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Original article

Intercellular Adhesion molecule-1 and Neutrophil Extracellular Traps in children on maintenance hemodialysis: Evidence of a chronic inflammatory state

Background: *Intercellular adhesion molecule-1 (ICAM-1) plays a key role in guiding leukocytes to sites of inflammation. Neutrophil extracellular traps (NETs) have been linked to vascular inflammation and blockages in patients with chronic kidney disease (CKD). The objective of this study was to measure serum levels of ICAM-1 and NETs both before and after a single session of high flux hemodialysis (HFHD) in children on maintenance hemodialysis.* ***Methods:*** *A total of 26 children who had been on HFHD for at least three months were enrolled, along with an equal number of healthy children matched for age and sex as controls. Patients with active inflammation, infections, or other relevant comorbid conditions were excluded from the study. Blood samples were collected from the patients both before and after their mid-week dialysis session to analyze complete blood counts (CBC), C-reactive protein (CRP), ICAM-1, and NETs levels. Same investigations were done for controls.* ***Results:*** *After the dialysis session, ICAM-1 and NETs levels showed a significant decrease compared to pre-dialysis measurements ($p=0.000$, $p<0.0001$ respectively). Despite this reduction, post-dialysis ICAM-1 and NETs levels remained higher than those observed in healthy controls ($p=0.003$, $p=0.033$ respectively).* ***Conclusion:*** *The findings support that end-stage kidney disease (ESKD) is characterized by ongoing inflammation. Unlike traditional views that suggest dialysis may add to the inflammatory process, our results indicate that effective hemodialysis can reduce inflammatory markers. Better dialysis membranes and novel modalities of dialysis should be tested to ensure they can exert a positive role in ameliorating this inflammatory status.*

Key words: Intercellular Adhesion Molecule-1 (ICAM-1), Neutrophil extracellular traps (NETs), Hemodialysis (HD), chronic kidney disease (CKD), End stage kidney disease (ESKD), High-flux hemodialysis (HFHD)

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INTRODUCTION

Chronic kidney disease (CKD) in pediatric population is increasingly recognized as a significant public health concern within our community, particularly given the challenges associated with kidney transplantation, which remains the definitive form of kidney replacement therapy (KRT). CKD is characterized by its impact on multiple organ systems due to its nature as a chronic inflammatory disorder. When compared to healthy individuals, patients with end-stage kidney disease (ESKD) exhibit approximately three times higher serum concentrations of inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6). [1] This elevation is attributed to increased production and decreased clearance of these substances. Several factors contribute to the persistent inflammation observed in CKD patients, including coexisting health conditions, uremic toxins, infections, genetic predispositions, and aspects related to dialysis procedures. [2]

Hemodialysis (HD), which is the predominant form of KRT for ESKD, involves circulating blood through an external circuit containing a synthetic membrane and tubing system designed to eliminate metabolic waste products. This process can provoke an immune response characterized by activation of various protein cascade systems such as the complement and coagulation pathways, along with activation of endothelial cells and circulating blood cells like platelets, lymphocytes, neutrophils, and erythrocytes. These cellular activations lead to the

release of soluble mediators including enzymes, pro-inflammatory cytokines, and reactive oxygen species.[3,4]

The cytokine-mediated inflammatory response in CKD notably increases the expression of intercellular adhesion molecule-1 (ICAM-1) on immune cells as well as epithelial and endothelial cells.[5] Additionally, it is hypothesized that the formation of Neutrophil Extracellular Traps (NETs), a process known as NETosis, serves as an indicator of immune activation triggered by hemodialysis.[6] Elevated levels of NETs byproducts—such as elastase, myeloperoxidase (MPO), and cell-free DNA—have been observed in hemodialysis patients during treatment sessions.[7] However, there is limited data regarding these inflammatory markers specifically in pediatric ESKD patients. Therefore, this study aims to evaluate serum levels of ICAM-1 and NETs as indicators of inflammation in children undergoing maintenance hemodialysis.

