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Inflammatory markers in end-stage renal disease patients on maintenance hemodialysis, hemodiafiltration (HDF), early post-renal transplant patients, and their relation to quality of life (SGA Score)

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Abstract

Chronic kidney disease (CKD) is associated with malnutrition-inflammation-atherosclerosis (MIA) syndrome—persistent inflammation and protein-energy wasting, both of which adversely affect nutritional status and quality of life. High-sensitivity C-reactive protein (hs-CRP) is a well-established marker of systemic inflammation, while circulating microRNA-223 (miR-223), an epigenetic biomarker, is a new frontier in the immune and inflammatory regulation of renal fibrosis in CKD. Therefore, we conducted this study to primarily investigate the associations between systemic inflammatory activity (assessed by hs-CRP), circulating levels of immunoregulatory miR-223, and nutritional status (evaluated by the Subjective Global Assessment, SGA) in end-stage kidney disease (ESKD) patients undergoing different renal replacement therapy modalities— hemodialysis (HD), hemodiafiltration (HDF), and kidney transplantation. A secondary objective was to explore how these immune inflammatory profiles differ across modalities and their potential impact on functional and nutritional outcomes. This cross sectional observational study included 75 ESKD adult patients recruited consecutively: 25 on HD, 25 on HDF and 25 kidney transplant recipients. A total of ten healthy volunteers were included as a reference group for miR-223 expression. ELISA measured hs-CRP levels, and miR-223 expression was quantified using real-time PCR and reported as relative expression levels using the 2^-ΔCt method. Nutritional status was assessed using the SGA score. Group comparisons and correlation analyses were performed. hs-CRP levels were significantly higher in HD patients (median 14.2 mg/L) compared with HDF (6.3 mg/L) and kidney transplant recipients (5.2 mg/L)(p = 0.003).miR-223 expression was significantly downregulated in both dialysis groups compared with kidney transplant recipients (p < 0.001), with post-transplant levels approaching those of healthy controls. Nutritional status differed significantly among groups (p < 0.001): 100% of kidney transplant recipients were classified as SGA Class A (well nourished) compared with 76% in the HDF group and 32% in the HD group. In conclusions, Kidney transplantation is associated with lower inflammatory burden and better nutritional status than dialysis modalities. Reduced miR-223 in dialysis patients and its improvement after transplantation suggest a potential association with

inflammatory and nutritional status in ESKD. This could be clinically relevant with potential implications for understanding the epigenetic regulation of inflammation in ESKD. Further longitudinal studies are needed to clarify causal relationships and to better understand the role of miR-223 in CKD pathophysiology (Protective role).

Keywords: CKD; ESKD; HD; HDF; hs-CRP; Inflammation; Kidney transplantation; miR-223; Nutritional status; Subjective Global Assessment.

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Introduction

Patients with end-stage kidney disease (ESKD) requiring renal replacement therapy (RRT) are estimated to number between 4.9 and 7 million worldwide.[1] The Standardized Outcomes in Nephrology (SONG HD) initiative highlighted that the burden of chronic kidney disease (CKD) remains a leading contributor to mortality and morbidity. Patients with CKD experience debilitating symptoms, including fatigue, pain and therapy-related adverse effects, and clinical complications like cardiovascular events.[2]

Nontraditional risk factors, including chronic inflammation, have gained recognition as important contributors to morbidity in ESKD.[3] Among these, malnutrition-inflammation-atherosclerosis (MIA) syndrome is a well-established framework that links protein-energy wasting, persistent inflammation, and atherosclerotic complications in dialysis patients.[4] Frailty and multiple comorbidities are also common in older CKD populations.[5]

Hemodiafiltration (HDF), which combines convective and diffusive clearance, offers improved removal of medium- and larger-molecular- weight uremic toxins compared with conventional hemodialysis (HD).[6] Recent evidence from a comprehensive 2026 meta-analysis demonstrated that HDF, compared with conventional HD, yields favorable effects on uremic toxin removal, inflammatory biomarkers, anemia, and nutritional parameters, supporting the broader clinical benefits of HDF beyond survival outcomes.[7] Moreover, the European Dialysis (EuDial) Working Group of the European Renal Association (ERA) 2025 recently reported that HDF is associated with improved overall and cardiovascular survival, consistent with findings from the CONVINCE trial, which also demonstrated benefits in patient quality of life with high-dose HDF.[8] Kidney transplantation provides longer life expectancy and better quality of life (QOL) compared with dialysis.[9]

High-sensitivity C-reactive protein (hs-CRP) is a widely used biomarker of systemic inflammation and atherosclerotic risk in CKD.[10] MicroRNAs (miRNAs) are small (20–25 nucleotides), non-coding RNA molecules involved in regulating gene expression.[11] Among them, miR-223 plays a key role in immune and inflammatory regulation and has been implicated in renal fibrosis and nutritional disturbances in CKD.[12]

There is a well-established correlation between nutritional status and QoL in patients with CKD, with optimal nutritional status contributing positively to QoL. Nutritional status, representing a key dimension of QoL outcomes, can be effectively evaluated using the Subjective Global Assessment (SGA)—a validated clinical tool widely recommended in nephrology practice for assessing nutritional status in CKD patients.[13]

While hs-CRP and miR-223 have been studied individually in CKD populations, their combined assessment across different RRT modalities and their correlation with nutritional status have not been previously investigated. It remains unclear whether differences in inflammatory burden among HD, HDF, and kidney transplantation are paralleled by coordinated changes in circulating miR-223 and clinical nutritional assessment. Addressing this gap may provide insight into the immunometabolic mechanisms underlying modality-specific outcomes and help refine biomarker-based risk stratification.

Therefore, we conducted a study with the primary objective to investigate the associations

between systemic inflammatory activity (assessed by hs-CRP), circulating levels of immunoregulatory miR-223, and nutritional status (evaluated by the Subjective Global Assessment, SGA) in patients undergoing different renal replacement therapy modalities—HD, HDF, and kidney transplantation. A secondary objective was to explore how these immune inflammatory profiles differ across modalities and their potential impact on functional and nutritional outcomes.

Materials and Methods

Study Design

This cross-sectional observational study was conducted at the Hemodialysis Units and Renal Transplant Clinic of Ain Shams University Hospitals, Cairo, Egypt, between December 2022 and August 2023. The manuscript was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Study Population

A total of 75 adult patients with ESKD were recruited consecutively and stratified into three equal groups (n = 25 per group):

-Group 1: Patients on maintenance hemodialysis (HD).
-Group 2: Patients on maintenance hemodiafiltration (HDF).
-Group 3: Early kidney transplant recipients (3–12 months post-transplantation): This time frame was selected to reflect a clinically stable early post-transplant phase, after resolution of immediate perioperative inflammation and before the development of long-term chronic allograft-related changes.

