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Stage-dependent alterations in MaR1 in pediatric chronic kidney disease: a potential candidate biomarker

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Abstract

Background Chronic kidney disease (CKD) in children is characterized by persistent inflammation and oxidative stress, contributing to progressive loss of renal function and multisystem involvement. Maresin 1 (MaR1), a specialized pro-resolving lipid mediator derived from docosahexaenoic acid (DHA), plays a role in the resolution of inflammation and tissue repair. However, its circulating concentrations in pediatric CKD have not been examined. This study aimed to determine serum MaR1 levels across CKD stages in children and to assess its potential relevance as a biomarker reflecting disease severity.

Methods Children were categorized as healthy controls or assigned to CKD stages 1–5 according to estimated glomerular filtration rate (eGFR). In patients receiving hemodialysis, blood samples were obtained 48 h after the preceding dialysis session and immediately before the subsequent session. Serum MaR1 concentrations were measured by enzyme-linked immunosorbent assay (ELISA). Group comparisons were performed using one-way ANOVA with Tukey's post-hoc test ($p<0.05$).

Results Serum MaR1 levels differed significantly among the six groups ($p<0.001$). Mean MaR1 concentrations were 110.20 ± 18.15 pg/mL in healthy controls, 20.01 ± 7.23 pg/mL in CKD stage 1, 39.61 ± 7.60 pg/mL in stage 2, 60.73 ± 12.79 pg/mL in stage 3, 203.86 ± 22.06 pg/mL in stage 4, and 284.56 ± 25.75 pg/mL in stage 5. MaR1 levels showed a marked reduction at stage 1, followed by progressive recovery and substantial elevation in advanced CKD.

Conclusions Serum MaR1 concentrations show a stage-dependent pattern in pediatric CKD, characterized by marked suppression at stage 1 followed by progressive recovery and elevation in advanced stages. These findings suggest that circulating MaR1 may represent a candidate biomarker of disease-related inflammatory dynamics; however, its clinical utility requires validation in larger longitudinal studies.

Keywords MaR1 · Chronic kidney disease · Pediatric nephrology

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Introduction

The kidneys play a central role in maintaining internal homeostasis and supporting normal growth in children. Consequently, pediatric renal disorders require specialized diagnostic and therapeutic frameworks. Despite this need, healthcare systems in many regions remain under-resourced, contributing to delayed diagnosis and suboptimal management of chronic kidney disease (CKD) in children [1, 2].

Chronic kidney disease (CKD) has emerged as a major global cause of pediatric morbidity and mortality [3]. Its prevalence varies geographically and is largely shaped by congenital anomalies of the kidney and urinary tract (CAKUT), hereditary nephropathies, and glomerulonephritis [4]. In low- and middle-income settings, late presentation is common, with many children first evaluated at end-stage renal disease (ESRD) [5]. Accurate staging of CKD through estimated or measured glomerular filtration rate (GFR) remains fundamental for assessing disease severity, monitoring complications, and guiding therapy [6].

Although CKD encompasses diverse etiologies, inflammation represents a unifying pathogenic mechanism. Systemic inflammation and oxidative stress are well-established hallmarks of CKD and intensify progressively with renal function decline [7]. Persistent immune activation—driven by uremic toxin accumulation, cytokine excess, oxidative stress, and impaired immune regulation—creates a chronic low-grade inflammatory milieu that promotes tubulointerstitial fibrosis, glomerular ischemia, and ongoing nephron loss [7]. In children, this chronic inflammatory state contributes to impaired growth, anemia, bone–mineral disturbances, protein–energy wasting (PEW), and accelerated cardiovascular risk [7, 8].

Pro-inflammatory mediators such as IL-6, TNF-α, and high-sensitivity C-reactive protein (hsCRP) correlate strongly with GFR decline and cardiovascular events [7, 9]. Multiple immune pathways and immune cell subsets contribute both to inflammatory activation and to the fibrotic progression characteristic of advanced CKD [10]. Up to half of adults with stage 5 CKD display evidence of inflammatory activation even prior to dialysis initiation [11, 12], and this inflammatory burden may worsen with hemodialysis (HD) or peritoneal dialysis (PD) due to membrane bio-incompatibility, oxidative stress, and infectious complications [13]. Chronic inflammation is a major predictor of mortality in dialysis populations [14].

Among upstream inflammatory regulators, the IL-1β/IL-18 axis plays a particularly important role. Elevated IL-18 concentrations correlate with monocyte chemoattractant protein-1 (MCP-1) levels, which are independently associated with reduced GFR and progressive vascular injury [14, 15].

Beyond classical inflammatory mediators, a growing body of interest surrounds specialized pro-resolving mediators (SPMs)—lipid-derived autacoids that actively orchestrate the resolution phase of inflammation. Maresins, biosynthesized from omega-3 fatty acids, are among the most potent SPM families [16, 17]. Maresin 1 (MaR1; 7,14-dihydroxydocosahexaenoic acid) is produced in macrophages through the 12-lipoxygenase (12-LOX) pathway, generating the intermediates 14 S-hydroperoxy-DHA and 13 S,14 S-epoxy-maresin prior to conversion into MaR1 [18].

MaR1 exerts pleiotropic anti-inflammatory and tissue-regenerative actions, including reducing neutrophil infiltration, enhancing macrophage efferocytosis, promoting tissue repair, and attenuating inflammatory pain [16, 17, 19]. In contrast to steroids or NSAIDs, SPMs—including MaR1—resolve inflammation without inducing global immunosuppression, presenting a favorable therapeutic profile [20].