METHODS

This study was carried out at the Pediatric Dialysis Unit of Children's Hospital, Ain Shams University, following approval from the Research Ethics Committee of the Faculty of Medicine at Ain Shams University (FWA 000017585; FMASU: R 124/2024). The study adhered to the principles outlined in the Declaration of Helsinki and relevant guidelines. The study population included 26 incident CKD-5d children who were stable on conventional HD using high flux membrane (HFHD) for more than 3 months, all aged 16 years or younger. These patients were compared with a control group consisting of twenty-six healthy children matched for age and sex. Exclusion criteria for patient selection encompassed individuals with failed kidney grafts, active infections, recent blood transfusions within the past month, autoimmune disorders, ongoing thrombosis, hepatitis, diabetes mellitus, malignancies, cardiomyopathy, infective endocarditis, those receiving immunosuppressive therapy, or patients who had been on HD for less than three months. Each participant underwent an initial assessment that gathered demographic data such as age and sex, details about their CKD cause and duration on HD (vintage in months), comprehensive medical histories, and physical examinations aimed at identifying any recent or ongoing infections, inflammation, or thrombosis.

Blood tests

Blood samples were collected both before and after mid-week HD sessions for laboratory analysis. A total of five milliliters of venous blood was drawn from a peripheral vein located away from the limb with an arteriovenous fistula. These samples were analyzed for complete blood count (CBC), C-reactive protein (CRP), serum intercellular adhesion molecule-1 (ICAM-1), and neutrophil extracellular traps (NETs). Prior to post-dialysis sampling, blood flow was reduced to 50 mL/minute along with halting dialysate flow. Serum ICAM-1 levels were measured using a Human Intercellular Adhesion Molecule-1 ELISA kit (Cat. No: E0212Hu) supplied by Bioassay Technology Laboratory in Shanghai, China. Serum NETs levels were assessed through a citrullinated histone H3 (CitH3)-based human neutrophil extracellular trap ELISA kit (Cat. No: E4548Hu) supplied by Bioassay Technology Laboratory in Shanghai, China.

Statistical Analysis

For data analysis, the Statistical Package for Social Sciences version 26 (SPSS Inc., Chicago) was utilized. The normality of data distribution was tested using the Shapiro-Wilk test. Quantitative variables were described as either mean ± standard deviation if normally distributed or as median with interquartile range if skewed. Categorical variables were expressed as counts and percentages. To compare parametric quantitative data between groups or time points, independent samples t-test or paired t-test was used respectively; non-parametric data comparisons employed Mann-Whitney U test or Wilcoxon signed-rank test accordingly. Correlations between variables were examined using Pearson's correlation coefficient or Spearman's rho test. A p-value less than 0.05 was considered statistically significant in all analyses.

RESULTS

Study demographics and disease characteristic

A total of 26 incident high flux hemodialysis (HFHD) patients along with 26 healthy age and sex matched controls were enrolled in this study. Patients' mean age was 12.2 ± 2.8 years (range: 5.8 - 15.6 years) including 16 (61.5%) males and 10 (38.5%) females. Controls' mean age was 10.9 ± 2.7 years (range: 6.0 - 15.0 years) including 13 males and 13 females. All patients were clinically stable throughout the study period with comparable CRP levels with the controls ($p>0.05$). None of our patients were reported to have high CRP (i.e. CRP > 6 mg/L) at any point of time during the study. HD was performed in thrice weekly sessions, each lasting for 3 hours using high flux dialyzers and pediatric blood lines through AV fistulae. Disease

characteristics of the studied population are shown in table (1).

ICAM-1 and NETs in HFHD

Pre-session ICAM-1 levels were significantly higher than controls (p= .000). HD resulted in a statistically significant reduction in post-session ICAM-1 compared to the pre-session levels (p= .000) but remained significantly higher than the controls (p= .003). Pre-session NETs' levels were significantly higher than controls (p <0.0001). However, HD session resulted in a statistically significant reduction in post-session NETs levels in comparison to pre-session levels (p <0.0001). Meanwhile NETs post-session levels were still significantly higher than controls (p= .033) (table 2, Fig 1, 2).

ICAM-1 and NETs clinical relations and correlations

There were no significant differences in pre-session ICAM-1 and NETs levels between hypertensive and non-hypertensive patients (p= 0.382, p= 0.305 respectively). Also, there were no significant differences between pre- and post-session counts of total leukocyte count, and absolute neutrophil count (p= 0.726, p= 0.468 respectively) and no significant correlations were found between pre-session ICAM-1, NETs and CRP (rho= -0.019, p= 0.930; rho= 0.044, p= .84 respectively). Neither pre- nor post-session serum ICAM-1, NETs levels showed any significant correlation with pre- or post-session hemoglobin levels, total leukocyte count, absolute neutrophil count or absolute lymphocyte count. No significant correlations were found between spKt/V and post-session ICAM-1 and NETs (rho= -0.12, p= 0.58; rho= 0.178, p= 0.395 respectively). Pre dialysis serum levels of ICAM-1 and NETs showed significant positive correlation (rho= 0.755, p< .0001) (fig 3) while post dialysis serum levels showed no significant correlation (rho= 0.125, p= 0.549).