Given the absence of standardized absolute reference ranges for miR-223 and the influence of genetic and ethnic variability, 10 age- and sex-matched healthy controls were included solely to establish a population-specific normal baseline for circulating miR-223 in Egyptians and to determine whether CKD levels were elevated or reduced relative to physiological norms. The study was not powered for full statistical comparisons with healthy individuals, as expected differences could detract from the primary objective of comparing the three patient groups. This approach aligns with published studies that use healthy controls mainly to define baseline reference values rather than as a fully powered comparative group as described by *Carmona et al.,* (2020).[14]

Sample size calculation: Sample size was calculated using G*Power software, assuming a large effect size (f = 0.40) for a one-way ANOVA comparing three independent groups with a significance level of 0.05 and statistical power of 80% (alpha = 0.05, power = 0.80). The required sample size was estimated to be at least 66 patients (22 patients per group) to detect a statistically significant difference in inflammatory markers among the different renal replacement modalities (ESKD patients on HD, HDF, and kidney transplant recipients). Therefore, in line with prior observational studies assessing hs-CRP and miR-223 in ESKD patients and given feasibility considerations, a final sample of 75 patients was recruited consecutively in our study, exceeding the minimum required sample size and thus ensuring adequate statistical power for the analysis. A post hoc power analysis confirmed that this sample size provided >80% power to detect medium effect sizes (Cohen's d ≈ 0.6) at $\alpha = 0.05$, indicating that the study was adequately powered to detect clinically relevant differences.

Inclusion Criteria: Adults aged 18-70 years old patients with stable ESKD on HD or HDF for more than or equal to three months and stable patients with early kidney transplant recipients (3-12 months post-transplantation).

Exclusion Criteria: Patients with active infection or inflammation; untreated hepatitis C virus (HCV) or hepatitis B virus (HBV) infection; patients with active rejection post-renal transplantation; patients with decompensated medical conditions and patients with malignancy.

Exposure/Study procedure

-Clinical data and laboratory measurement

All patients were subjected to detailed history taking, clinical examination, blood samples (pre-

dialysis session in dialysis patients) for inflammatory biomarkers; hs-CRP, miR-223, complete blood count (CBC), including hemoglobin and neutrophil-to-lymphocyte ratio (NLR), and serum albumin. Nutritional status, reflecting a key dimension of QOL measures, was assessed using the Subjective Global Assessment (SGA).

- Neutrophil-to-lymphocyte ratio (NLR): was calculated as an additional inflammatory marker. Absolute neutrophil and lymphocyte counts were obtained from the CBC, and NLR was computed by dividing the absolute neutrophil count by the absolute lymphocyte count.

- Dialysis Prescription and Adequacy

All HD and HDF patients underwent dialysis three times per week, with each session lasting 4 hours. The dialysate flow rate (QD) was maintained at 500 mL/min, while the average blood flow rate (QB) ranged from 250 to 300 mL/min. The net ultrafiltration volume was 2–3 L per session. In HDF patients, the mean substitution volume was 25 L per session, with a mean convection volume of 28 L per session.

Dialyzers used:

• HD: Fresenius FX series
• HDF: All med Platinum H series

Dialysis adequacy was assessed using the urea reduction ratio (URR). Both HD and HDF groups achieved target adequacy (mean URR≥65% per session), with no statistically significant differences between groups, ensuring comparable dialysis efficiency.

All kidney transplant recipients received kidneys from living biologically related donors. Their immunosuppressive regimens consisted of steroids, calcineurin inhibitors (CNIs), and either mycophenolate mofetil (MMF) or azathioprine, with or without sulfamethoxazole/trimethoprim prophylaxis.

Assay principle:

*Human serum high-sensitivity C-Reactive Protein (hs-CRP) Assay:

Serum hs-CRP was measured using a commercially available ELISA kit (Sunred Biotechnology, Shanghai, China; Cat. No. 201-12-1806). The assay employs a double-antibody sandwich method. The analytical sensitivity of the assay was 0.1 mg/L; intra- and inter-assay coefficients of variation were <8%. All samples were run in duplicate.

*miR-223 quantification by real-time PCR:

Kits were obtained from QIAGEN company, Germany (Human miR-223 complete system) by TaqMan ready-made qPCR (polymerase chain reaction) assays

The assay procedure included four steps:

1. Total RNA extraction (including miR): from the samples by using miRNeasy Mini kit (cat. No. 217004) supplied by Qiagen

2. Reverse transcription (RT) was performed on the extracted RNA prepared in the previous step using specific miR primers for each miR. The reagents used were TaqMan miR specific RT-primers and reagents from the TaqMan® MicroRNA Reverse Transcription (RT) kit (Cat. No. 339340) supplied by ThermoFisher.

3. PCR amplification:Amplification of the target cDNA samples was performed using the TaqMan microRNA assay for hsa-miR-223*and RNU6 housekeeping gene (Cat no. 339306 for all) together with the TaqMan® Universal PCR Master Mix (Cat no. 4440043). The kits were supplied by ThermoFisher. RNU6 was initially used as a reference gene; however, due to concerns about serum stability, miR-223 expression was normalized using spiked-in synthetic cel-miR-39 as an external control, in line with recommended practices for circulating miRNA analysis.

A fixed amount of synthetic cel-miR-39 was added to each sample before RNA extraction to control for extraction efficiency and technical variability.

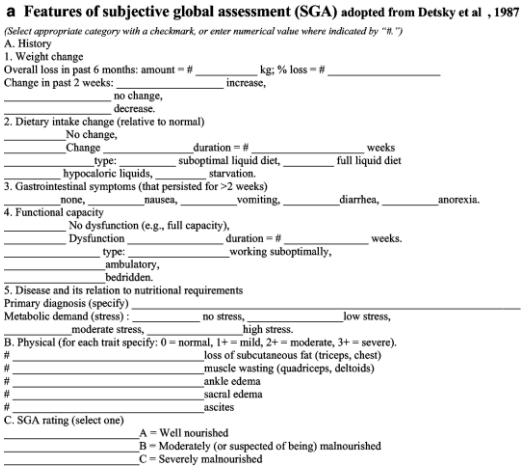
Relative miR-223 expression levels were calculated using the 2^−ΔΔCt method as follows: ΔCt = Ct(miR-223) − Ct(cel-miR-39)
ΔΔCt = ΔCt(sample) − mean ΔCt(healthy controls)
Relative expression = 2^−ΔΔCt
Results were expressed as fold-change relative to the healthy control group, which served as

the calibrator and was assigned a baseline value of approximately 1. All samples were run in duplicate. The amplification was performed using 5 Plex Rotor Gene real time PCR analyzer.

4. Detection and calculation of results.

*Subjective Global Assessment (SGA):

Nutritional status was evaluated using SGA. This tool is used to assess nutritional status and is recommended by the Kidney Disease Outcomes Quality Initiative (K/DOQI) in renal patients as "shown in Figure 1".[15]



a Features of subjective global assessment (SGA) adopted from Detsky et al , 1987

(Select appropriate category with a checkmark, or enter numerical value where indicated by "#.")

