Print ISSN 1110-208X.

Online ISSN 2357-0016

Kidney Function and Renal Resistive Index in Children with Juvenile Idiopathic Arthritis

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Received:
Accepted:

Abstract:

Background: Juvenile idiopathic arthritis (JIA) represented the most common chronic rheumatologic disorder in children. While joint inflammation was the primary manifestation, growing evidence indicated that extra-articular complications, particularly renal involvement, could develop early and often remain asymptomatic. Aim: To evaluate early renal functional changes in children with JIA and examine their association with disease activity and treatment regimens. **Methods:** This case–control study conducted on 50 children with JIA and 50 age- and sex-matched healthy controls. All participants underwent detailed clinical and laboratory assessments. Renal evaluation included serum creatinine, estimated glomerular filtration rate (eGFR), urinary albumin excretion, and Doppler ultrasonography for measurement of the renal resistive index (RRI). Disease activity was assessed using the Juvenile Arthritis Disease Activity Score (JADAS-27). **Results:** Compared with controls, children with JIA showed a significant reduction in eGFR and an elevation in RRI ($p < 0.05$). Higher RRI values correlated with increased disease activity, were more pronounced in cases receiving biologic agents than those on methotrexate, and were associated with ANA/RF positivity, greater urinary albumin levels, and reduced eGFR. **Conclusion:** JIA is linked with subtle renal dysfunction that may not be evident clinically. Routine incorporation of Doppler-based RRI into follow-up protocols could aid in the early recognition and surveillance of renal involvement in affected children.

Keywords: Kidney function; Renal Resistive Index; Children; JIA: RRI

Introduction

Juvenile idiopathic arthritis (JIA) is recognized as the most commonly occurring chronic rheumatologic disorder within the pediatric population and represents a condition of substantial clinical relevance due to its long-term implications on growth, development, and overall health. According to the internationally accepted criteria set forth by the International League of Associations for Rheumatology (ILAR), JIA is characterized as a type of arthritis with unknown or uncertain etiology that develops prior to the age of 16 years and persists for a minimum duration of six weeks, following careful exclusion of other identifiable, secondary, or well-characterized causes [(1)].

The ILAR classification system further subdivides JIA into six primary categories based on several key factors, including clinical manifestations, laboratory findings, disease trajectory, and long-term outcomes. These categories comprise systemic JIA, oligoarticular JIA, polyarticular rheumatoid factor (RF)–positive, polyarticular RF–negative, enthesitis-related arthritis (ERA), and psoriatic arthritis (PsA). In instances where the clinical presentation does not conform clearly to a single subtype or exhibits overlapping features across multiple categories, the disease is classified as undifferentiated arthritis [(2)].

While joint involvement represents the hallmark of the disease, JIA may also give rise to extra-articular complications, which can include ocular manifestations such as uveitis and systemic involvement such as cardiovascular disease (CVD). Moreover, although it is less commonly emphasized in the literature, renal impairment can develop in children with JIA, likely due to systemic inflammatory processes and subclinical endothelial dysfunction. These pathophysiological changes may predispose affected children to hypertension, renal injury, and an increased long-term cardiovascular risk [(3)].

In rare and severe scenarios, persistent uncontrolled inflammation may progress to secondary amyloidosis, whereas prolonged or intensive exposure to disease-modifying anti-rheumatic drugs (DMARDs) has the potential to contribute to nephrotoxic effects [(4)]. Early renal alterations can often be detected via laboratory investigations or advanced imaging techniques. One particularly informative and non-invasive parameter is the renal resistive index (RRI), which is measured via Doppler ultrasonography of the renal vasculature. RRI has emerged as a sensitive indicator of intrarenal vascular resistance and early hemodynamic changes that may precede overt renal dysfunction [(5,6)].

In light of these considerations, the present investigation was specifically designed to evaluate early renal functional changes in children diagnosed with JIA, and to explore potential associations between these renal alterations, disease activity, and the effects of ongoing therapeutic regimens.