Experimental evidence indicates that MaR1 is renoprotective across diverse models of kidney injury. In acute kidney injury, MaR1 attenuates neutrophil-driven renal inflammation and accelerates tissue recovery [21]. In diabetic nephropathy, MaR1 reduces reactive oxygen species (ROS) generation, suppresses NLRP3 inflammasome activation, and downregulates IL-1β expression [22]. In ischemia–reperfusion injury, MaR1 protects renal tissue by inhibiting TLR4-mediated MAPK signaling cascades [23].

Taken together, these data suggest that MaR1 may function as an important endogenous mediator modulating inflammation, oxidative stress, and fibrosis. However, circulating MaR1 levels have not been systematically studied in pediatric CKD, and the stage-dependent behavior of MaR1 remains unknown. Considering the central

role of chronic inflammation in CKD, we aimed to investigate serum MaR1 levels across the full spectrum of pediatric CKD. Establishing this relationship may help determine whether circulating MaR1 could serve as a candidate biomarker of stage-dependent inflammatory changes in pediatric CKD and provide a basis for future longitudinal and mechanistic studies.

Methods

Study design and setting

This prospective, controlled, cross-sectional study was conducted in the pediatric nephrology departments of a university hospital and a state hospital. Demographic and clinical data, including age, sex, renal function parameters, and underlying CKD etiology, were obtained from patient records. Patients were classified according to CKD stage based on estimated glomerular filtration rate (eGFR), calculated using the 2009 CKiD bedside Schwartz equation: eGFR = 0.413 × height (cm) / serum creatinine (mg/dL), expressed as mL/min/1.73 m². Approval was obtained from the Local Ethics Committee of Atatürk University Faculty of Medicine.

Study population

A total of 90 children aged 24–220 months were enrolled and distributed into six groups: five CKD groups categorized according to the Kidney Disease: Improving Global Outcomes (KDIGO) pediatric staging system (stages 1–5) and one control group of healthy children with similar demographic characteristics. Each group consisted of 15 participants. Healthy controls were recruited from children undergoing routine pediatric evaluation. They were considered healthy if they had no known chronic disease, no acute infection or inflammatory condition, no history suggestive of renal disease, and no clinically relevant abnormalities on physical examination or available routine laboratory assessments.

Exclusion criteria

Exclusion criteria included: acute infection or inflammatory disease; receipt of steroids or immunosuppressants within the preceding three months; presence of another chronic illness; and lack of parental consent or subsequent withdrawal of consent.

Data collection and laboratory measurements

Clinical and laboratory data—including age, sex, past medical history, serum creatinine, serum electrolytes, and serum MaR1 levels—were recorded for all participants.

Serum samples were obtained at random time points in controls and in CKD patients not requiring dialysis. For patients undergoing hemodialysis, blood sampling occurred 48 h after the last dialysis session, immediately before the subsequent session.

For MaR1 measurement, venous blood was collected into biochemical tubes, allowed to clot for 10–20 min, and centrifuged at +4 °C for 10 min at 4,500 rpm. Serum aliquots were stored at −80 °C until analysis. MaR1 concentrations were determined using a commercially available ELISA kit (Human MaR1 ELISA Kit, YL Biont, Cat. No. YLA4082HU, China), following the manufacturer's instructions. According to the manufacturer's specifications, the analytical measurement range of the assay was 15.63–1,000 pg/mL, with a reported minimum detectable concentration of approximately 6.2 pg/mL. Optical density was measured at 450 nm following completion of the assay, and MaR1 concentrations were calculated from the corresponding standard curve.

Sample size calculation

An a priori sample size calculation was performed using G*Power 3.1 for a one-way analysis of variance involving six independent groups. Assuming an effect size of f = 0.40, an alpha error probability of 0.05, and a statistical power of 0.80, the required total sample size was approximately 86 participants. To allow equal allocation across the six study groups, a total of 90 participants were included, with 15 participants in each group.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 10.3 (GraphPad Software, Boston, MA, USA). Descriptive statistics for MaR1 measurements were expressed as frequencies (n), percentages, and means ± standard deviations (SD). The normality of data distribution was assessed using the Shapiro-Wilk test and Q-Q plots. Since the data were normally distributed, group comparisons were conducted using a one-way analysis of variance (ANOVA), followed by Tukey's Honestly Significant Difference (HSD) test for post hoc analysis. To evaluate the continuous relationship between eGFR and MaR1 levels, correlation and regression analyses were performed. Spearman's rank correlation test was utilized to assess the strength and direction of the association between these variables. Furthermore, simple linear regression analysis was conducted to determine the explanatory power of eGFR decline on MaR1 elevation. Age and gender variables were analyzed using the Kruskal-Wallis and Chi-square tests, respectively.

Artificial intelligence disclosure

ChatGPT (OpenAI) was used to support clarity and improve grammar during the writing of this article. No content, analysis, or interpretation was generated by AI.

Results

Demographic and clinical characteristics of the study groups

There were no significant differences among the groups in terms of age or gender distribution ($p = 0.999$ and $p = 0.922$, respectively). eGFR progressively decreased from the healthy and CKD stage 1 groups to CKD stage 5, whereas creatinine values increased with advancing CKD stage. The underlying disease etiologies were heterogeneous, with CAKUT being the most frequently observed cause across CKD stages (Table 1).