A. History

1. Weight change

Overall loss in past 6 months: amount = # _____ kg; % loss = # _____

Change in past 2 weeks: _____ increase,

_____ no change,

_____ decrease.

2. Dietary intake change (relative to normal)

_____No change,

_____Change _____duration = # _____ weeks

_____type: _____ suboptimal liquid diet, _____ full liquid diet

_____ hypocaloric liquids, _____ starvation.

3. Gastrointestinal symptoms (that persisted for >2 weeks)

_____none, _____nausea, _____vomiting, _____diarrhea, _____anorexia.

4. Functional capacity

_____ No dysfunction (e.g., full capacity),

_____ Dysfunction _____ duration = # _____ weeks.

_____ type: _____working suboptimally,

_____ ambulatory,

_____ bedridden.

5. Disease and its relation to nutritional requirements

Primary diagnosis (specify) _____

Metabolic demand (stress) : _____ no stress, _____low stress,

_____moderate stress, _____high stress.

B. Physical (for each trait specify: 0 = normal, 1+ = mild, 2+ = moderate, 3+ = severe).

_____loss of subcutaneous fat (triceps, chest)

_____muscle wasting (quadriceps, deltoids)

_____ankle edema

_____sacral edema

_____ascites

C. SGA rating (select one)

_____A = Well nourished

_____B = Moderately (or suspected of being) malnourished

_____C = Severely malnourished

Figure 1. The SGA assessment component, the SGA calculation recommended by KDOQI.[15] SGA: Subjective Global Assessment.

SGA items: includes five components of medical history (weight change/loss, change in dietary intake, gastrointestinal symptoms, change in functional capacity (dysfunction), disease state affecting nutritional needs) and three components of physical examination (loss of subcutaneous fat, muscle wasting, edema "related to undernutrition/used to evaluate weight change") and the overall SGA score categorizes patients into the following:

-Category A: well-nourished

-Category B: mild-to-moderate malnutrition

-Category C: severe malnutrition

SGA assessments were performed by a trained nephrology physician who was blinded to laboratory biomarker results. To ensure reliability, a second trained evaluator independently assessed a subset of 15 patients, and inter-rater agreement was evaluated using Cohen's kappa coefficient.

Trial Registration

This study was registered retrospectively at Pan African Clinical Trials Registry, https://pactr.samrc.ac.za. Trial Number=PACTR202601515034576.

Statistical Analysis

Data were collected, coded, tabulated, and analyzed. Data were revised for completeness and consistency. Data entry was done on Statistical Package for Social Science IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, New York, United States of America). Descriptive statistics: The distribution of quantitative variables was assessed prior to analysis using the Shapiro–Wilk test and visual inspection of histograms and Q–Q plots. Parametric data/normally distributed variables were expressed as mean ± standard deviation (SD). Non-parametric data/non-normally distributed variables were expressed as median and interquartile range (IQR).Based on normality testing, serum hs-CRP and miR-223 levels were found to be non-normally distributed; therefore, they were presented as median (IQR) and analyzed using non-parametric tests. Qualitative non-numerical data were presented as numbers and percentages (%)**.** Analytical statistics: For parametric data, independent t-test was used to assess the statistical significance of the difference between the two study group means of parametric numerical data. One-way analysis of variance (one-way ANOVA) was used to compare quantitative data with parametric distribution between more than two groups. For non-parametric data, Mann-Whitney test was used to assess the statistical significance of the difference between two groups of quantitative data with non-parametric distribution. A Kruskal–Wallis test, followed by post hoc analysis using the Mann–Whitney test, was used to compare quantitative data and assess nonparametric differences among more than two groups. For qualitative non-numerical data, comparison between groups Chi-Square (X2) test was employed. Multivariable linear regression analyses for confounders like age, dialysis vintage, diabetes mellitus (DM), hypertension (HTN), and immunosuppressive medications were

performed to assess whether treatment modality was independently associated with inflammatory biomarkers. Dialysis vintage was expressed in months. DM and HTN were coded as binary variables (0 = No, 1 = Yes). Separate models were constructed for hs-CRP and miR-223. Model assumptions were verified prior to analysis. A two-tailed *p*-value < 0.05 was considered statistically significant. Correlation analysis was performed using Spearman's rank correlation coefficient, as several continuous variables were non-normally distributed. To control for inflation of Type I error in multiple correlation testing, the Bonferroni correction was applied. With six correlations tested, since $\alpha = 0.05 / 6 = 0.0083$, the adjusted level of statistical significance was set at $p < 0.0083$. Receiver operating characteristic curve (ROC-curve) analyses**:** were performed in our study as exploratory analyses to examine the discriminatory capacity of biomarkers between pre- and post-transplant states. They were used quantitatively to assess the validity of certain continuous variables in predicting patient outcomes. The kidney transplant recipients (n = 25) were compared with a pooled dialysis group comprising HD and HDF patients (n = 50). Dialysis modalities were merged into a single comparator category representing the dialysis state. The confidence interval was set up to 95%, and the margin of error accepted was set to 5%. A *p*-value < 0.05 was considered significant.

Results

Demographic and Clinical Characteristics

Patients were stratified into three groups: hemodialysis (HD, n = 25), hemodiafiltration (HDF, n = 25), and kidney transplant recipients (n = 25). Their demographic, clinical characteristics & immunosuppressive treatments of kidney transplant recipients are summarized in Tables 1 and 2. Age (mean ± SD) was significantly higher in the HDF group (55.36 ± 13.82 years) compared with the HD group (44.08 ± 15.14 years) and the kidney transplant recipient's group (31.04 ± 11.39 years) ($p < 0.001$).

Table 1. Demographic and clinical characteristics, comparison between the three groups; hemodialysis, hemodiafiltration (HDF) and kidney transplant recipients.

Demographic & clinical data		Hemodialysis N= 25	HDF N= 25	Kidney transplant recipients N= 25	Healthy controls¶ N=10	*p* value
Age (Years)	Mean ± SD	44.08 ± 15.14	55.36 ± 13.82	31.04 ± 11.39	35.70 ± 12.68	<0.001••
	Range	19.00 – 67	21 – 70	18 – 56	19 – 61	<0.001
Sex	Male	12 (48%)	18 (72%)	18 (72%)	5 (50%)	NS*
	Female	13 (52%)	7 (28%)	7 (28%)	5 (50%)	NS*
Positive smoking history	N (%)	5 (20%)	11 (44%)	6 (24%)	--	NS*
Diabetes (DM)	N (%)	5 (20%)	4 (16%)	8 (32%)	--	NS*
Hypertension	N.(%)	19 (76%)	21 (84%)	22 (88%)	--	NS*
Systolic blood pressure (≤120mm/Hg)	Mean ± SD	132.00 ± 19.15	125.20 ± 15.03	119.20 ± 6.40	--	0.011••
	Range	100.00 – 160	100 – 150	110 – 130		
Diastolic blood pressure (≤80 mm/Hg)	Mean ± SD	80.60 ± 10.93	76.00 ± 5.77	77.60 ± 5.97	--	NS••
	Range	60.00 – 100	60 – 80	70 – 90		

Table 1. Continued.

Demographic & clinical data		Hemodialysis N= 25	HDF N= 25	Kidney transplant recipients N= 25	Healthy controls¶ N=10	*p* value
Duration of renal replacement therapy(dialysis/transplant)= Vintage (months)	Median(IQR)	48 (36 - 120)	60 (36 - 84)	5 (4 - 10)	--	<0.001‡‡
	Range	10.00 – 204	7 – 204	4 – 12		
TMP (mm Hg)	Mean ± SD	78.40 ± 18.18	159.40 ± 34.71	--	--	<0.001•
Vascular access N(%)	Hemodialysis catheter (mahurkar/per mcath	5 (20%)	4 (16%)	--	--	NS*
	AV fistula/graft	20 (80%)	21 (84%)			

¶: The healthy control group was included for miR-223 reference purposes only and was not subjected to intergroup statistical analysis. p-value > 0.05: Non-significant (NS). ••: one way ANOVA; *: Chi-square test; ‡‡: Kruskal–Wallis test; •: independent t-test. AV: arteriovenous; HDF: hemodiafiltration; TMP: transmembrane pressure.