Subjects and Methods

Study Design and Population

The current investigation utilized a case–control study design and was conducted within the Pediatrics Department at Benha University Hospitals over a one-year period spanning from May 2024 to May 2025. The study cohort consisted of 50 children diagnosed with JIA, including 35 female participants and 15 male participants, with a mean age of 8.5 years and a standard deviation of 2.8 years. For comparative purposes, a control group comprising 50 age- and sex-matched healthy children was also recruited. This control group included 32 females and 18 males, with a mean age of 7.8 years and a standard deviation of 3.2 years.

Eligibility Criteria

Children ranging from 2 to 16 years of age were considered eligible for inclusion if they satisfied the ILAR classification criteria for JIA, had experienced the

disease for a minimum of six months, and were categorized as either oligoarticular or polyarticular subtypes. Participants were excluded if they exhibited systemic disease activity, obesity, other chronic medical conditions, or a family history of hypertension or renal disorders in first-degree relatives. These rigorous inclusion and exclusion criteria were applied to establish a well-defined and homogeneous study population, thereby enhancing the validity and reliability of the results.

Ethical Considerations

Before enrollment, written informed consent was secured from the parents or legal guardians of all participants, ensuring full compliance with ethical standards throughout the investigation. The study protocol was approved by the Ethics Committee of Benha University Hospital (MS 17-2-2024) and was conducted in line with internationally accepted ethical guidelines for research involving pediatric subjects.

Clinical Assessment and Laboratory Investigations

Participants were divided into two groups: the JIA cohort and the control group, each comprising 50 children. All children underwent a comprehensive clinical evaluation, which included a detailed medical history and thorough physical examination. Laboratory investigations were conducted to assess hematological, inflammatory, and renal parameters. These investigations included complete blood count (CBC), erythrocyte sedimentation rate, C-reactive protein, blood urea, serum creatinine (SCr), serum amyloid A, uric acid, and urinary albumin excretion.

Disease activity among children in the JIA cohort was quantified via the Juvenile Arthritis Disease Activity Score-27 (JADAS-27), while renal function was evaluated via the RRI. Together, these assessments provided a comprehensive overview of both inflammatory status and renal health, allowing for correlations between disease activity, laboratory findings, and early renal functional changes to be systematically analyzed.

Assessment of Disease Activity (JADAS-27) The JADAS-27 score, ranging from 0 to 57, served as a comprehensive indicator of disease activity by combining assessments from physicians, parents, or patients with objective evaluations of joint involvement and systemic inflammation. ESR values were adjusted to a standardized 0–10 scale, with readings below 20 mm/h assigned a value of zero and those exceeding 120 mm/h capped at 120. Elevated JADAS-27 scores corresponded to heightened disease activity, more extensive joint involvement, and increased inflammatory burden, reflecting a more severe clinical course. In contrast, lower scores signified milder disease activity and a comparatively better prognosis. By integrating subjective perceptions of well-being with clinical and laboratory parameters, JADAS-27 enabled a multidimensional appraisal of disease severity, offering a robust tool for monitoring disease progression and therapeutic response [7].

Evaluation of Renal Function

Kidney function was assessed through the estimation of glomerular filtration rate (GFR) via the Modification of Diet in Renal Disease (MDRD) equation:

. $GFR = 186 \times (\text{serum creatinine [mg/dL]})^{-1.154} \times age^{-0.203}$ [8].

The calculation incorporated serum creatinine levels and the age of each participant to provide an approximate measure of renal clearance.

Renal resistive index (RRI)

Renal hemodynamics were further evaluated by measuring the RRI via real-time color duplex Doppler ultrasonography. All examinations were conducted via a Toshiba SSA-770 Aplio 80 system equipped with a multifrequency curved-array transducer operating at 3.3–5 MHz. To maintain consistency and minimize variability between operators, all scans were performed by a single highly experienced radiologist. Children were

positioned either in the supine or lateral decubitus posture depending on the orientation that provided optimal visualization of the kidneys.

RRI measurements were obtained from the interlobar or arcuate arteries in the upper, middle, and lower poles of each kidney. Only waveforms showing three or more consecutive uniform cycles were included for analysis. To enhance accuracy, the insonation angle was minimized, wall filters were set at the lowest practical level to preserve late diastolic flow, and pulse repetition frequency was reduced to avoid technical artifacts [(9)]. Three separate measurements per kidney were averaged to obtain a mean RRI for each organ, and a global mean RRI was then calculated by averaging values from both kidneys for each child.