Table 1 Demographic characteristics and clinical parameters of the groups

Group	Age (months) Median IQR (Q1–Q3)	Gender (F/M) (*n*)	eGFR (mL/min/1.73 m^2) Mean ± SD	Creatinine (mg/dL) Mean ± SD
Healthy	94 (45.5–172.5)	7/8	128.11 ± 15.46	0.44 ± 0.13
CKD-Stage1	91 (42.5–169.5)	8/7	126.03 ± 22.12	0.45 ± 0.13
CKD-Stage2	96 (39.0–168.5)	6/9	74.24 ± 6.06	0.77 ± 0.23
CKD-Stage3	90 (43.5–169.0)	8/7	46.65 ± 7.74	1.46 ± 0.36
CKD-Stage4	88 (40.5–167.0)	9/6	21.87 ± 4.33	3.43 ± 0.97
CKD-Stage5	85 (49.0–170.0)	8/7	9.80 ± 2.32	6.60 ± 1.25

F: Female, M: Male, SD: Standart deviation, Age: No significant difference among groups (Kruskal–Wallis, $p = 0.999$), Gender: No significant difference among groups (Chi-square test, $p = 0.922$)

Etiological distribution of CKD

CKD etiology varied across stages, with CAKUT being the most common underlying cause. Cystic, tubular, glomerular diseases and neurogenic bladder were observed at varying frequencies across the CKD groups (Table 2).

Serum MaR1 levels across the study groups

All patients in CKD stage 5 were receiving hemodialysis every other day; none of the other CKD groups required dialysis.

Serum MaR1 concentrations differed significantly among the six groups ($p < 0.001$). Mean ± SD MaR1 concentrations were 110.20 ± 18.15 pg/mL in healthy controls, 20.01 ± 7.23 pg/mL in CKD stage 1, 39.61 ± 7.60 pg/mL in stage 2, 60.73 ± 12.79 pg/mL in stage 3, 203.86 ± 22.06 pg/mL in stage 4, and 284.56 ± 25.75 pg/mL in stage 5.

Serum MaR1 levels displayed a significant stage-dependent pattern. Compared with healthy controls, MaR1 levels showed a pronounced decrease at CKD stage 1, representing the lowest concentration observed among all groups. This initial suppression was followed by a progressive increase through stages 2 and 3, with a further marked elevation at stages 4 and 5, reaching the highest concentrations at stage 5. Pairwise comparisons demonstrated significant differences among the study groups, as illustrated in Fig. 1.

Overall, MaR1 demonstrated a biphasic distribution: an initial decline in early CKD followed by a pronounced increase in advanced stages.

Correlation between eGFR and MaR1 levels

To further substantiate the stage-dependent alterations, a continuous analysis was performed to evaluate the relationship between eGFR and MaR1 levels. Spearman correlation analysis revealed a strong and highly significant negative correlation between continuous eGFR values and MaR1 concentrations ($r = -0.713$, $p < 0.001$). Furthermore, simple linear regression confirmed this inverse relationship ($R^2 = 0.474$, $p < 0.001$), demonstrating that progressive decline in renal function is robustly associated with elevated MaR1 levels (Fig. 2).

Discussion

In this study, we evaluated serum MaR1 concentrations across different stages of pediatric CKD and identified a distinct stage-dependent, biphasic pattern. MaR1 levels were significantly suppressed in early CKD (stages 1–3) and progressively elevated in later stages (stages 4–5). These findings provide new insight into the dynamic interplay between inflammatory activation and resolution pathways in pediatric CKD.

CKD is characterized by persistent low-grade inflammation and oxidative stress extending beyond the kidney, contributing to systemic metabolic and cardiovascular complications [24, 25]. The inflammatory cascade begins early and is sustained by interactions among uremic toxins, dysregulated cytokine signaling, intestinal dysbiosis,

Table 2 Disease etiology of the groups

Group	CAKUT (*n*)	Cystic diseases (*n*)	Tubular diseases (*n*)	Glomerular diseases (*n*)	Neurogenic bladder (*n*)	Unknown (*n*)
CKD-Stage1	5	2	1	1	5	1
CKD-Stage2	6	3	1	4	0	1
CKD-Stage3	6	2	2	4	1	0
CKD-Stage4	4	2	3	3	2	1
CKD-Stage5	6	1	1	2	5	0