Table 2. Immunosuppressive medications of kidney transplant recipients.

Immunosuppressive treatment		Kidney transplant recipients (N = 25)
1-Steroids Solupred ® (mg/day)	N.(%)	25 (100%)
	Mean ± SD (dose)	10.2 ± 2.27
	Range (dose)	5 – 20
2-CNI (tacrolimus) Prograf ® (mg/day)	N.(%)	9 (36%)
	Mean ± SD (dose)	6.78 ± 1.86
	Range (dose)	4 – 9
3-CNI (tacrolimus) Adport ® (mg/day)	N.(%)	14 (56%)
	Mean ± SD (dose)	5 ± 2.29
	Range (dose)	3 – 11
4-CNI (cyclosporine) Neoral ® (mg/day)	N.(%)	2 (8%)
	Mean ± SD (dose)	275 ± 35.36
	Range (dose)	250 – 300
5-MMF Cellcept ® (g/day)	N.(%)	20 (80%)
	Mean ± SD(dose)	1.98 ± 0.11
	Range(dose)	1.5 – 2
6-MMF Myfortic ® (mg/day)	N.(%)	4 (16%)
	Mean ± SD (dose)	1260 ± 360
	Range(dose)	720 – 1440
7-Azathioprine Imuran™ (mg/day)	N.(%)	1 (4%)
	Mean ± SD (dose)	100 (n=1)
	Range(dose)	100 – 100
8-Co-trimoxazole (Septrin DS™)	N.(%)	15 (60%)

CNI: Calcineurin inhibitor, MMF: Mycophenolate mofetil.

Laboratory Parameters

Baseline laboratory investigations are presented in Table 3. Continuous variables were expressed as either mean ± SD or median (IQR), as appropriate. The transplant group exhibited significantly better laboratory profiles compared with both dialysis groups, including lower

inflammatory markers, improved Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) parameters, and better hemoglobin (all $p < 0.001$).Between dialysis modalities, the HDF group demonstrated significantly better results than the HD group regarding inflammatory markers, CKD-MBD parameters, and hemoglobin levels ($p < 0.001$).

Inflammatory Biomarkers: hs-CRP and Circulating miR-223

Serum hs-CRP levels (median [IQR]) were significantly higher in HD patients than those in HDF and kidney transplant recipients (Table 3, Figure 2) ($p = 0.003$). Post hoc analysis revealed that both HDF and kidney transplant recipients differed from HD, while no significant difference was observed between HDF and kidney transplant recipients.

Relative expression of circulating miR-223 (2^−ΔΔCt fold-change) indicated a highly significant difference among groups ($p < 0.001$). Both HD and HDF groups demonstrated marked down-regulation compared with kidney transplant recipients and healthy controls. Post hoc analysis confirmed significant differences between dialysis groups and kidney transplant recipients ($p < 0.001$), but not between HD and HDF ($p = 0.372$). Healthy controls demonstrated the highest relative expression (reference fold-change ≈1). (Table 3, Figure 2)

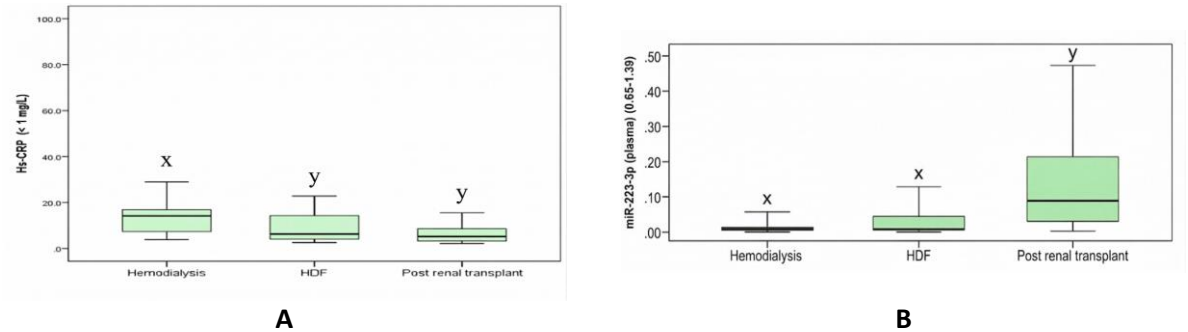
Table 3. Laboratory parameters and inflammatory biomarkers: hs-CRP and circulating miR-223: Comparison between the three groups; hemodialysis, hemodiafiltration and kidney transplant recipients.

Baseline laboratory investigations		Hemodialysis N= 25	HDF N= 25	Kidney transplant recipients N= 25	*p*-value.
		CBC			
NLR ratio (1-2)	Median(IQR) Range	2.7 (2.01 - 3.72) 0.81 – 6	2 (1.6 - 2.5) 1.2 – 5.57	1.6 (1.1 - 1.94) 0.54 – 2.3	<0.001‡‡
HGB (13-17 g/dL)	Mean ± SD Range	10.28 ± 1.17 8.00 – 13	10.93 ± 0.88 9 – 12.6	11.87 ± 1.14 10.2 – 14.2	<0.001••
		KFTs			
BUN (6-20 mg/dL)	Median(IQR) Range	64 (61 - 75) 26 – 92	58 (53 - 64) 33 – 77	14 (12 - 18) 10 – 27	<0.001‡‡
URR (≥ 65)	Mean ± SD -	68.09 ± 17.22 -	76.03 ± 11.57 -	-- -	NS•
S. creatinine (0.7-1.2 mg/dL)	Median(IQR) Range	10 (8 - 11.5) 6.00 – 14	9.5 (7.8 - 11.2) 5.4 – 14.5	1 (0.8 - 1.2) 0.5 – 1.4	<0.001‡‡
eGFR (≥ 90 ml/min/1.73m2) †	Median(IQR) Range	8 (7 - 9) 6 – 13	10 (7 - 11) 6 – 14	96 (92 - 120) 64 – 193	<0.001‡‡
Serum albumin (3.5-5.2 g/dL)	Mean ± SD Range	3.94 ± 0.55 2.50 – 4.7	4.11 ± 0.35 3.5 – 4.8	4.20 ± 0.39 3.6 – 5	NS••
Ca x PO4 product (< 55 mg^2/dl^2)	Mean ± SD Range	40.02 ± 16.27 14.80 – 92.8	33.31 ± 10.11 19.4 – 58.6	29.07 ± 6.11 17.3 – 44.2	0.005••
Ferritin (30-400 ng/ml)	Median(IQR) Range	1124 (258.8 - 1891) 12.6 – 4048	658.7 (334.2–1122.8) 26.7 – 2572	-- --	NS‡‡‡

Table 3. Continued.