Statistical Analysis

All gathered data were meticulously organized, encoded, and analyzed using SPSS version 24 (IBM, Chicago, USA). Descriptive statistics, such as means, standard deviations, ranges, frequencies, and percentages, were calculated to provide a comprehensive profile of the study cohort. Results were illustrated through tables and figures, accompanied by detailed explanations. Statistical significance was determined at a p-value of less than 0.05. Relationships between categorical variables were assessed using the Chi-square test, whereas continuous variables were compared between two independent groups via the Student's t-test, under the assumption of normally distributed data. When more than two groups were compared, one-way ANOVA was applied. Associations between quantitative measures were examined using Spearman's rank correlation, defining one variable as independent and the other as dependent. The diagnostic performance of the parameters was evaluated through receiver operating characteristic (ROC) curve analysis, where sensitivity reflected the ability to correctly identify true positives and specificity represented the accuracy in detecting true negatives. The area under the curve (AUC) indicated overall diagnostic accuracy, with values closer to 1.0 denoting near-perfect discrimination. The diagonal line on the ROC graph served as a reference, dividing the plot into two equivalent halves [(10)].

Results

This study included 50 children with the diagnosis of JIA (JIA group) and 50 healthy children (control group). There was no statistical difference between JIA group and control group as regarding to age, sex or consanguinity, however, JIA had statistically higher frequencies relative to control group.

The mean age of disease onset was 6.4±1.9 years, the mean disease duration was 2.4±1.3 years, 60% of cases were oligoarticular and 40% were polyarticular, most cases receive methotrexate and steroids (48%), and 30 % received biologic drugs. The mean JADAS score was 3.1±1.8.

JIA had statistically lower hemoglobin relative to control group. While there was no statistical difference between JIA group and control group as regarding to WBCs or platelets count. JIA had statistically higher CRP, ESR, serum amyloid and statistically higher frequencies of positive ANA and rheumatoid factor relative to control group. JIA had statistically lower eGFR relative to control group. JIA had statistically higher frequencies of decrease eGFR, abnormal urine analysis and increased urine albumin relative to control group. While groups exhibited comparability as regarding to urea and creatinine. **Table 1**

JIA had statistically higher RRI relative to control group. **Figure 1**, **Table 2**

RRI was statistically higher in children received biologic treatment relative to children received methotrexate. While there was no statistical difference in RRI as regarding to sex, family history, consanguinity or type of JIA. **Figure 2**

RRI was found to be significantly elevated in children with positive ANA relative to those with negative ANA, and in cases with positive RF relative to their negative counterparts. Likewise, children presenting with albuminuria exhibited higher RRI values than those with normal urinary findings. Similarly, cases with reduced eGFR demonstrated a significant rise in RRI relative to those with preserved renal function. **Table 3**

Correlation analysis revealed that RRI had a strong positive association with CRP, ESR, creatinine, SAA, and JADAS, while showing a significant negative relationship with weight, BMI, Hb, and eGFR. **Table 4**

Further evaluation through ROC analysis highlighted the diagnostic performance of RRI. For detecting reduced eGFR, the AUC reached 0.826 (95% CI: 0.726–0.927, p<0.001). At a threshold of >0.67, sensitivity was 60% and specificity 94.2%. For detecting albuminuria, the AUC was 0.940 (95% CI: 0.859–1, p<0.001), with sensitivity of 80% and specificity of 92.6% at the same cutoff. **Figure 3**, **Figure 4**