Table 1. Disease characteristics of the studied population

Parameters	Patients (n= 26)	Controls (n= 26)
Underlying kidney diagnosis (n) (%)	* Unknown (8) (30.77%) * CAKUT (7) (26.92%) * Chronic glomerulopathy (6) (23.08%) * ARPKD (2) (7.69%) * Joubert syndrome (2) (7.69%) * Alport syndrome (1) (3.85%)	-
HD vintage (Mdn; IQR)	35.5; 32.6 months	-
Presence of hypertension	14 (53.85%)	-
CRP (mg/L) (Mdn; IQR)	0.9; 1.2	1.4; 0.06
BUN (mg/dL) (Mdn; IQR)	70.7; 16.9	9.82; 1.86
Creatinine (mg/dL) (Mdn; IQR)	5.30; 1.70	0.47; 0.07
spKt/V (Mdn; IQR)	1.35; 0.2	-

CAKUT, congenital anomalies of kidney & urinary tract; HD, hemodialysis; Mdn, median; IQR, interquartile range; CRP, C-reactive protein; BUN, blood urea nitrogen; spKt/V, single-pool urea Kt /V (measure of adequacy of small molecule removal by a single dialysis treatment)

Table 2. Comparison between serum NETs, ICAM-1 levels in cases versus controls

	Cases		Controls		P- value	
	NETs (ng/L) $\bar{x}$ ± SD (Mdn ; IQR)	**ICAM-1 (ng/L) $\bar{x}$ ± SD (Mdn ; IQR)**	**NETs (ng/L) $\bar{x}$ ± SD (Mdn ; IQR)**	**ICAM-1 (ng/L) $\bar{x}$ ± SD (Mdn ; IQR)**	**NETs**	**ICAM-1**
Pre-session	986.29 ± 483 (954.40; 812.75)	1665.82 ±1566.27 (1080.00; 1223.75)	147.12 ± 51.73 (149.05; 69.72)	174.61 ± 55.50 (171.15; 101.75)	<0.0001[b*]	0.000[a*]
Post-session	200.35 ± 108.70 (175.20; 184.69)	361.63 ± 290.86 (251.40; 301.10)			0.033[b*]	0.003[a*]
P- value	<0.0001[b]	0.000[a*]				

$\bar{x}$ ± SD, mean ± standard deviation; Mdn, median; IQR, interquartile range; NETs, neutrophil extracellular traps; ICAM-1, intercellular adhesion molecule-1; a, Mann-Whitney test; b, Student t-test.

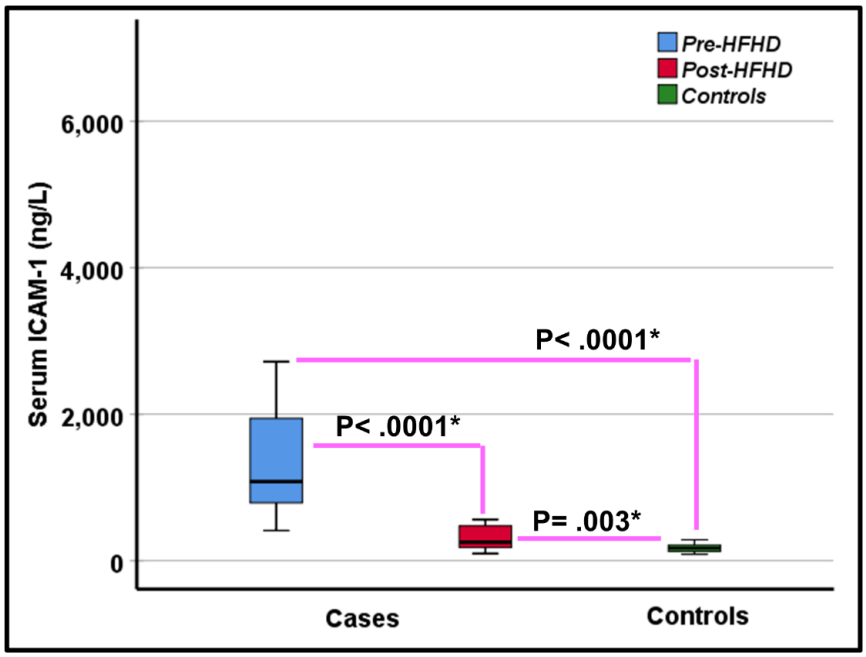

Figure 1. Boxplots of changes in serum sICAM-1 levels with HFHD
ICAM-1, intercellular adhesion molecule-1; HFHD, high flux hemodialysis; *, p-value is statistically significant.