Novel inflammatory biomarkers		Hemodialysis (N = 25)	HDF (N = 25)	Kidney transplant recipients (N = 25)	Healthy control (N = 10)	*p*-value
Inflammatory biomarkers						
hs-CRP (< 1 mg/L)	Median (IQR)	14.2 (7.4–16.9)	6.3 (4.1–14.3)	5.2 (3.3–8.6)	-----	0.003‡
	Range	3.90–89.7	2.6–22.8	2.2–15.6	-----	
hs-CRP Heart disease (cardiovascular) risk classification (mg/L) ¶¶ N (%)	Low risk (<1)	0 (0%)	0 (0%)	0 (0%)	-----	0.022*
	Average risk (1-3)	0 (0%)	2 (8%)	6 (24%)		
	High risk § (3.1 - 10)	10 (40%)	13 (52%)	13 (52%)		
	High risk ¶ (>10)	15 (60%)	10 (40%)	6 (24%)		
Post Hoc Analysis (hs-CRP) (*p*- value)						
Hemodialysis vs HDF		Hemodialysis vs kidney transplant recipients		HDF vs kidney transplant recipients		
0.048		0.001		NS		
Novel inflammatory biomarkers		Hemodialysis (N = 25)	HDF (N = 25)	Kidney transplant recipients (N = 25)	Healthy control (N = 10)	*p*-value
miR-223	Range	0.00037–0.14	0.00062–0.14	0.011–0.50	0.65–1.39	<0.001‡
	Mean ± SD	0.018 ± 0.034	0.030 ± 0.041	0.153 ± 0.128	0.97 ± 0.28	
	Median (IQR)	0.0067 (0.0023–0.014)	0.0073 (0.0039–0.043)	0.11 (0.046–0.22)	0.92 (0.74–1.24)	
Post Hoc Analysis (miR-223) (*p*- value)						
Hemodialysis vs HDF		Hemodialysis vs kidney transplant recipients		HDF vs kidney transplant recipients		
NS		<0.001		<0.001		

†= eGFR by CKD-EPI. ¶¶: according to American Heart Association/Centers for Disease Control and Prevention (AHA/CDC) guidelines, §: exclude benign transient elevation by retesting in 2 weeks, ¶: if persistent, consider inflammation.
p-value > 0.05: Non-significant (NS); ‡‡: Kruskal–Wallis test; ••: one-way ANOVA; •: independent *t*-test; ‡‡‡:Mann-Whitney test, ‡: Kruskall–Wallis test followed by post hoc analysis using Mann–Whitney test, *: Chi-square test. BUN: blood urea nitrogen; Ca: calcium; CBC: complete blood count; eGFR: estimated glomerular filtration rate; HDF: hemodiafiltration; HGB: hemoglobin; hs-CRP: high-sensitivity C-reactive protein; KFTs: Kidney function tests, NLR: neutrophil-to-lymphocyte ratio; PO_4: phosphorus; S.: serum; URR: urea reduction ratio.



A **B**

Figure 2. Comparison between groups with regard to hs-CRP (A) and miR-223 (B). Statistical differences are indicated by letters (x, y). Groups sharing the same letter are not significantly different. HDF: hemodiafiltration; hs-CRP: high-sensitivity C-reactive protein.

Multivariable linear regression analyses were performed to adjust for potential confounders, including age, dialysis vintage, DM, HTN, and immunosuppressive medications

In multivariable linear regression analyses including age, dialysis vintage, DM, and HTN, both age (B = −0.0018, *p* = 0.048) and dialysis vintage (B = −0.00055, *p* = 0.008) were

independently associated with circulating miR-223 levels. In contrast, DM and HTN were not significant predictors. None of the studied variables demonstrated a significant association with hs-CRP levels. β = regression coefficient: change in hs-CRP or miR-223 per unit increase in drug dose. Steroids were significantly positively associated with hs-CRP, whereas other drugs were mostly not individually significant. miR-223 tended to decrease with higher steroid/MMF doses, with borderline significance. (Table 4)

Table 4. Multivariable linear regression analysis adjusted for confounding factors associated with hs-CRP and miR-223 (age, dialysis vintage, DM, HTN and immunosuppressive medications).

Predictor	Dependent Variable							
	hs-CRP (mg/L)				miR-223			
	B	SE	β	*p*-value	B	SE	β	*p*-value
Age (years)	0.071	0.071	0.116	NS	−0.0018	0.0009	−0.223	0.048
Dialysis vintage (months)	0.039	0.024	0.190	NS	−0.00055	0.00020	−0.319	0.008
DM	0.58	3.12	0.025	NS	0.034	0.026	0.144	NS
HTN	1.74	2.84	0.078	NS	−0.018	0.024	−0.086	NS
Constant	4.21	3.71	—	NS	0.165	0.043	—	< 0.001
Immunosuppressive medications								
Steroids (mg)	0.15	0.07	0.15	0.043	−0.32	0.18	-0.32	0.089
Tacrolimus (mg)	0.08	0.05	0.08	NS	−0.14	0.12	-0.14	NS
Cyclosporine (mg)	0.05	0.06	0.05	NS	0.02	0.13	0.02	NS
MMF (g)	0.12	0.08	0.12	NS	−0.25	0.14	-0.25	0.088
Azathioprine (mg)	0.03	0.09	0.03	NS	0.05	0.16	0.05	NS
Septrin DS	0.04	0.06	0.04	NS	−0.07	0.12	-0.07	NS
Constant	4.21	3.71	—	NS	0.165	0.043	—	< 0.001

	hs-CRP				miR-223			
	R^2	Adjusted R^2	F-statistic	Model *p*-value	R^2	Adjusted R^2	F-statistic	Model *p*-value
Model-1 Summary for age, dialysis vintage, DM, and HTN confounders	0.061	0.006	1.12	NS	0.206	0.159	4.44	0.003
Model-2 Summary for immunosuppressive medications confounder	0.52	0.47	2.16	NS	0.47	0.42	1.79	NS

Model-1 adjusted for age, dialysis vintage, DM and HTN. Model-2 adjusted for immunosuppressive medications. $p > 0.05$ is not significant (NS). B: unstandardized regression coefficient; β: standardized regression coefficient; DM: diabetes mellitus; F-statistic: F-statistic for overall model significance; hs-CRP: high-sensitivity C-reactive protein; HTN: hypertension; MMF: mycophenolate mofetil; R^2 = proportion of variance explained by the model; SE: standard error.

Nutritional Status: Subjective Global Assessment (SGA)

Nutritional status evaluated using SGA categories was presented as frequencies and percentages [n (%)] (Table 5, Figures 3 and 4). SGA category A (normal nutritional status) was observed in: 25/25 (100%) of kidney transplant recipients, 19/25 (76%) of HDF patients, 8/25 (32%) of HD patients. The differences were highly statistically significant ($p < 0.001$). These findings indicated a substantially higher prevalence of malnutrition among HD patients.

Table 5. Nutritional Status: Subjective Global Assessment (SGA): Comparison between the three groups; hemodialysis (HD), hemodiafiltration (HDF) and kidney transplant recipients.

QOL by Subjective global assessment (SGA score)		Hemodialysis (N= 25)	HDF (N= 25)	Kidney transplant recipients (N= 25)	*p*-value
SGA final score (A or B or C)					
SGA final score (A/B/C) (%)	N. Normal (optimal) nutritional status(A)	8 (32%)	19 (76%)	25 (100%)	<0.001*
	Moderate malnutrition (B)	17 (68%)	6 (24%)	0 (0%)	
	Severe malnutrition (C)	0 (0%)	0 (0%)	0 (0%)	
Post Hoc Analysis (SGA score)‡ (*p*- value)					
Hemodialysis vs HDF		Hemodialysis vs kidney transplant recipients		HDF vs kidney transplant recipients	
0.001		<0.001		0.004	

p-value < 0.05: Significant; *: Chi-square test; ‡: Kruskal–Wallis test followed by post hoc analysis using Mann–Whitney test. HDF: hemodiafiltration; QOL: quality of life; SGA: Subjective Global Assessment.