Table 1: Laboratory investigations in the studied groups

		JIA group N=50	%	Control group N=50	%	Test	P value
Hemoglobin (mg/dl)	**Mean±SD**	9.6±1.6		11.7±0.9		t=7.9	<0.001*
	Range	7.5-13.5		10-13.8			
WBCs (10^3/L)	**Mean±SD**	7.8±1.8		7.5±1.9		t=0.80	0.41
	Range	4.6-11.6		4.9-10.5			
Platelets (10^3/L)	**Mean±SD**	232±44		251±49		t=1.8	0.07
	Range	168-303		189-395			
CRP (mg/dl)	**Mean±SD**	8.5±1.9		3.5±1		t=15.4	<0.001*
	Range	6-12		2-6			
ESR	**Mean±SD**	35.7±11.9		8.5±1.9		t=15.9	<0.001*
	Range	15-87		6-12			
Serum amyloid A	**Mean±SD**	2.7±1.1		2.3±0.8		t=2.2	0.028*
	Range	1.3-6.8		1.3-3.3			
ANA	**Negative**	34	68.0%	50	100.0%	X^2=19.1	<0.001*
	Positive	16	32.0%	0	0.0%		
Rheumatoid factor	**Negative**	43	86.0%	50	100.0%	X^2=7.5	0.006*
	Positive	7	14.0%	0	0.0%		
Urea (mg/dl)	**Mean±SD**	23.4±5.4		21.9±5.9		t=1.2	0.18
	Range	17-35		11-32			
Creatinine (mg/dl)	**Mean±SD**	0.7±0.2		0.5±0.1		t=0.77	0.26
	Range	0.3-1.1		0.3-0.8			
eGFR	**Mean±SD**	102.6±24.1		119.8±24.8		t=3.5	<0.001*
	Range	59.1-152.5		91.1-177			
	Normal	35	70.0%	50	100.0%		
	<90	15	30.0%	0	0.0%		
Urine analysis	**NAD**	40	80.0%	50	100.0%	X^2=11.1	0.001*
	Proteinuria	5	10.0%	0	0.0%		
	Hematuria	2	4.0%	0	0.0%		
	Pus	3	6.0%	0	0.0%		
Urine albumin	**Normal**	45	90.0%	50	100.0%	X^2=5.2	0.022*
	Increased	5	10.0%	0	0.0%		

t: Student t-test, *: significant, JIA : Juvenile Idiopathic Arthritis **WBCs :**White Blood Cells, **CRP :**C-Reactive Protein, **ESR :**Erythrocyte Sedimentation Rate, **ANA:** Antinuclear Antibodies, **eGFR**: Estimated Glomerular Filtration Rate, **NAD** :No Abnormality Detected, **SD :**Standard Deviation, **χ^2:** Chi-square test

Table 2: Renal resistive index in the studied group

		JIA group N=50 %	Control group N=50 %	Test	P value
Right RRI	**Mean±SD**	0.62±0.06	0.56±0.05	t=6.3	<0.001*
	Range	0.55-0.82	0.46-0.64		
Left RRI	**Mean±SD**	0.64±0.06	0.55±0.05	t=6.2	<0.001*
	Range	0.56-0.81	0.47-0.65		
Mean RRI	**Mean±SD**	0.63±0.06	0.55±0.05	t=6.4	<0.001*
	Range	0.56-0.82	0.46-0.65		

t: Student t-test, *: significant, **JIA :** Juvenile Idiopathic Arthritis, **RRI** : Renal Resistive Index, **SD** : Standard Deviation

Table 3: Renal resistive index as regarding to inflammatory markers and kidney affection

		RRI Mean±SD	Min.	Max.	Test	P value
ANA	**Negative**	0.58±0.07	0.46	0.82	t=2.6	0.009*
	Positive	0.63±0.06	0.56	0.74		
Rheumatoid factor	**Negative**	0.59±0.07	0.46	0.82	t=2.3	0.021*
	Positive	0.63±0.08	0.57	0.79		
Urine albumin	**No**	0.58±0.06	0.46	0.74	t=6.5	<0.001*
	Increased	0.73±0.08	0.62	0.82		
eGFR	**Normal**	0.57±0.05	0.46	0.74	t=5.1	0.001*
	<90	0.66±0.09	0.62	0.82		

t: Student t-test, *: significant, **RRI :**Renal Resistive Index, **ANA :**Antinuclear Antibodies, **eGFR:** Estimated Glomerular Filtration Rate**, SD :** Standard Deviation

Table 4: Correlation between renal resistive index and cases' clinical data and laboratory investigations