CAKUT: Congenital anomalies of the kidney and urinary tract

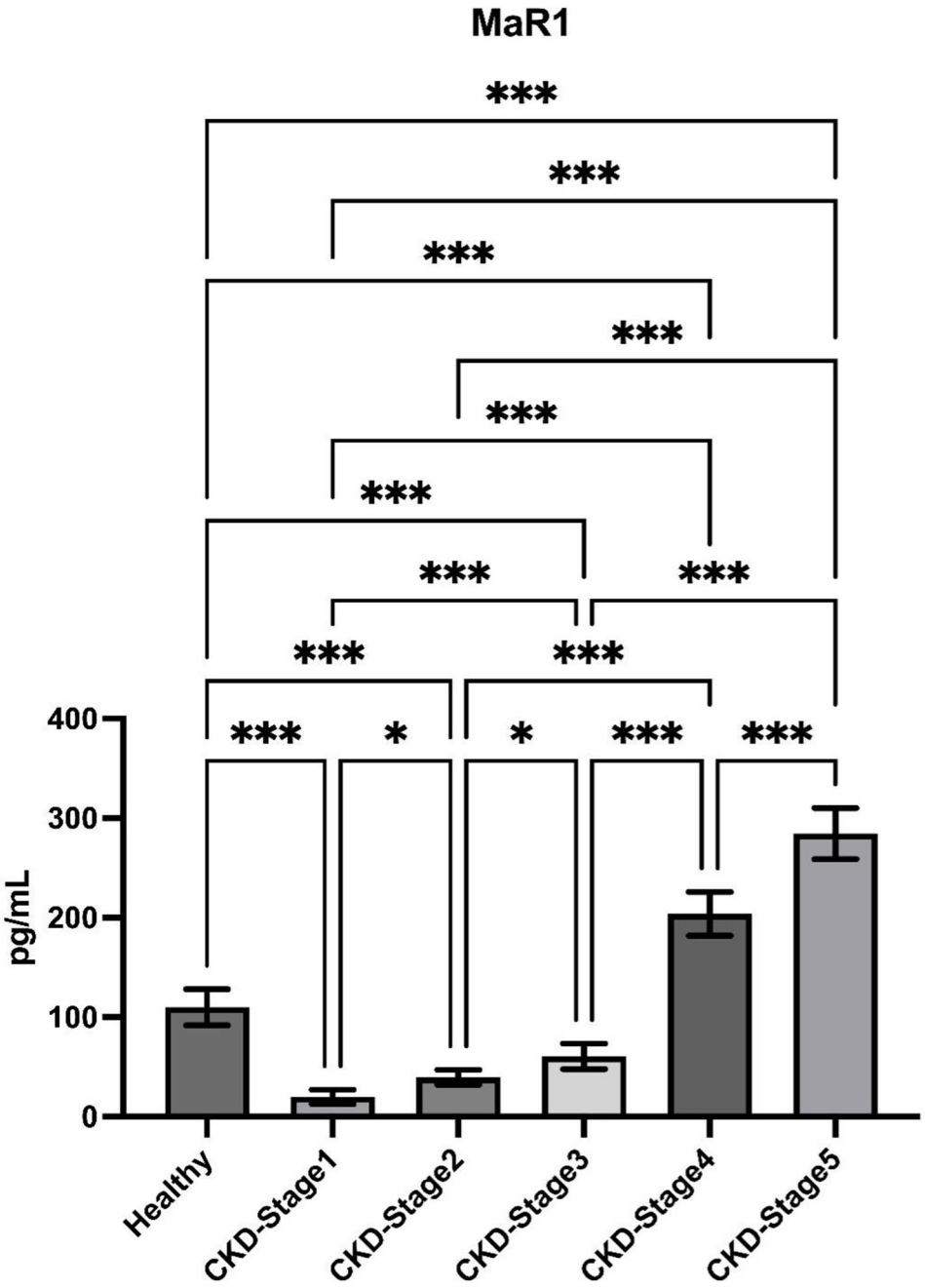


Fig. 1 Serum MaR1 levels across the study groups. Results are presented as mean ± standard deviation. Tukey's HSD post-hoc test was performed following one-way ANOVA. Asterisks indicate statistically significant pairwise differences (*$p<0.05$; **$p<0.01$; ***$p<0.001$). CKD, chronic kidney disease

and oxidative stress [26, 27]. Elevated cytokines—including IL-1β, IL-6, TNF-α, and MCP-1—promote endothelial dysfunction, vascular calcification, and tubulointerstitial fibrosis.

Proteinuria is a major prognostic marker in CKD [28]. Even asymptomatic proteinuria is associated with early endothelial activation [29]. Persistent proteinuria triggers podocyte expression of TGF-β, promoting epithelial and mesangial cell transdifferentiation into fibroblasts and stimulating extracellular matrix (ECM) production [19, 30]. Additional factors—albuminuria, complement activation, cytokine leakage, and hypoxia from endothelial dysfunction—further intensify tubular inflammation [31–33].

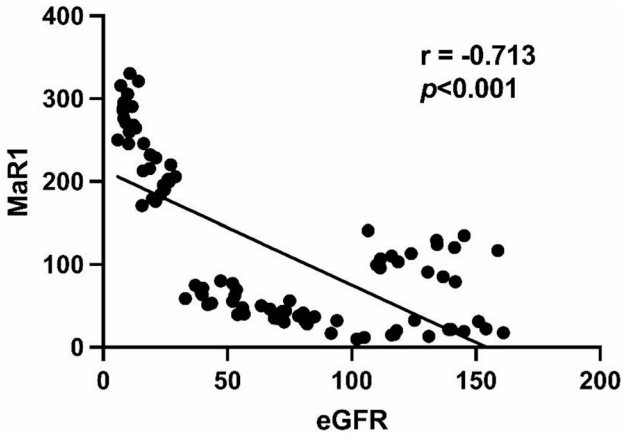


Fig. 2 Correlation between estimated glomerular filtration rate (eGFR) and Maresin 1 (MaR1) levels.A scatter plot illustrating the significant inverse relationship between continuous eGFR values and Maresin 1 concentrations. The solid black line represents the line of best fit derived from simple linear regression analysis. Statistical evaluation was performed using Spearman's rank correlation test

Early decline in MaR1

The pronounced reduction in MaR1 observed at CKD stage 1 may reflect impairment of endogenous inflammation-resolution pathways during early disease. Several mechanisms could potentially contribute to this pattern. Previous studies have implicated persistent pro-inflammatory cytokine signaling, oxidative stress, NF-κB activation, and alterations in immune-cell and macrophage responses in the pathophysiology and progression of CKD [15, 26, 27, 31, 33]. Such inflammatory conditions could potentially disturb the balance between pro-inflammatory and pro-resolving pathways. However, inflammatory cytokines, oxidative stress markers, and macrophage phenotypes were not directly assessed in the present study. Therefore, these mechanisms should be regarded as biologically plausible hypotheses rather than direct explanations for the observed reduction in circulating MaR1.