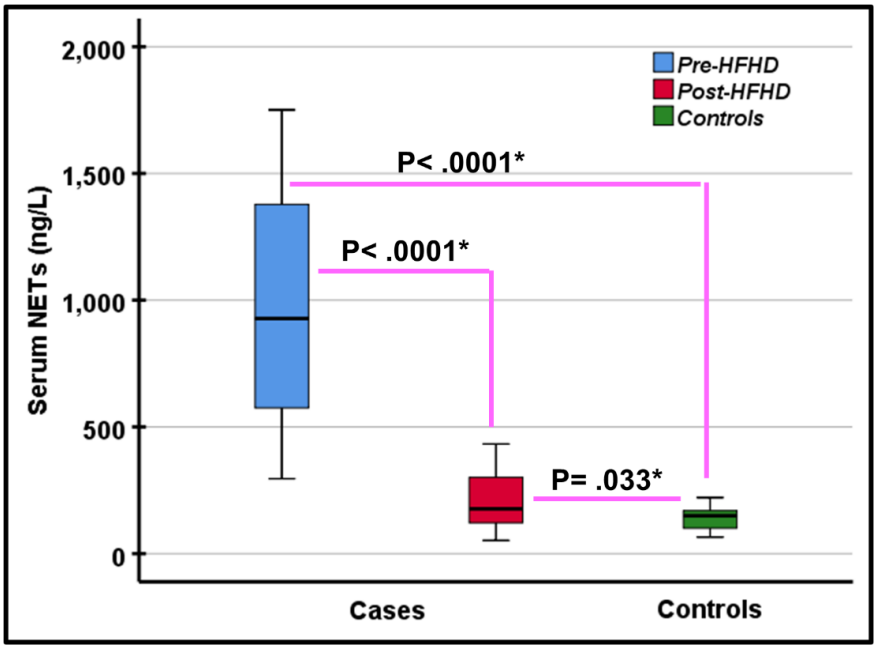

Figure 2. Boxplots of changes in serum NETs levels with HFHD
NETs, neutrophil extracellular traps; HFHD, high flux hemodialysis; *, p-value is statistically significant

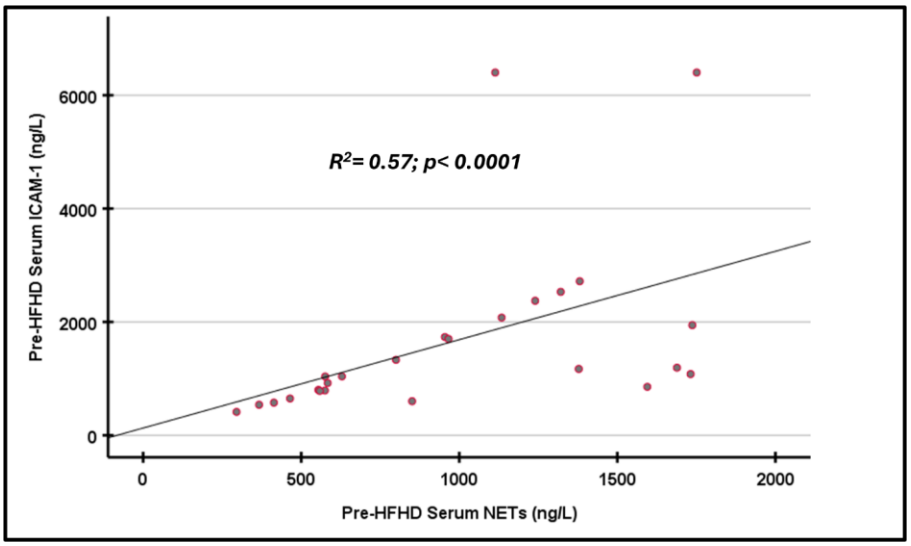

Figure 3. Correlation between pre dialysis serum levels of ICAM-1 and NETs
ICAM-1, intercellular adhesion molecule-1; NETs, neutrophil extracellular traps; HFHD, high flux hemodialysis; *, p-value is statistically significant

