 123 patients were included. The median age was 7 years (range 1-18), and 52.8% were female. Diagnostic testing had been initiated without symptoms in 26% of patients. Overall, 23.6% received a rheumatologic diagnosis, while 76.4% were classified as having non-rheumatologic conditions. Periodic fever syndromes and juvenile idiopathic arthritis were the most common rheumatologic diagnoses. Healthy children and allergic diseases represented a substantial proportion of the non-rheumatologic outcomes. Male sex, fever, arthritis, elevated acute-phase reactants, and decreased complement levels were significantly associated with a rheumatologic diagnosis, whereas isolated arthralgia and myalgia were more frequent in non-rheumatologic cases.

Conclusion: Most children referred because of abnormal laboratory findings did not receive a rheumatologic diagnosis. Objective inflammatory findings were more predictive of true rheumatic disease than isolated laboratory abnormalities. A symptom-based approach to testing and referral may improve diagnostic accuracy and reduce unnecessary specialist consultations.

Keywords: Pediatrics, rheumatology, laboratory markers, inflammation, autoantibody



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Öz

Amaç: Çocuk romatoloji kliniklerine yapılan başvurular geniş bir klinik çeşitlilik göstermekte olup, bu başvurular arasında pozitif saptanan laboratuvar sonuçlarına bağlı yönlendirmeler de bulunmaktadır. Bu çalışmanın amacı, anormal laboratuvar bulguları nedeniyle çocuk romatoloji bölümüne yönlendirilen hastaların klinik özelliklerini ve tanısal sonuçlarını değerlendirmektir.

Yöntem: Bu retrospektif çalışmaya, Nisan 2025 ile Şubat 2026 tarihleri arasında hastanemiz çocuk romatoloji kliniğinde, belirgin klinik romatolojik hastalık şüphesi olmaksızın anormal laboratuvar sonuçları nedeniyle değerlendirilen pediatrik hastalar dahil edilmiştir. Demografik özellikler, yönlendirme nedenleri, laboratuvar bulguları, klinik özellikler ve son tanımlar kaydedilmiştir. Daha önce romatolojik hastalık tanısı almış olan hastalar çalışma dışı bırakılmıştır. Romatolojik tanı alan ve almayan hastalar arasında istatistiksel karşılaştırmalar yapılmıştır.

Bulgular: Çalışmaya dahil edilen 123 hastanın ortalama (min-maks) yaşı 7 (1-18) yıl olup, %52,8'i kızdı. Hastaların %26'sında tanısal testlerin herhangi bir semptom olmaksızın yapıldığı görüldü. Hastaların %23,6'sına romatolojik tanı konulurken, %76,4'ü romatolojik olmayan durumlar olarak sınıflandırılmıştır. Periyodik ateş sendromları ve juvenil idiyopatik artrit en sık romatolojik tanımlar olmuştur. Sağlıklı çocuklar ve alerjik hastalıklar romatolojik olmayan sonuçların önemli bir kısmını oluşturmuştur. Erkek cinsiyet, ateş, artrit, yüksek akut faz reaktanları ve düşük kompleman düzeyleri romatolojik tanı ile anlamlı şekilde ilişkili bulunurken, izole artralji ve miyalji romatolojik olmayan hastalarda daha sık saptanmıştır.

Sonuç: Anormal laboratuvar bulguları nedeniyle yönlendirilen çocukların çoğuna romatolojik tanı konulmamıştır. Objektif enflamatuvar bulgular, izole laboratuvar anormalliklerine kıyasla gerçek romatolojik hastalığı daha iyi öngörmektedir. Test isteme ve yönlendirme süreçlerinde semptom temelli yaklaşımın benimsenmesi, tanısal doğruluğu artırabilir ve gereksiz uzman başvurularını azaltabilir.

Anahtar Kelimeler: Pediatri, romatoloji, laboratuvar belirteçleri, enflamasyon, otoantikör

Introduction

Pediatric rheumatic diseases (PRDs) are autoinflammatory or autoimmune conditions that can affect multiple organs and systems, primarily the musculoskeletal system, connective tissues, and vascular structures. The true prevalence of PRDs is not precisely known and varies across geographic regions⁽¹⁾. Although an estimated 6-7 million children worldwide are affected, the number of pediatric rheumatologists remains insufficient globally⁽²⁾. As for Türkiye, pediatric rheumatology is a developing subspecialty, and the country's genetic and geographic background contributes to a relatively high frequency of autoinflammatory diseases⁽³⁾.