Later elevation in MaR1

In advanced CKD, chronic inflammation becomes intertwined with fibrosis, driven largely by TGF-β/SMAD2/3 signaling [34, 36]. One possible explanation for the rise in MaR1 during advanced CKD is compensatory activation of endogenous pro-resolving pathways in response to persistent inflammatory and fibrotic stress. Experimental evidence demonstrates that MaR1 can modulate inflammatory, oxidative, and fibrotic pathways in renal injury [23, 37, 38]. Alterations in macrophage phenotype and feedback regulation of lipid mediator synthesis may therefore contribute to such a compensatory response; however, these mechanisms were not directly evaluated in the present study and should be regarded as hypotheses requiring further investigation.Experimental studies demonstrate that MaR1 attenuates renal fibrosis by inhibiting SMAD phosphorylation, reducing collagen I and fibronectin expression, and suppressing epithelial-to-mesenchymal transition [23, 37]. MaR1 also downregulates NLRP3 inflammasome activation, reduces oxidative stress, and modulates MAPK pathways [37, 38]. Thus, elevated MaR1 levels in late CKD may represent a compensatory attempt to counterbalance persistent inflammation and fibrosis. Importantly, the elevation of circulating MaR1 in advanced CKD should not be interpreted as evidence of effective resolution of inflammation. Rather, it may represent an insufficient compensatory response to an overwhelming and persistent pro-inflammatory and profibrotic milieu. Continued activation of pathways

involving pro-inflammatory cytokines, oxidative stress, uremic toxins, and fibrotic signaling may exceed the endogenous resolution capacity mediated by MaR1, thereby allowing renal injury to progress despite increased circulating MaR1 levels. Since these inflammatory mediators were not directly measured in the present study, this interpretation should be regarded as a mechanistic hypothesis that requires confirmation in future studies.

Nrf2–MaR1 interaction

Recent evidence highlights a critical role for the Nrf2 pathway in renal pathophysiology [39–45]. Reduced Nrf2 expression and increased NF-κB activity have been observed in advanced CKD [46]. Nrf2 deficiency enhances ROS generation, DNA damage, inflammation, and fibrosis, whereas activation of Nrf2 signaling mitigates renal injury [46–48].

Emerging data suggest that MaR1 activates Nrf2 signaling, thereby enhancing antioxidant defenses and attenuating inflammation [49, 50]. MaR1 also modulates cytokine production, reduces fibrosis, and restores redox balance through interactions with NF-κB and TGF-β pathways [51–53]. These findings support a cooperative relationship between MaR1 and Nrf2 that may become more prominent in advanced CKD.

Interpretation

Taken together, our findings indicate that MaR1 exhibits a dual, stage-dependent role in pediatric CKD: early suppression is associated with unchecked inflammatory signaling, whereas later elevation reflects compensatory activation of anti-inflammatory and antifibrotic pathways. This biphasic behavior underscores a transition from a predominantly pro-inflammatory state to a chronic, partially resolution-driven phase.

Conclusion

Serum MaR1 levels demonstrate a distinct stage-dependent pattern across pediatric CKD stages, with pronounced suppression at stage 1 followed by progressive recovery and marked elevation in advanced disease. These findings suggest that circulating MaR1 may represent a candidate biomarker reflecting changes in inflammatory and resolution pathways across CKD stages. However, its diagnostic performance and clinical relevance require confirmation in larger, longitudinal cohorts and direct comparison with established clinical and inflammatory biomarkers.

Limitations

This study has several limitations that should be considered when interpreting the results. First, the relatively modest sample size, particularly within individual CKD stages, may limit statistical power and the generalizability of the findings. This constraint is partly inherent to pediatric CKD research, given the heterogeneity of disease etiologies and the limited availability of well-characterized patient cohorts.

Second, the cross-sectional design precludes definitive conclusions regarding causality or temporal relationships. Although the observed suppression of MaR1 in early CKD stages and its elevation in advanced stages suggest a stage-dependent association, longitudinal studies are needed to determine whether these changes represent adaptive, compensatory, or disease-related responses during CKD progression.

In addition, potential confounding factors, including medication use, nutritional status, and residual renal function, could not be fully controlled and may have influenced circulating MaR1 levels. Furthermore, although blood samples from patients receiving maintenance hemodialysis were collected 48 h after the dialysis session to reduce the potential impact of acute dialysis-related fluctuations, the hemodialysis procedure itself may

influence circulating lipid mediators and systemic inflammatory responses. Therefore, the potential contribution of dialysis-related effects should be considered when interpreting the elevated MaR1 levels observed in patients with stage 5 CKD.

Despite these limitations, this study provides clinical evidence of stage-dependent alterations in circulating MaR1 levels in pediatric CKD and supports the potential utility of MaR1 as a candidate biomarker associated with CKD stage. However, the observed associations should not be interpreted as evidence of a causal or mechanistic role for MaR1 in CKD progression.