	RRI r	P value
Age	0.160	0.112
Age at onset	-0.032	0.826
Duration	0.203	0.157
Weight	-0.267	0.007*
Height	-0.067	0.507
BMI	-0.372	<0.001*
Hemoglobin	-0.384	<0.001*
WBCs	0.041	0.687
Platelets	-0.129	0.200
CRP	0.507	<0.001*
ESR	0.587	<0.001*
Urea	0.094	0.355
Creatinine	0.293	0.003*
S. Amyloid A	0.334	0.001*
eGFR	-0.364	<0.001*
JADAS-27	0.794	<0.001*

r: Correlation coefficient, *: significant, **RRI :** Renal Resistive Index, **JIA:** Juvenile Idiopathic Arthritis, **BMI** :Body Mass Index, WBCs:White Blood Cells, **CRP :** C-Reactive Protein, **ESR :** Erythrocyte Sedimentation Rate, **eGFR :**Estimated Glomerular Filtration Rate, **JADAS-27**: Juvenile Arthritis Disease Activity Score (27-joint version)

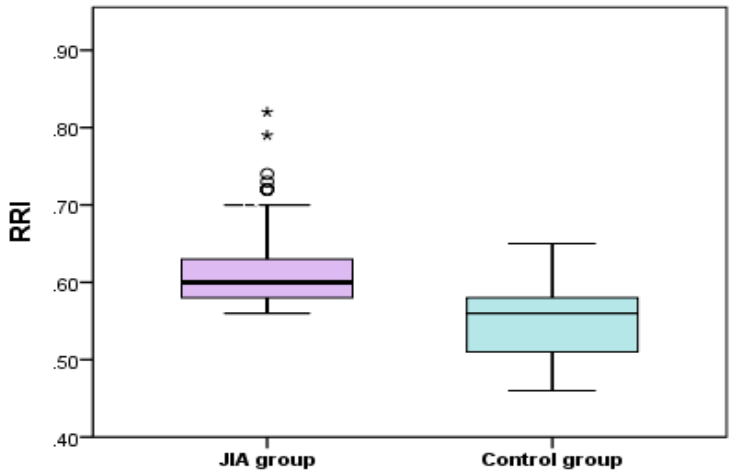

Figure 1*:* Renal resistive index of the studied groups

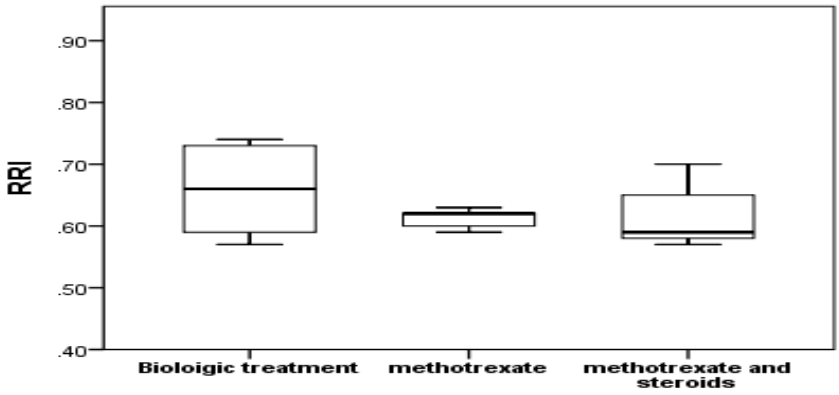

Figure 2*:* RRI as regarding to received medication

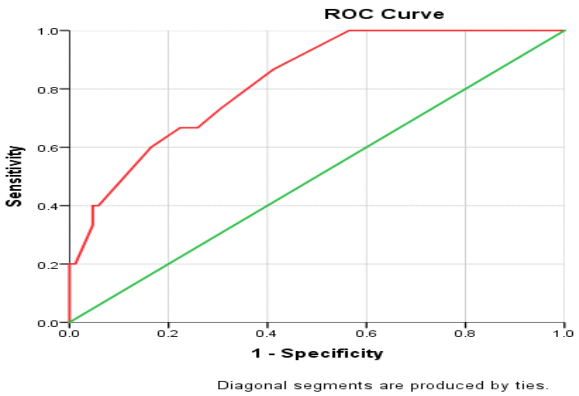

Figure 3*:* ROC curve of performance of renal resistive index to detect cases with decreased eGFR.