Children suspected of having rheumatic disease often present with nonspecific complaints, leading to frequent referrals to pediatric rheumatology clinics. However, previous reports indicate that only approximately half of referred patients ultimately receive a rheumatic diagnosis^(4,5). In daily practice, referrals are frequently triggered by isolated laboratory abnormalities that are not supported by compatible clinical findings. Such referrals may cause unnecessary family anxiety, delay the appropriate evaluation of other conditions, and increase the healthcare burden.

Given the limited availability of specialists and the increasing demand for consultations, distinguishing clinically meaningful laboratory findings from incidental test positivity is essential. Better characterization of these referrals may improve referral accuracy and optimize

healthcare utilization. Therefore, this study aimed to evaluate the characteristics and clinical outcomes of children referred to pediatric rheumatology clinics for abnormal laboratory findings.

Materials and Methods

This retrospective study included pediatric patients who were evaluated at the pediatric rheumatology clinic of our institution between April 2025 and February 2026 after being referred for abnormal laboratory results in the absence of a definite clinical suspicion of rheumatic disease.

Abnormal laboratory findings were defined as any positive or elevated rheumatologic or inflammatory laboratory parameter detected prior to referral. Because laboratory cut-off values may vary between centers, these findings were interpreted according to the reference ranges and cut-off values of the referring institution. Patients with a previously established diagnosis of rheumatic disease, patients referred primarily due to clinical findings suggestive of rheumatic disease (e.g., persistent arthritis, vasculitic rash, serositis), patients with a follow-up period shorter than six months, and patients with incomplete medical records were excluded from the study.

All patients had undergone a comprehensive evaluation by an experienced pediatric rheumatologist, including a detailed medical history and a complete systemic and musculoskeletal physical examination. All pathological

findings were documented in standardized medical records. Data extracted from patient files were recorded in a standardized case report form and included demographic characteristics, clinical features, referral indications, laboratory parameters (including the abnormal test results prompting referral), final diagnoses, and clinical outcomes.

All procedures were performed in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital Ethics Committee (approval no: 2025/03-30, date: 10.04.2025). Prior to inclusion in the study, written informed consent was obtained from each participant's parent or legal guardian.

Statistical Analysis

Data analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as mean $\pm$ standard deviation or median (min-max) for continuous variables, and as number (percentage) for categorical variables. The normality of the distribution was assessed using the Kolmogorov-Smirnov test. Comparisons between groups were performed using the independent samples t-test or Mann-Whitney U test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables, as appropriate. A p-value of <0.05 was considered statistically significant.

Results

A total of 123 patients were included in the study. The cohort comprised 65 females (52.8%) and 58 males (47.2%), with a median age of 7 years (range: 1-18 years) and a median follow-up duration of 7 months (range: 6-14 months). Most referrals originated from general pediatrics and primary care/family health centers. Baseline demographic characteristics, referral sources, indications, and presenting clinical features are summarized in Table 1.

The most common referral indication was heterozygous *Mediterranean Fever (MEFV)* gene mutation positivity, followed by antinuclear antibodies (ANA) positivity, elevated antistreptolysin O (ASO) titers, and increased acute-phase reactants (APR), whereas complement abnormalities, urinary findings, and cytopenias were less frequent (Table 1).