DISCUSSION

Although extensive research has been conducted on the immunological consequences of chronic kidney disease (CKD) and long-term hemodialysis, the precise ways in which these conditions influence the immune system remain not fully understood. Conventional inflammatory markers often lack the sensitivity needed to detect subtle or low-grade inflammation, making the development of more sensitive indicators essential for better assessment in affected patients. In this context, intercellular adhesion molecule-1 (ICAM-1) and neutrophil extracellular traps (NETs) are emerging as potential biomarkers that could provide valuable insights.

Our current investigation found that children undergoing hemodialysis exhibited significantly elevated levels of ICAM-1 prior to their dialysis sessions when compared to healthy individuals. These results align with findings from previous studies.[8,9-14] Nonetheless, Liakopoulos et al. reported contrasting results, indicating that serum ICAM-1 concentrations in adult patients on chronic hemodialysis were similar to those observed in healthy controls. [15] The mechanisms underlying increased pre-dialysis ICAM-1 levels in HD patients are not yet fully clarified, especially given the inconsistent findings across different studies and the limited number of investigations available. Patients with CKD generally tend to have higher serum ICAM-1 levels, which may be further elevated by ongoing hemodialysis treatment. [16] Chronic uremia is associated with increased production of pro-inflammatory cytokines, which can stimulate endothelial cells to produce and release adhesion molecules such as ICAM-1.[15] Additionally, elevated ICAM-1 levels might result from enhanced synthesis and secretion by endothelial cells stimulated by pro-inflammatory cytokines generated during dialysis through contact with the extracorporeal circuit. [5, 15] The presence of increased ICAM-1 in patients with CKD who are not yet on dialysis or are on continuous ambulatory peritoneal dialysis suggests that renal function may play a role in its breakdown or clearance. [8]

Furthermore, our study observed a notable increase in NETs levels before dialysis sessions among HD patients compared to healthy controls. This elevation could be linked to the accumulation of uremic toxins, which promote a persistent state of low-grade inflammation and oxidative stress—factors known to impair both innate and adaptive immune responses. [17] Laboratory studies have shown that exposing normal neutrophils to uremic plasma accelerates their apoptosis more rapidly than other leukocytes; this effect is likely due to increased expression of Fas and Fas ligand on neutrophil surfaces induced by uremic conditions. [18]

Post-dialysis measurements revealed a significant decrease in ICAM-1 levels following treatment. This contrasts with findings from Papayianni et al., who reported an increase in ICAM-1 levels within blood samples taken from arteriovenous fistulas at the end of a 4-hour dialysis session compared to pre-session values. [8] Similarly, Bieber et al. observed higher intradialytic ICAM-1 concentrations in adults during HD sessions relative to pre-dialysis levels and control subjects.[12] Conversely, Liakopoulos et al. found no significant

change in ICAM-1 levels in blood samples taken every hour, and at the end of a single 4-hour HD session in adult patients. [15]

The discrepancy regarding post-dialysis ICAM-1 reduction in our study may be attributed to our use of high-flux membranes—these are more effective at removing larger middle-molecular-weight substances such as pro-inflammatory cytokines and other uremic toxins—compared to membranes used in other studies. High-flux membranes also tend to induce less inflammation during dialysis because they interact less with leukocytes, potentially leading to decreased production or upregulation of ICAM-1 related to membrane-leukocyte interactions. [19, 20] Age differences and site of blood sampling are also possible explanations.

In our study, we observed a notable reduction in post-dialysis NETs levels compared to those measured before the HD session. This could reflect a potential contribution of dialysis in reducing the inflammatory environment associated with uremia, likely due to more efficient clearance of uremic toxins. However, the period between dialysis sessions may allow for the reaccumulation of these toxins, potentially reactivating polymorphonuclear cells and promoting the formation of NETs, which may explain the observed increase in NETs levels prior to dialysis. Efthymios et al. examined neutrophil phagocytic function and found a significant decline in this activity in all patients following dialysis. [21] Additionally, Bieber et al. proposed that other unidentified elements involved in neutrophil activation during dialysis should be considered—these include variables such as blood and dialysate flow rates, the chemical composition of the dialysate, the surface area of the dialyzer, tubing materials and structure, as well as the total duration of the HD session. [12]