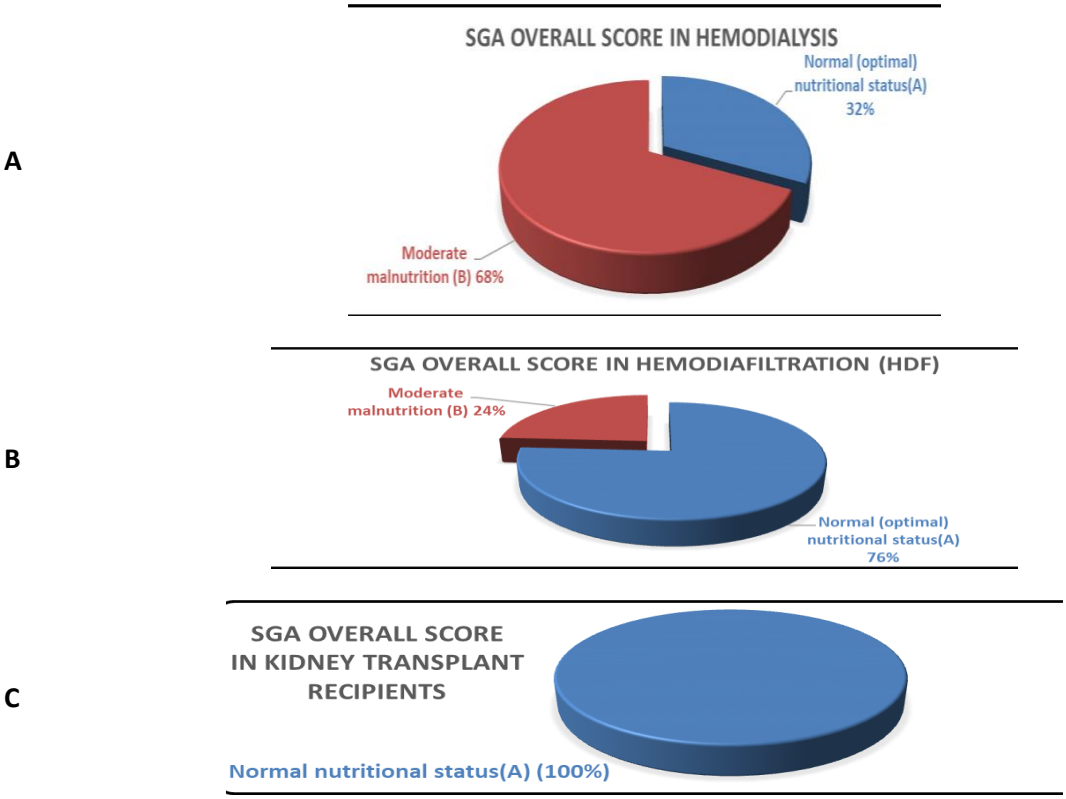


Figure 3. Comparison between groups with regard to the SGA overall score. [A: Hemodialysis; B: Hemodiafiltration (HDF); C: Kidney transplant recipients]. SGA: Subjective Global Assessment.

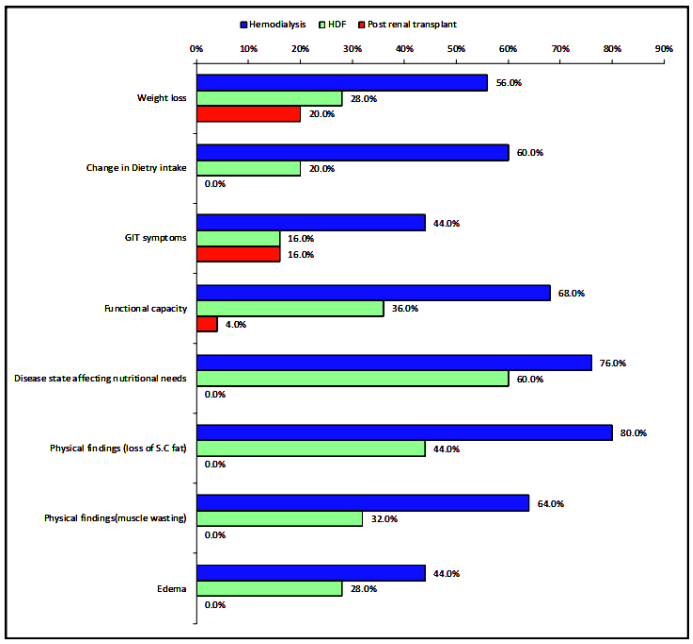


Figure 4. Comparison between groups concerning SGA items. GIT: gastrointestinal tract; HDF: hemodiafiltration; S.C.: subcutaneous.

Comparison of hs-CRP, miR-223, and Nutritional Status (SGA) to sex in the study population

Given that sex is a recognized modulator of immune and inflammatory responses, a subgroup analysis was performed to evaluate potential sex-related differences in inflammatory markers and nutritional status. As clearly indicated in Table (6), continuous variables (hs-CRP and miR-223) were presented as medians (interquartile ranges, IQRs) due to non-normal distributions. In contrast, categorical variables (SGA categories) were presented as numbers and percentages [n (%)]**.**There were no statistically significant differences between males and females regarding hs-CRP levels (p = 0.947) or miR-223 expression (p = 0.274). Furthermore, nutritional status, as assessed by SGA, revealed no statistically significant association with sex (Chi-square test, p = 0.052). Overall, sex did not significantly influence inflammatory marker levels or nutritional status in the studied population. (Table 6)

Table 6. Comparison of hs-CRP, miR-223, nutritional status (SGA), and sex in the study population

		Sex		*p*-value
		Male	Female	
hs-CRP (mg/L)	Median(IQR)	8 (4.1−15.45)	9 (4.4−14.2)	NS•
miR-223	Median(IQR)	0.02 (0.01−0.08)	0.01 (0−0.08)	NS•
SGA Normal (optimal) nutritional status (SGA A)	N (%)	37(71.2%)	15(28.8%)	NS*
Moderate malnutrition (SGA B)		11(47.8%)	12(52.2%)	

p-value > 0.05: Non significant; •: Mann–Whitney *U* test; *: Chi-square test. hs-CRP: high-sensitivity C-reactive protein; SGA: Subjective Global Assessment.