Diagnostic testing was initiated in 26% (n=32) of patients without symptoms, whereas 74% (n=91) underwent testing because of at least one clinical complaint. Among

Table 1. Demographic and clinical characteristics of the referred patients

Variables	Patients n (%) 123 (100%)
Demographics	
Gender (male/female)	58 (47.2%)/65 (52.8%)
Age, years, median (min-max)	7 (1-18)
Age at presentation, years, median (min-max)	6 (0.6-17)
Follow-up duration, months, median (min-max)	7 (6-14)
Family history	26 (21.1%)
Consanguinity	10 (8.1%)
Referral indication	
MEFV gene variation	30 (24.4%)
ANA positivity	27 (22.0%)
Elevated ASO titer	17 (13.9%)
Elevated APR	12 (9.8%)
RF positivity	11 (8.9%)
Elevated CK	11 (8.9%)
HLA-B27 positivity	6 (4.9%)
Cytopenia	3 (2.4%)
Low C3 level	2 (1.6%)
Proteinuria	2 (1.6%)
Hematuria	2 (1.6%)
Indication for testing	
No symptoms (incidental finding/screening)	32 (26%)
Symptoms present	91 (74%)
Presenting complaints	
Musculoskeletal symptoms	38 (41.7%)
Arthralgia	18 (14.6%)
Myalgia	12 (9.8%)
Limb pain	10 (8.1%)
Arthritis	7 (5.7%)
Fever	21 (17.1%)
Aphthous stomatitis	13 (10.6%)
Rash	10 (8.1%)
Abdominal pain	9 (7.3%)
Referring unit	
General pediatrics	50 (40.6%)
Primary care/family health center	32 (26%)
Pediatric allergy and immunology	17 (13.9%)
Orthopedics	12 (9.8%)
Physical medicine and rehabilitation	7 (5.7%)
Otorhinolaryngology	5 (4%)
MEFV: Mediterranean Fever, ANA: Antinuclear antibody, ASO: Antistreptolysin O, APR: Acute-phase reactants, RF: Rheumatoid factor, CK: Creatine kinase, HLA-B27: Human leukocyte antigen B27, C3: Complement component 3	

symptomatic patients, musculoskeletal manifestations were the most frequent, followed by fever, aphthous stomatitis, rash, and abdominal pain (Table 1).

Final diagnoses during follow-up are summarized in Table 2. Overall, 23.6% (n=29) of patients received a rheumatologic diagnosis, whereas the majority (76.4%, n=94) received a non-rheumatologic diagnosis. Among rheumatologic diseases, periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome and juvenile idiopathic arthritis (JIA) were the most common diagnoses. Notably, 13.3% of patients carrying a heterozygous mutation in the *MEFV* gene exhibited clinical features of Familial Mediterranean fever (FMF) or evidence of subclinical inflammation. Within the non-rheumatologic group, healthy children made up the largest proportion, followed by those with allergic disorders, vitamin D deficiency, hypermobility, and infections; other diagnoses occurred less frequently (Table 2).

Among the 29 patients ultimately diagnosed with a rheumatologic disease, 13.8% (n=4) had been tested

while asymptomatic, whereas 86.2% (n=25) had been tested because of at least one clinical symptom (p=0.08). Although the difference did not reach statistical significance, rheumatologic diagnoses were proportionately more frequent among symptomatic patients (Table 3).

When patients with and without a rheumatologic diagnosis were compared with respect to clinical, laboratory, and demographic characteristics, male sex, fever, arthritis, elevated APR, and decreased complement component 3 (C3) levels were significantly more frequent in patients with a rheumatologic diagnosis, whereas arthralgia and myalgia were significantly more common among those without a rheumatologic diagnosis (Table 3). No significant differences were observed between the two groups regarding mucocutaneous symptoms, abdominal pain, or rash. Likewise, consanguinity, family history of rheumatic disease, and laboratory parameters-including cytopenia, hematuria, and proteinuria; elevated ASO and creatine kinase levels; rheumatoid factor (RF) levels; human leukocyte antigen B27 (HLA-B27) positivity; and ANA positivity-did not differ significantly between the groups (data not shown).

Discussion

This study evaluated the diagnostic yield and clinical outcomes of children referred to pediatric rheumatology primarily because of abnormal laboratory findings. Only 23.6% of referred patients ultimately received a rheumatologic diagnosis, a rate substantially lower than previously reported national and international figures. While earlier studies reported diagnostic yields between 40% and 73%⁽⁶⁻⁸⁾, our findings align more closely with recent data specifically examining laboratory-driven referrals, in which approximately 30% of patients received a rheumatologic diagnosis⁽⁹⁾. While early referral remains essential in suspected inflammatory disease, our findings suggest that indiscriminate testing in the absence of clinical suspicion may reduce diagnostic efficiency.