An additional limitation concerns the analytical method used for MaR1 quantification. MaR1 was measured using a commercially available ELISA kit rather than liquid chromatography–tandem mass spectrometry (LC–MS/MS), which provides greater analytical specificity for specialized pro-resolving lipid mediators. Therefore, potential cross-reactivity and differences in analytical specificity inherent to immunoassay-based measurements cannot be completely excluded. The absolute MaR1 concentrations reported in the present study should consequently be interpreted with appropriate caution, and confirmation using validated LC–MS/MS-based lipidomic methods would strengthen future studies.

Abbreviations

AKI	Acute kidney injury
ANOVA	Analysis of variance
CAKUT	Congenital anomalies of the kidney and urinary tract
CKD	Chronic kidney disease
DHA	Docosahexaenoic acid
ECM	Extracellular matrix
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
HD	Hemodialysis
hsCRP	High-sensitivity C-reactive protein
IL	Interleukin
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
LOX	Lipoxygenase
MaR1	Maresin 1
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemoattractant protein-1
NLRP3	NOD-like receptor family pyrin domain-containing 3
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NSAIDs	Non-steroidal anti-inflammatory drugs
Nrf2	Nuclear factor erythroid 2–related factor 2
PD	Peritoneal dialysis
PEW	Protein–energy wasting
ROS	Reactive oxygen species
SMAD	Mothers against decapentaplegic homolog (SMAD2/3 signaling pathway)
SPM	Specialized pro-resolving mediator
TGF-β	Transforming growth factor-beta

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work as co-first authors); methodology and investigation: Muhammet Celik and Zafer Bayraktutan; software and validation, data curation, conceptualization, supervision: Hamza Halici, Emir Enis Yurdgulu and Yusuf Anil Ay; funding acquisition: All authors. All authors read and approved the final manuscript.

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Data availability The raw datasets analyzed in this study are available from the corresponding author upon reasonable request and with permission from the institutional review board.

Declarations

Ethics approval and consent to participate This prospective, controlled, cross-sectional study was conducted in accordance with the Declaration of Helsinki and approved by the Local Ethics Committee of Atatürk University Faculty of Medicine (Approval No: B.30.2.ATA.0.01.00/639). Written informed consent to participate was obtained from the parents or legal guardians of all patients.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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References

1. Wise PH. The future pediatrician: the challenge of chronic illness. J Pediatr. 2007;151(5). https://doi.org/10.1016/j.jpeds.2007.08.013.
2. Jain S, Dewey RS. The role of special clinics in imparting clinical skills: medical education for competence and sophistication. Adv Med Educ Pract. 2021;12. https://doi.org/10.2147/AMEP.S306214.
3. Perin J, Mulick A, Yeung D, Villavicencio F, Lopez G, Strong KL, et al. Global, regional, and national causes of under-5 mortality in 2000–19: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet Child Adolesc Health. 2022;6(2). https://doi.org/10.1016/S2352-4642(21)00311-4.
4. Harada R, Hamasaki Y, Okuda Y, Hamada R, Ishikura K. Epidemiology of pediatric chronic kidney disease/kidney failure: learning from registries and cohort studies. Pediatr Nephrol. 2022;37(6):1215–29. https://doi.org/10.1007/S00467-021-05145-1.
5. Chadban SJ, Ahn C, Axelrod DA, Foster BJ, Kasiske BL, Kher V, et al. KDIGO clinical practice guideline on the evaluation and management of candidates for kidney transplantation. Transplantation. 2020;104(4). https://doi.org/10.1097/TP.0000000000003136.
6. Stevens PE, Ahmed SB, Carrero JJ, Foster B, Francis A, Hall RK, et al. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2024;105(4). https://doi.org/10.1016/j.kint.2023.10.018.
7. Akchurin OM, Kaskel F. Update on inflammation in chronic kidney disease. Blood Purif. 2015. https://doi.org/10.1159/000368940.
8. Lai HL, Kartal J, Mitsnefes M. Hyperinsulinemia in pediatric patients with chronic kidney disease: the role of tumor necrosis factor-α. Pediatr Nephrol. 2007;22(10). https://doi.org/10.1007/s00467-007-0533-z.
9. Larkins NG, Craig JC. Hypertension and cardiovascular risk among children with chronic kidney disease. Curr Hypertens Rep. 2024;26(10):389–98. https://doi.org/10.1007/S11906-024-01308-1.
10. Miguel V, Shaw IW, Kramann R. Metabolism at the crossroads of inflammation and fibrosis in chronic kidney disease. Nat Rev Nephrol. 2025;21(1):39–56. https://doi.org/10.1038/s41581-024-00889-z.