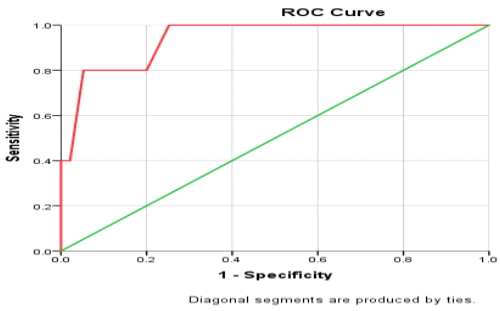

Figure 4*:* ROC curve of performance of renal resistive index to detect cases with albumin in urine.

Discussion

The investigation enrolled 50 children diagnosed with JIA (35 females and 15 males) alongside 50 healthy controls (32 females and 18 males). Consistent with earlier reports, the investigation detected a higher proportion of female cases [11–13]. Evidence indicated that sex-specific differences, potentially mediated by miRNA expression, contributed to variations in immune responses and disease susceptibility. Approximately 10% of miRNAs were located on the X chromosome, which may have influenced sex-dependent gene expression and partially explained immunological differences between males and females [13]. A positive family history was documented more frequently among cases. Straalen and co-authors [14] exhibited similar findings, demonstrating higher parental prevalence of autoimmune disorders in families of affected children compared with the general population. Such observations suggested that genetic predisposition played a role in disease development alongside environmental factors.

The mean age at disease onset in the investigation was 6.4 ± 1.9 years, and the mean disease duration was 2.4 ± 1.3 years. These values aligned with those exhibited by Hussein [15], who documented a mean onset of 6.1 ± 2.8 years, and Geita and co-authors [16], who z 6.8 ± 2.56 years. In contrast, Roemer and co-authors [17] described a median disease duration of 4 years (IQR: 2–7), while Abou El-Soud and co-authors [11] exhibited a higher mean onset of 10.5 ± 3.6 years. Differences among studies may have reflected variations in sample size, genetic background, subtype distribution, environmental factors, diagnostic criteria, methodology, and access to pediatric rheumatology services, potentially leading to underreported adolescent-onset cases (12–16 years) [18].

Within the investigation, 60% of cases were oligoarticular, and 40% were polyarticular. Treatment regimens included methotrexate combined with corticosteroids in 48% of cases, while 30% received biologic therapy. The mean JADAS score was 3.1 ± 3.8. These observations were similar to those exhibited by Fair and co-authors [19], who documented oligoarticular predominance (36%, with 50% extended) and polyarticular cases (32%, 81% RF-negative). Abdelaleem and co-authors [20] also detected oligoarticular predominance (60%), followed by polyarticular (28%) and systemic onset (12%).

Renal assessment revealed significantly lower eGFR among cases compared with controls. Children in the investigation also exhibited higher frequencies of decreased eGFR, abnormal urinalysis findings, and elevated urinary albumin, while urea and creatinine values did not differ significantly. These results corresponded with the observations of Cafarotti and co-authors [22], who exhibited reduced eGFR and higher albumin excretion among affected children. Del Giudice and co-

authors [3] similarly documented higher rates of hematuria and proteinuria, although no significant differences in GFR were detected between cases and controls. Comparable results were detected in adults with RA, where Hickson and co-authors [23] exhibited an increased risk of renal impairment relative to healthy individuals.

RRI values were elevated in cases (0.63 ± 0.06) compared with controls (0.55 ± 0.05; $p < 0.001$). These findings were consistent with Cafarotti and co-authors [22], who exhibited higher right, left, and mean RRI values among cases (0.7 ± 0.04 vs. 0.6 ± 0.04; $p < 0.001$).