The predominance of non-rheumatologic and even healthy outcomes in our cohort highlights a critical issue in pediatric practice: laboratory abnormalities in children frequently lack specificity when interpreted outside an appropriate clinical context. Incidental positive laboratory findings often coexist with common pediatric conditions, lowering pretest probability and inflating referral rates. Although periodic fever syndromes and inflammatory arthritis accounted for most confirmed rheumatologic diagnoses, these conditions remain fundamentally clinical diagnoses and are best

Table 2. Final diagnoses during follow-up in patients referred for suspected laboratory abnormalities	
Diagnoses	Patients n (%)
Rheumatologic diagnoses	29 (23.6%)
PFAPA	10 (8.1%)
JIA	5 (4%)
FMF	4 (3.3%)
RAS	4 (3.3%)
PSRA	2 (1.6%)
ARF	2 (1.6%)
CTD	2 (1.6%)
Non-rheumatologic diagnoses	94 (76.4%)
Allergic disease	15 (12.2%)
Vitamin D deficiency	10 (8.1%)
Hypermobility	8 (6.5%)
Infection	7 (5.7%)
Orthopedic condition	4 (3.3%)
Dermatologic condition	4 (3.3%)
Growing pains	4 (3.3%)
Gastroenterologic disease	3 (2.4%)
Hematologic disorder	1 (0.8%)
Healthy child	38 (30.9%)
PFAPA: Periodic fever, aphthous stomatitis, pharyngitis, adenitis, JIA: Juvenile idiopathic arthritis, FMF: Familial Mediterranean fever, RAS: Recurrent aphthous stomatitis, PSRA: Post-streptococcal reactive arthritis, ARF: Acute rheumatic fever, CTD: Connective tissue disease	

Table 3. Comparison of clinical, laboratory, and demographic features and test indications between patients with and without rheumatologic diagnosis at final follow-up

Variable	Patients with rheumatologic diagnosis (n=29)	Patients without rheumatologic diagnosis (n=94)	p-value
Gender, n (%)			
Male	21 (72.4%)	37 (39.4%)	0.002
Female	8 (27.6%)	57 (60.6%)	
Indications for laboratory testing, n (%)			
Asymptomatic (screening/incidental finding)	4 (13.8%)	28 (29.8%)	0.08
Symptomatic	25 (86.2%)	66 (70.2%)	
Symptoms, n (%)			
Fever	14 (66.7%)	7 (33.3%)	<0.001
Arthritis	7 (100%)	0	<0.001
Myalgia	0	12 (100%)	0.04
Arthralgia	0	18 (100%)	0.01
Laboratory, n (%)			
Elevated APR	9 (100%)	0	<0.001
Decreased C3	2 (100%)	0	0.01
Percentages for demographic, symptom and laboratory variables represent row proportions, whereas percentages for referral variables represent column proportions			
APR: Acute phase reactants, C3: Complement component 3			

identified through structured history and examination rather than by laboratory screening alone.

Referrals were most frequently triggered by positivity for heterozygous *MEFV* mutation, ANA, or elevated ASO titers. In regions such as Türkiye, where FMF prevalence and carrier frequency are high⁽¹⁰⁾, widespread genetic testing may increase the risk of overinterpreting heterozygous variants. However, FMF remains primarily a clinical diagnosis, with genetic findings serving a supportive role⁽¹¹⁾. Although a subset of heterozygous carriers in our cohort met diagnostic criteria based on compatible clinical features and subclinical inflammation, most carriers did not meet these criteria. As emphasized in European Alliance of Associations for Rheumatology/Paediatric Rheumatology European Society recommendations⁽¹²⁾, the marked phenotypic heterogeneity of FMF and the complexity of variant interpretation necessitate expert clinical judgment. These findings reinforce that heterozygosity alone should not be considered diagnostic in the absence of clinical correlation.

ANA positivity did not differentiate between patients with and without rheumatologic disease in our cohort. Although ANA is classically associated with connective tissue diseases, particularly systemic lupus erythematosus, its prevalence may reach up to 15% in otherwise healthy children^(13,14).