Previous studies exploring the impact of conventional HD on neutrophil activation at various time points in relation to the dialysis procedure (before, during, and after) and comparing it to healthy individuals has produced inconsistent outcomes. [12, 18, 22-27] This variability may be attributed to differences in patient demographics, such as age—since most studies focused on adults—or the presence of additional health conditions that could affect NETs levels independently of CKD. These include conditions like diabetes, cardiovascular disease, amyloidosis A, vasculitis, liver transplantation, failed kidney transplants, and immunosuppressive therapy. [12, 18] Another significant contributor to the heterogeneity in findings is the use of different techniques for evaluating neutrophil activation and apoptosis. These methods include the measurement of plasma myeloperoxidase, circulating cell-free DNA, NETs (MPO-DNA complexes), elastase, calprotectin, and various CD markers. For example, Lee et al. analyzed plasma nucleosome (histone-DNA) and MPO-DNA complex levels in 201 dialysis patients and 51 healthy controls, noting, as in our study, that markers of NETosis were markedly higher in the HD group. [18] Bieber et al. also assessed NETs via MPO-DNA complexes in 24 adults undergoing HD and compared their levels to those in 27 healthy individuals. They reported that NETs levels were elevated during dialysis compared to pre-dialysis levels. [12] Similarly, Fukushi et al. found increased plasma MPO levels after dialysis in 70 adult HD patients. [27] Costa et al. identified a significant post-dialysis rise in neutrophil elastase levels when compared to pre-dialysis levels. [24]

In our present study, neither pre- nor post-dialysis levels of ICAM-1 demonstrated a significant correlation with total white blood cell count, neutrophil count, or lymphocyte count. In contrast, Sawires et al. found that ICAM-1 levels after a low-flux HD session in pediatric patients positively correlated with total leukocyte count and inversely with absolute neutrophil count. [10] Abbas similarly identified a significant positive correlation between pre-dialysis ICAM-1 and total leucocytic count in adults on dialysis. [11] These contradictory findings across studies could stem from several factors, such as differences in age groups, sample sizes, and the presence of other diseases that may influence ICAM-1 concentrations. Many adult-based studies enrolled patients with comorbidities like diabetes, hypertension, amyloidosis A, liver transplants, failed grafts, and those receiving immunosuppression. Moreover, technical considerations—such as the location of blood sampling, the assay type, and the specificity and sensitivity of ELISA kits—are critical. For example, drawing blood directly from an arteriovenous fistula may artificially elevate ICAM-1 levels due to localized endothelial damage, which is why we avoided this method in our protocol. Furthermore, Abbas included subjects with significantly elevated absolute neutrophil counts and CRP levels compared to controls, without adjusting for these potential confounders. [11]

According to findings by Fukushi et al. total leukocyte count, neutrophils, absolute neutrophil count, lymphocytes, and monocyte count significantly declined following dialysis, alongside

marked increases in early apoptotic ratios in white blood cells, neutrophils, and monocytes—though lymphocyte apoptosis was not significantly altered.[27] These changes did not show any significant correlation with cell counts, a result aligning with our data, where we found no notable correlation between pre- and post-dialysis NETs and total leukocyte, neutrophil, or lymphocyte counts. This suggests that functional changes in leukocytes may play a more prominent role than changes in their absolute numbers.

We identified a significant positive correlation between pre-dialysis ICAM-1 levels and NETs, which is an expected result as both are indicative of an inflammatory response. However, based on our review, this specific association has not been previously documented in the literature. Our study limitation includes small sample size and lack of comparison of these markers in different modalities of hemodialysis.

In conclusion, ICAM-1 and NETs has proven ESKD a chronic inflammatory condition. Unlike the common concept, HD can improve the inflammatory status but only when high flux efficient dialyzers are used. Better dialysis membranes and novel modalities of dialysis should be tested to ensure they can exert a positive role in ameliorating this inflammatory status.

AUTHORS' CONTRIBUTION

RS supervised the data collection, shared in data analysis and wrote the manuscript, **MK** designed the study and did the statistical analysis of data, **NM** did the laboratory investigations, **NH** did the data analysis and shared in data collection. All authors revised and agreed on the manuscript.

CONFLICTS OF INTEREST

Authors declare they have no conflicts of interest related to this work.

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