RRI was considered a highly sensitive and reliable indicator of renal vascular resistance, utilized extensively across both pediatric and adult populations to assess hemodynamic changes within the kidneys in a variety of parenchymal disorders. These conditions encompassed diabetic nephropathy, hemolytic uremic syndrome, systemic lupus erythematosus, hepatorenal syndrome, polycystic kidney disease, and interstitial nephritis [24]. By measuring intrarenal blood flow and vascular resistance noninvasively, RRI enabled clinicians and investigators to detect early hemodynamic alterations that often preceded noticeable declines in renal function. Its clinical importance was rooted in its capacity to identify patients at elevated risk for progressive renal impairment, thereby supporting timely monitoring, early intervention, and informed therapeutic strategies aimed at mitigating long-term kidney damage.

Children receiving biologic therapy exhibited higher RRI compared with those treated with methotrexate, whereas no significant differences were detected for sex, family history, consanguinity, or disease subtype. Cafarotti and co-authors [22] exhibited similar findings, suggesting that biologics were typically prescribed for patients with more severe disease who inherently demonstrated higher RRI. The effect of therapeutic regimens on RRI in JIA remained underexplored, indicating the need for further investigations to clarify these associations and guide early preventive strategies.

RRI was also higher in children with positive ANA, positive RF, elevated urinary albumin, and decreased eGFR. These results aligned with previous investigations [25, 26], indicating that eGFR served as a significant predictor of RRI. Correlation analyses revealed positive associations between RRI and CRP, ESR, creatinine, amyloid A, and JADAS score, while negative associations were detected with weight, BMI, hemoglobin, and eGFR. No significant correlations were detected with age, age at onset, WBCs, platelets, or urea. Cafarotti and co-authors [22] similarly exhibited associations between RRI, disease activity, and eGFR, with multivariate regression identifying JADAS as the only independent predictor of RRI ($p < 0.001$).

ROC analysis demonstrated diagnostic performance of RRI for detecting decreased eGFR, with an AUC of 0.826 (95% CI: 0.726–0.927; $p < 0.001$), sensitivity of 60%, and specificity of 94.2% at a cutoff >0.67. For urinary albumin positivity, RRI had an AUC of 0.940 (95% CI: 0.859–1; $p < 0.001$), with 80% sensitivity and 92.6% specificity at the same cutoff.

The investigation acknowledged limitations, including its cross-sectional design, small sample size, and variability in treatment regimens, which may have influenced outcomes. Despite these limitations, it represented one of the few investigations evaluating renal function and RRI in children with JIA. Findings suggested that affected children exhibited impaired renal function and elevated RRI compared with controls, indicating potential complications of disease and therapy. Monitoring of renal parameters, including creatinine, eGFR, and urinalysis, was recommended, and RRI provided a noninvasive measure for detecting subclinical renal changes. Future longitudinal investigations were advised to

evaluate disease severity and treatment impact on renal outcomes.

Conclusion

Children with JIA exhibited compromised renal function and consistently higher RRI values compared with their healthy peers. RRI measurements were markedly elevated in participants who received biologic therapies relative to those treated with conventional regimens. Elevated RRI was also associated with positive ANA status, positive rheumatoid factor, increased urinary albumin excretion, and diminished eGFR. Correlation analyses revealed that RRI was positively linked with inflammatory and disease activity markers, including CRP, ESR, creatinine, amyloid A, and JADAS score, while inversely associated with weight, BMI, hemoglobin, and eGFR.

Sources of Funding

This research was carried out independently and did not receive financial support from any public, commercial, or nonprofit organizations. The work reflects the authors' own initiative and resources.

Author Contributions

The investigation was conducted with equal participation from all authors. Each author was actively involved in every stage of the investigation, including formulating the research question, designing the methodology, collecting and analyzing data, and preparing the manuscript. All authors reviewed and approved the final version and take responsibility for the content of the investigation.

Conflicts of Interest

The authors confirm that the investigation was carried out without any conflicts of interest. No financial, personal, or professional relationships influenced the design, conduct, or interpretation of the investigation.

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To cite this article: Wesam E. Afify, Mohamed S. Sleem, Inas M. Sweed, Olfat G. ElSaeid, Tasneem H. Elshony. Kidney Function and Renal Resistive Index in Children with Juvenile Idiopathic Arthritis. BMFJ XXX, DOI: 10.21608/bmfj.2025.417488.2652.