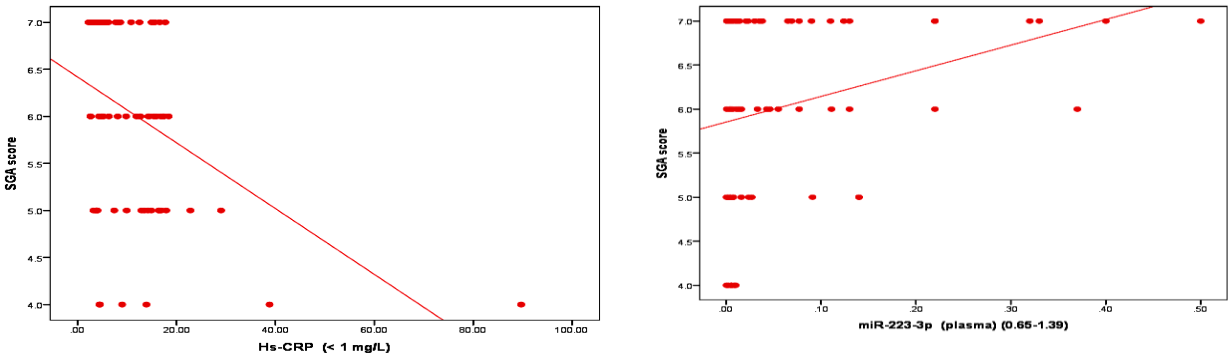
Correlations between Inflammatory Biomarkers and Nutritional Status

Spearman correlation coefficients analysis (Table 7, Figure 5), after Bonferroni correction (adjusted significance threshold $p < 0.0083$), demonstrated that SGA score was negatively correlated with hs-CRP (r = - 0.337, p =0.003), and NLR= (r =-0.316, p = 0.006), and positively correlated with circulating miR-223 (r = 0.324, p = 0.005), and hemoglobin (r = 0.349, p = 0.002); indicating that worsening nutritional status was associated with higher inflammatory burden and lower miR-223 expression.

Table 7. Correlations between Inflammatory Biomarkers and Nutritional Status.

All patients (N=75)	QOL "SGA score"	
	r	*p*-value
Inflammatory biomarkers		
NLR ratio (Neutrophil-to-lymphocyte ratio) (1-2)	-0.316	0.006
HGB (13-17 g/dL)	0.349	0.002
Serum albumin (3.5-5.2 g/dL)	0.093	NS
Ca x PO4 product (< 55 mg^2/dL^2)	-0.301	NS
hs-CRP (< 1 mg/L)	-0.337	0.003
miR-223 (0.65-1.39) ¶	0.324	0.005

Values represent Spearman's rank correlation coefficients. Statistically significant after Bonferroni correction for multiple comparisons (adjusted significance threshold $p < 0.0083$); to control for multiple comparisons (n = 6), since $\alpha = 0.05 / 6 = 0.0083$. ¶: Normal miR-223 expression range in healthy controls: 0.65–1.39.
Ca: calcium; HGB: hemoglobin; hs-CRP: high-sensitivity C-reactive protein; PO_4: phosphorus;
QOL: quality of life; SGA: Subjective Global Assessment.



A B

Figure 5. Significant correlations between quality of life (by SGA) and inflammatory biomarkers [hs-CRP (A) and miR-223(B)]. hs-CRP: high-sensitivity C-reactive protein; SGA: Subjective Global Assessment.

ROC curve analysis of the performance of inflammatory biomarkers

ROC analysis compared kidney transplant recipients (n = 25) with pooled dialysis patients (hemodialysis and HDF combined; n = 50) to evaluate the utility of circulating miR-223 and hs-CRP as biomarkers of systemic inflammatory and metabolic changes after transplantation. Although not a traditional diagnostic test, ROC analyses in our study were performed as exploratory analyses to quantify the discriminatory capacity of these biomarkers between pre- and post-transplant states.

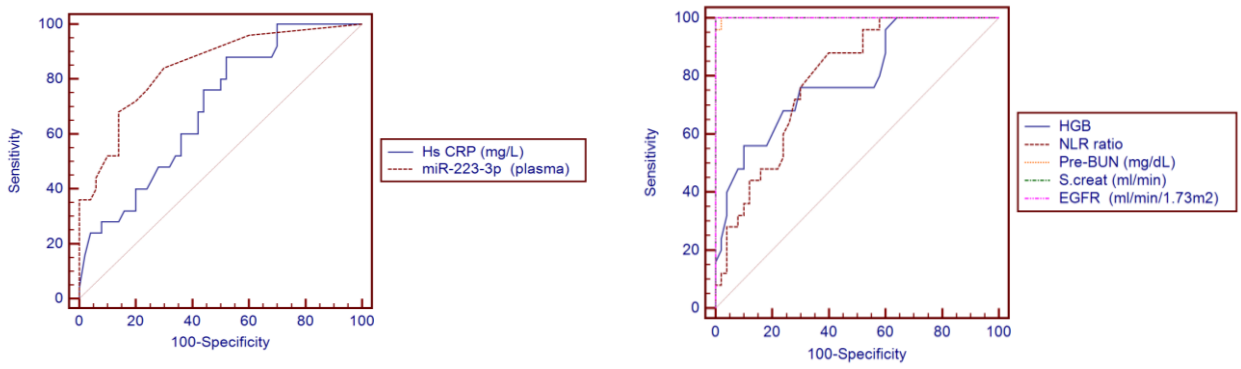
Among the novel inflammatory biomarkers, hs-CRP showed modest discriminative ability (AUC = 0.694). A cut-off value of ≤12.6 mg/L provided 88% sensitivity and 48% specificity. In contrast, circulating miR-223 demonstrated

good diagnostic performance (AUC = 0.844). At a cut-off value of > 0.04, miR-223 achieved 68% sensitivity and 86% specificity, with positive and negative predictive values of 70.8% and 84.3%, respectively. Importantly, the optimal cut-off (> 0.04) was well below the established reference range in healthy individuals (0.65 – 1.39). The majority of dialysis patients had markedly lower median values HD and HDF values (0.0067 and 0.0073, respectively), well below the kidney transplant recipients' median (0.11), reflecting a relative increase in transplant recipients compared with suppressed dialysis levels, yet still below healthy reference values. These results indicate that ROC-derived thresholds captured treatment-related shifts rather than normalization, highlighting that both biomarkers effectively reflected the post-transplant improvement in inflammatory and nutritional status. (Table 8, Figure 6)

Table 8. ROC curve analysis of the performance of inflammatory biomarkers: Cut-off levels for the novel inflammatory biomarkers (hs-CRP, miR-223) and conventional biomarkers in detecting response to kidney transplantation.

Parameter	AUC	Cut of Point	Sensitivity	Specificity	PPV	NPV
HGB (13-17 g/dL)	0.789	>11.1	56.0	90.0	73.7	80.4
NLR ratio (1-2)	0.791	≤2	88.0	60.0	52.4	90.9
BUN (6-20 mg/dL)	0.999	≤27	100.0	98.0	96.2	100.0
Serum creatinine (0.7-1.2 mg/dL)	1.000	≤1.4	100.0	100.0	100.0	100.0
eGFR (≥90 ml/min/1.73m²)†	1.000	>14	100.0	100.0	100.0	100.0
hs-CRP (< 1mg/L)	0.694	≤12.6	88.0	48.0	45.8	88.9
miR-223 (0.65-1.39)¶	0.844	>0.04	68.0	86.0	70.8	84.3

ROC analysis was performed by comparing kidney transplant recipients (n = 25) versus pooled dialysis patients (hemodialysis and HDF combined; n = 50), representing the dialysis treatment state. †= eGFR by CKD-EPI; ¶: Normal miR-223 expression range in healthy controls: 0.65–1.39**.** AUC: area under the curve; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; HGB: hemoglobin; hs-CRP: high-sensitivity C-reactive protein; NLR: neutrophil-to-lymphocyte ratio; NPV: negative predictive value; PPV: positive predictive value; ROC: receiver operating characteristic.