11. Stenvinkel P, Heimbürger O, Paultre F, Diczfalusy U, Wang T, Berglund L, et al. Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. Kidney Int. 1999;55(5). https://doi.org/10.1046/j.1523-1755.1999.00422.x.
12. Pecoits-Filho R, Lindholm B, Stenvinkel P. End-stage renal disease: a state of chronic inflammation and hyperleptinemia. Clin Sci (Lond). 2003. https://doi.org/10.1046/j.1365-2362.2003.01175.x.
13. Liakopoulos V, Roumeliotis S, Gorny X, Eleftheriadis T, Mertens PR. Oxidative stress in patients undergoing peritoneal dialysis: a current review of the literature. Oxid Med Cell Longev. 2017. https://doi.org/10.1155/2017/3494867.
14. Kadatane SP, Satariano M, Massey M, Mongan K, Raina R. The role of inflammation in CKD. Cells. 2023;12(12):1581. https://doi.org/10.3390/cells12121581.
15. Mihai S, Codrici E, Popescu ID, Enciu AM, Albulescu L, Necula LG, et al. Inflammation-related mechanisms in chronic kidney disease prediction, progression, and outcome. J Immunol Res. 2018;2018:2180373. https://doi.org/10.1155/2018/2180373.
16. Serhan CN, Dalli J, Colby JK, Winkler JW, Chiang N, Petasis NA. Macrophage proresolving mediator maresin 1 stimulates tissue regeneration and controls pain. FASEB J. 2012;26(4):1755. https://doi.org/10.1096/FJ.11-201442.
17. Dalli J, Chiang N, Serhan CN. The novel 13S,14S-epoxy-maresin is converted by human macrophages to maresin 1 (MaR1), inhibits leukotriene A4 hydrolase (LTA4H), and shifts macrophage phenotype. FASEB J. 2013;27(7). https://doi.org/10.1096/fj.13-227728.
18. Freedman C, et al. Biosynthesis of the Maresin intermediate, 13S,14S-epoxy-DHA, by human 15-lipoxygenase and 12-lipoxygenase and its regulation through negative allosteric modulators. Biochemistry. 2020;59(19):1832–44. https://doi.org/10.1021/acs.biochem.0c00233.
19. Serhan CN, Yang R, Martinod K, Kasuga K, Pillai PS, Porter TF, et al. Maresins: novel macrophage mediators with potent antiinflammatory and proresolving actions. J Exp Med. 2009;206(1). https://doi.org/10.1084/jem.20081880.
20. Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: a current perspective. Biochem Pharmacol. 2020. https://doi.org/10.1016/j.bcp.2020.114147.
21. Hong S, Lu Y. Omega-3 fatty acid-derived resolvins and protectins in inflammation resolution and leukocyte functions: targeting novel lipid mediator pathways in mitigation of acute kidney injury. Front Immunol. 2013;4:13. https://doi.org/10.3389/fimmu.2013.00013.
22. Tang S, et al. Maresin 1 mitigates high glucose-induced mouse glomerular mesangial cell injury by inhibiting inflammation and fibrosis. Mediators Inflamm. 2017;2017:2438247. https://doi.org/10.1155/2017/2438247.
23. Qiu Y, Wu Y, Zhao H, Sun H, Gao S. Maresin 1 mitigates renal ischemia/reperfusion injury in mice via inhibition of the TLR4/MAPK/NF-κB pathways and activation of the Nrf2 pathway. Drug Des Devel Ther. 2019;13. https://doi.org/10.2147/DDDT.S188654.
24. Anders HJ, Schaefer L. Beyond tissue injury—damage-associated molecular patterns, toll-like receptors, and inflammasomes also drive regeneration and fibrosis. J Am Soc Nephrol. 2014. https://doi.org/10.1681/ASN.2014010117.
25. Liu H, et al. Oxidative stress and inflammation in renal fibrosis: novel molecular mechanisms and therapeutic targets. Chem Biol Interact. 2025;421:111784. https://doi.org/10.1016/J.CBI.2025.111784.
26. Ruiz-Ortega M, Rayego-Mateos S, Lamas S, Ortiz A, Rodrigues-Diez RR. Targeting the progression of chronic kidney disease. Nat Rev Nephrol. 2020. https://doi.org/10.1038/s41581-019-0248-y.
27. Mihai S, Codrici E, Popescu ID, Enciu AM, Albulescu L, Necula LG, et al. Inflammation-related mechanisms in chronic kidney disease prediction, progression, and outcome. J Immunol Res. 2018;2018:2180373. https://doi.org/10.1155/2018/2180373.
28. Ying T, Clayton P, Naresh C, Chadban S. Predictive value of spot versus 24-hour measures of proteinuria for death, end-stage kidney disease or chronic kidney disease progression. BMC Nephrol. 2018;19(1). https://doi.org/10.1186/S12882-018-0853-1.
29. Paisley KE, Beaman M, Tooke JE, Mohamed-Ali V, Lowe GDO, Shore AC. Endothelial dysfunction and inflammation in asymptomatic proteinuria. Kidney Int. 2003;63(2). https://doi.org/10.1046/j.1523-1755.2003.00768.x.
30. Brennan EP, Cacace A, Godson C. Specialized pro-resolving mediators in renal fibrosis. Mol Aspects Med. 2017;58:102–13. https://doi.org/10.1016/J.MAM.2017.05.001.
31. Tecklenborg J, Clayton D, Siebert S, Coley SM. The role of the immune system in kidney disease. Clin Exp Immunol. 2018. https://doi.org/10.1111/cei.13119.
32. Nangaku M. Chronic hypoxia and tubulointerstitial injury: a final common pathway to end-stage renal failure. J Am Soc Nephrol. 2006. https://doi.org/10.1681/ASN.2005070757.
33. Meng XM, Nikolic-Paterson DJ, Lan HY. Inflammatory processes in renal fibrosis. Nat Rev Nephrol. 2014. https://doi.org/10.1038/nrneph.2014.114.
34. Sayers R, Kalluri R, Rodgers KD, Shield CF, Meehan DT, Cosgrove D. Role for transforming growth factor-β1 in Alport renal disease progression. Kidney Int. 1999;56(5):1662–73. https://doi.org/10.1046/J.1523-1755.1999.00744.X.
35. Lee SB, Kalluri R. Mechanistic connection between inflammation and fibrosis. Kidney Int. 2010. https://doi.org/10.1038/ki.2010.418.