Furthermore, a national cohort study of children referred exclusively for ANA positivity reported that none developed ANA-associated rheumatic disease during more than four years of follow-up⁽¹⁵⁾. Notably, in our cohort, ANA positivity among non-rheumatologic conditions was most frequently observed in children with allergic diseases, a finding consistent with previous reports demonstrating ANA reactivity in atopic populations⁽¹⁶⁾. These observations underscore that ANA testing, when used indiscriminately, has limited specificity and may contribute to over-referral.

A comparable pattern was noted for other commonly requested tests, including ASO, RF, and HLA-B27. ASO levels rise about one week after infection, peak within three to five weeks, and may remain elevated for several months. Interpretation of streptococcal serology can be challenging in regions where group A streptococcal infections are common, as a positive ASO titer often reflects prior exposure rather than active rheumatic pathology^(17,18). Therefore, isolated ASO positivity in the absence of compatible clinical findings should not be considered evidence of rheumatic disease. Likewise, RF and HLA-B27 are primarily used for subclassifying JIA after a clinical diagnosis has been established and have limited value as screening tools⁽¹⁹⁾. Our findings suggest that ordering these tests in the absence

of objective inflammatory findings may create diagnostic ambiguity rather than clarity.

In our study, objective inflammatory and immunologic findings—including fever, arthritis, elevated APR, and decreased C3 levels—were significantly associated with confirmed rheumatologic disease, whereas isolated arthralgia and myalgia were more common in non-rheumatologic cases. These findings highlight the critical importance of objective inflammatory markers in distinguishing true immune-mediated disorders from non-specific complaints. Fever, arthritis, and elevated inflammatory markers reflect ongoing systemic inflammation and substantially increase the likelihood of an underlying rheumatologic condition⁽²⁰⁾. In contrast, isolated arthralgia and myalgia, particularly in the absence of laboratory evidence of inflammation, are common in childhood and are more frequently attributable to benign, mechanical, infectious, or functional etiologies. The differential diagnosis of pediatric musculoskeletal pain is broad and includes orthopedic, infectious, inflammatory, and malignant conditions^(21,22). Therefore, careful assessment of pain characteristics such as morning stiffness, objective joint swelling, limitation of movement, and response to activity is essential to determine whether the pattern is inflammatory⁽²³⁾. Collectively, our findings reinforce that clinical reasoning grounded in inflammatory pattern recognition appears far more predictive than reliance on isolated laboratory abnormalities.

Study Limitations

This study has limitations inherent in its retrospective single-center design. Referral practices may reflect local patterns and disease prevalence; follow-up duration, although sufficient for most diagnoses, may not fully exclude late-onset disease in a minority of patients. Nevertheless, the study provides real-world data from a high-prevalence autoinflammatory setting and specifically addresses laboratory-driven referral patterns, a topic that remains underexplored.

Conclusion

Pediatric rheumatology encompasses a broad range of clinical presentations, including referrals prompted solely by laboratory abnormalities. In our cohort, most children referred for abnormal test results did not receive a rheumatologic diagnosis. Objective inflammatory findings such as fever, arthritis, and elevated APR, were more predictive of true rheumatic disease than isolated

laboratory abnormalities or non-specific pain complaints. In settings where genetic and autoantibody testing is widely available, laboratory-driven referrals may reduce pretest probability and increase healthcare burden. A symptom-based approach to testing and referral is therefore essential to improve diagnostic accuracy and minimize unnecessary specialist consultations. While early referral remains crucial in suspected inflammatory disease, indiscriminate testing without clinical suspicion may compromise diagnostic efficiency.

Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital Ethics Committee (approval no: 2025/03-30, date: 10.04.2025).

Informed Consent: Prior to inclusion in the study, written informed consent was obtained from each participant's parent or legal guardian.

Footnotes

Authorship Contributions

Concept: R.B.T., Design: R.B.T., F.D., Data Collection or Processing: R.B.T., D.O., M.A., F.D., Analysis or Interpretation: R.B.T., D.O., M.A., F.D., Literature Search: R.B.T., D.O., M.A., F.D., Writing: R.B.T.

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