A **B**

Figure 6. ROC curves illustrating response to kidney transplantation by novel biomarkers [hs-CRP and miR-223 (A)] and conventional biomarkers [BUN, S. creatinine, eGFR by CKD-EPI, NLR, HGB (B)].

BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; HGB: hemoglobin; hs-CRP: high-sensitivity C-reactive protein; NLR: neutrophil-to-lymphocyte ratio; S. creat: serum creatinine.

Discussion

The present study evaluated systemic inflammatory burden and nutritional status across renal replacement modalities and explored the clinical relevance of circulating miR-223 alongside hs-CRP. Our findings support the concept that restoration of renal function post-renal transplant attenuates systemic inflammation and improves nutritional status, while conventional dialysis modalities remain associated with persistent inflammatory burden. This corresponds with evidence that inflammation and malnutrition remain significant determinants of health status in CKD and ESKD populations.[16]

Elevated hs-CRP in dialysis patients aligns with contemporary understanding of CKD and ESKD as chronic inflammatory states driven by oxidative stress, endothelial dysfunction, uremic toxin accumulation, and dialysis-related bioincompatibility.[17] Chronic inflammation contributes substantially to cardiovascular risk and protein-energy wasting in this population.[18] The comparatively lower inflammatory profile observed in the HDF group, despite an older mean age, is noteworthy. Convective therapies enhance middle-molecule clearance and may attenuate inflammatory mediators[19] The randomized CONVINCE trial demonstrated improved survival with high-dose HDF, and inflammatory modulation has been proposed as a potential mechanism.[20] Moreover, our findings indicate that the observed differences in inflammatory biomarkers across treatment modalities are not solely attributable to age differences between groups. Transplant recipients demonstrated lower hs-CRP levels than dialysis patients, consistent with evidence that restoration of renal function partially reverses systemic inflammation.[21]

Together with hs-CRP, miR-223 may provide complementary information on inflammatory status, capturing both classical acute-phase responses and epigenetic regulation of immune pathways. The observed pattern of circulating miR-223 expression across treatment modalities further supports its role as a regulator of immune-inflammatory pathways in renal disease. Circulating miR-223 expression varied significantly across renal replacement modalities and correlated with inflammatory and nutritional parameters. Experimental studies have demonstrated that miR-223 modulates inflammatory signaling pathways, including regulation of NLRP3 inflammasome activation and downstream cytokine responses in preclinical models.[22] These findings provide biological plausibility for its involvement in inflammatory regulation.Downregulation of miR-223 has been reported in CKD populations and is associated with inflammatory activation. The mechanisms underlying reduced circulating expression in CKD remain uncertain and may include reduced immune cell production, altered extracellular vesicle trafficking, transcriptional dysregulation induced by uremic toxins, or dialysis-related clearance effects.[23] More importantly, miR-223 dysregulation has also been described in systemic inflammatory, sepsis and cardiovascular diseases, supporting its broader role as a regulator of immune-inflammatory pathways.[24] The ROC-derived cutoff (>0.04) represents a statistical discrimination threshold within the ESKD population. It does not correspond to the physiological reference range (0.65–1.39), which reflects relative fold-change expression calculated using the 2^−ΔΔCt method. Overall, miR-223 should be considered a candidate biomarker reflecting immune-inflammatory activity.

Our findings extend this evidence by demonstrating significant associations between miR-223 expression, nutritional status (assessed by SGA), and modality-related inflammatory differences, highlighting miR-223's discriminatory performance relative to hs-CRP. SGA is a validated nutritional assessment tool that reflects a key dimension in quality of life outcomes. The association between inflammatory markers and SGA-defined nutritional status is consistent with the MIA paradigm described in ESKD. Chronic inflammation promotes anorexia, muscle catabolism, hypoalbuminemia, and metabolic dysregulation, contributing to protein-energy wasting.[25] Recent studies emphasized the bidirectional relationship between nutrition and inflammation in CKD progression.[26] In our study,

the inverse association between hs-CRP and SGA scores and the positive association between miR-223 and better nutritional status reinforce the interplay between immune dysregulation and nutritional impairment in these patients. Moreover, our findings suggest that hs-CRP, as a systemic inflammatory marker, is largely independent of age, dialysis duration, and comorbidities, which may reflect its acute-phase nature and susceptibility to transient factors rather than chronic dialysis-related influences. In contrast, circulating miR-223 appears more sensitive to both age and cumulative dialysis exposure, indicating that it may serve as a more specific biomarker of dialysis-associated physiological stress or vascular alterations. These observations further suggest that longitudinal monitoring of miR-223 in dialysis patients could provide valuable insights into dialysis-related cellular and vascular changes. Patients with higher inflammatory markers (hs-CRP) tend to receive higher doses of immunosuppressive drugs, particularly steroids. This does not necessarily mean that the drugs cause the inflammation; rather, the association likely reflects dose escalation in response to higher baseline inflammation.

Clinically, these findings suggest that incorporating inflammatory biomarkers (e.g., hs-CRP) together with epigenetic biomarkers (e.g., miR-223) into routine assessment may improve risk stratification and guide nutritional and therapeutic interventions in patients undergoing dialysis or post-transplant care. While hs-CRP remains an established inflammatory biomarker, miR-223 may provide complementary insight into immune regulatory processes.

Several limitations must be acknowledged; cross-sectional design precludes causal inference; miR-223 is measured at a single time point & no mechanistic experiments are performed to support causal claims; ROC findings lack external validation. Defining early post-transplantation as 3–12 months and using healthy controls only for baseline miR-223 reference limits temporal assessment and formal comparative analyses.

In conclusions, this study highlights the close interaction between inflammation, immune regulation, and nutritional status across renal replacement therapy modalities. The findings support the potential utility of circulating miR-223 as a biomarker reflecting immune-inflammatory activity in this population and reinforce the importance of addressing inflammation in the management of ESKD; supporting continued exploration of epigenetic biomarkers in nephrology to allow earlier intervention, thereby preventing protein-energy wasting and its downstream complications. Future research should focus on validating miR-223 as a prognostic biomarker in larger, multicenter cohorts and clarifying its mechanistic role in renal inflammation. Additionally, studies evaluating standardization, feasibility, and cost-effectiveness are needed before integration into routine nephrology practice.

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Author Contributions

Conceptualization, HE and ME; Data curation, MA, MO and ME; Formal analysis, MA, MO and ME; Investigation, MA, MO and ME; Methodology, ME; Project administration, HE and ME; Resources, MO and ME; Supervision, HE, AH, AE, MA and ME; Validation, HE, AH, AE, MA and ME; Visualization, AH, AE, MA and ME; Writing original draft, MA and MO; Writing review & editing, HE, AE, MA, MO and ME.

Declaration of Conflicting Interests

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Ethical approval

The study was carried out in accordance with the ethical principles of the Declaration of Helsinki of the World Medical Association (WMA). The research ethics committee (REC) of the Faculty of Medicine of Ain Shams University approved this study (reference number; FWA 000017585) on 8 September 2022. Additionally, the institutional ethical committee at the Faculty of Medicine, Ain Shams University, approved all study protocols.

Informed consent

Prior to intervention, written informed consent was obtained from all study participants.

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