36. Tang PMK, Zhang YY, Mak TSK, Tang PCT, Huang XR, Lan HY. Transforming growth factor-β signalling in renal fibrosis: from Smads to non-coding RNAs. J Physiol. 2018;596(16). https://doi.org/10.1113/JP274492.
37. Li X, et al. Maresin 1 alleviates diabetic kidney disease via LGR6-mediated cAMP-SOD2-ROS pathway. Oxid Med Cell Longev. 2022;2022:7177889. https://doi.org/10.1155/2022/7177889.
38. Li J, et al. Maresin 1 attenuates lipopolysaccharide-induced acute kidney injury via inhibiting NOX4/ROS/NF-κB pathway. Front Pharmacol. 2021;12:782660. https://doi.org/10.3389/FPHAR.2021.782660.
39. Jiang T, Huang Z, Lin Y, Zhang Z, Fang D, Zhang DD. The protective role of Nrf2 in streptozotocin-induced diabetic nephropathy. Diabetes. 2010;59(4). https://doi.org/10.2337/db09-1342.
40. Al-Sawaf O, et al. Nrf2 in health and disease: current and future clinical implications. Clin Sci (Lond). 2015. https://doi.org/10.1042/CS20150436.
41. Lu MC, et al. CPUY192018, a potent inhibitor of the Keap1-Nrf2 protein-protein interaction, alleviates renal inflammation in mice by restricting oxidative stress and NF-κB activation. Redox Biol. 2019;26:101266. https://doi.org/10.1016/j.redox.2019.101266.
42. Feng YL, et al. Activated NF-κB/Nrf2 and Wnt/β-catenin pathways are associated with lipid metabolism in CKD patients with microalbuminuria and macroalbuminuria. Biochim Biophys Acta Mol Basis Dis. 2019;1865(9):2317–32. https://doi.org/10.1016/J.BBADIS.2019.05.010.
43. Lu Y, et al. Activation of NRF2 ameliorates oxidative stress and cystogenesis in autosomal dominant polycystic kidney disease. Sci Transl Med. 2020;12(554). https://doi.org/10.1126/SCITRANSLMED.ABA3613.
44. Juul-Nielsen C, Shen J, Stenvinkel P, Scholze A. Systematic review of the nuclear factor erythroid 2-related factor 2 (NRF2) system in human chronic kidney disease: alterations, interventions and relation to morbidity. Nephrol Dial Transpl. 2022;37(5). https://doi.org/10.1093/ndt/gfab031.
45. Leal VO, et al. NRF2 and NF-κB mRNA expression in chronic kidney disease: a focus on nondialysis patients. Int Urol Nephrol. 2015;47(12):1985–91. https://doi.org/10.1007/S11255-015-1135-5.
46. Aminzadeh MA, Reisman SA, Vaziri ND, Khazaeli M, Yuan J, Meyer CJ. The synthetic triterpenoid RTA dh404 (CDDO-dhTFEA) restores Nrf2 activity and attenuates oxidative stress, inflammation, and fibrosis in rats with chronic kidney disease. Xenobiotica. 2014;44(6):570–8. https://doi.org/10.3109/00498254.2013.852705.
47. Tsai PY, et al. Antroquinonol reduces oxidative stress by enhancing the Nrf2 signaling pathway and inhibits inflammation and sclerosis in focal segmental glomerulosclerosis mice. Free Radic Biol Med. 2011;50(11). https://doi.org/10.1016/j.freeradbiomed.2011.02.029.
48. Tosi MER, Bocanegra V, Manucha W, Lorenzo AG, Vallés PG. The Nrf2-Keap1 cellular defense pathway and heat shock protein 70 (Hsp70) response: role in protection against oxidative stress in early neonatal unilateral ureteral obstruction (UUO). Cell Stress Chaperones. 2011;16(1). https://doi.org/10.1007/s12192-010-0221-y.
49. Li D, et al. Maresin 1 alleviates the inflammatory response, reduces oxidative stress and protects against cardiac injury in LPS-induced mice. Life Sci. 2021;277:119467. https://doi.org/10.1016/j.lfs.2021.119467.
50. Soto G, et al. Maresin 1, a proresolving lipid mediator, ameliorates liver ischemia-reperfusion injury and stimulates hepatocyte proliferation in Sprague-Dawley rats. Int J Mol Sci. 2020;21(2). https://doi.org/10.3390/ijms21020540.
51. Rodríguez MJ, et al. Pro-resolving lipid mediator resolvin E1 mitigates the progress of diethylnitrosamine-induced liver fibrosis in Sprague-Dawley rats by attenuating fibrogenesis and restricting proliferation. Int J Mol Sci. 2020;21(22). https://doi.org/10.3390/ijms21228827.
52. AlZahrani S, Shinwari Z, Gaafar A, Alaiya A, Al-Kahtani A. Anti-inflammatory effect of specialized proresolving lipid mediators on mesenchymal stem cells: an in vitro study. Cells. 2023;12(1). https://doi.org/10.3390/cells12010122.
53. Wang Y, et al. Maresin 1 inhibits epithelial-to-mesenchymal transition in vitro and attenuates bleomycin-induced lung fibrosis in vivo. Shock. 2015;44(5). https://doi.org/10.1097/SHK.0000000000000446.

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