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Exploring the Association between Chronic Kidney Disease and Eosinophilia

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Abstract: *The present study aimed to investigate the prevalence of eosinophilia (EOS) changes with the progression of renal function. Identify whether EOS is an independent risk factor in Chronic kidney disease (CKD) progression. Patients with end-stage renal disease (ESRD) experience changes in the prevalence of EOS before and after hemodialysis (HD) or peritoneal dialysis (PD). This study included 1870 CKD patients who underwent long-term hospitalization and follow-up at our nephrology department from January 2018 to December 2021. Peripheral blood eosinophil count (PBE), renal function parameters [such as creatinine, urea nitrogen, urea, estimated glomerular filtration rate (eGFR)], c-reactive protein(CRP), white blood cells, hemoglobin, and other indicators were statistically analyzed to analyze the correlation between EOS and the above indicators. The prevalence of EOS exhibited a notable increase with advancing stages of renal dysfunction, and the difference was statistically significant. The prevalence of EOS increased by 12.7% for every 1 ml/min decrease in eGFR. Progression of renal function in CKD patients is positively correlated with the prevalence of EOS. The prevalence of EOS is higher in HD patients than in non-dialysis patients.*

Keywords: *Chronic kidney disease, Eosinophilia, End-stage renal disease, Hemodialysis, Peritoneal dialysis*

1. Introduction

Chronic kidney disease (CKD) poses a significant threat to human health. It is characterized by a high prevalence, low awareness, poor prognosis, substantial economic burden, and elevated mortality, particularly in patients reaching end-stage renal disease (ESRD). Therefore, the early diagnosis and treatment of CKD are essential. Eosinophilia (EOS) is defined as an increase in circulating eosinophils exceeding 0.5×10^9/L [1] and is categorized into hereditary (familial), secondary (reactive), primary (clonal), and undetermined significance (idiopathic) [2]. Secondary EOS is frequently associated with various conditions, including allergic diseases, non-allergic skin diseases, medications, infectious diseases, gastrointestinal diseases, vasculitis, rheumatic diseases, respiratory diseases, and tumors [2]. While some reports exist on the association between EOS and specific renal diseases such as Henoch–Schonlein purpura nephritis, eosinophilic granulomatous vasculitis, IgG4-related nephritis, acute allergic interstitial nephritis, uveitis syndrome [3], and cholesterol embolism syndrome [4], limited information is available on the association between EOS and CKD, especially in ESRD patients.

Currently, there is a lack of international data supporting the overall prevalence of peripheral blood eosinophilia (PBE) in CKD patients, including variations across different CKD stages (CKD1-5) and distinctions in PBE prevalence among nondialysis, hemodialysis (HD), and peritoneal dialysis (PD) in CKD5 patients. This study aimed to address this gap by providing large-scale, accurate statistical results, serving as a foundational dataset for further research. The focus of this article is to summarize and discuss the findings related to such patients.

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2. Materials and methods

2.1 Data source and study population

This study included 1870 CKD patients who underwent long-term hospitalization and follow-up at our nephrology department from January 2018 to December 2021. Clinical diagnosis and staging of CKD were conducted according to the International Kidney Organization Task Force on Clinical Management of Chronic Kidney Disease 2012 [5].

Inclusion criteria encompassed CKD patients with a PBE count exceeding 0.5×10^9/L and aged 18 years or older. Exclusion criteria were as follows: CKD stage 5 confirmed with parasitic infections, allergic diseases, rheumatic diseases, malignant tumors, and specific renal conditions (Henoch–Schonlein purpura nephritis, eosinophilic granulomatous vasculitis, IgG4-related nephritis, acute allergic interstitial nephritis, uveitis syndrome, and cholesterol embolism syndrome); patients with acute renal insufficiency based on chronic renal insufficiency; CKD patients with significant inflammatory status, defined as white blood cells exceeding 11×10^9/L and/or c-reactive protein (CRP) of 40 mg/dL or more; leukopenia with less than 3.0×10^9/L; patients undergoing treatment with hormonal drugs; and patients with incomplete clinical data.

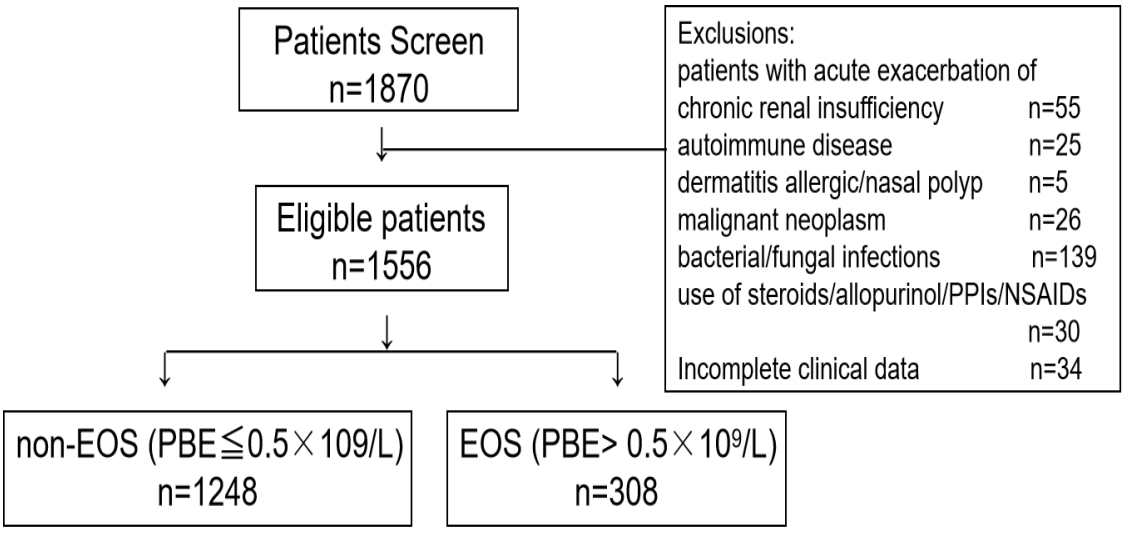

Figure 1: Study Subject Screening Flow Chart

Applying these criteria, we excluded patients with acute exacerbation of chronic renal insufficiency (n = 55), autoimmune diseases (n = 25), allergic dermatitis (n = 5), malignant tumors (n = 26), bacterial infections (n = 139), use of steroids/allopurinol/proton pump inhibitors(PPIs)/nonsteroidal antiinflammatory drugs (NSAIDs) (n = 30), and incomplete clinical data (n = 34). Following exclusions, the study comprised 1556 patients aged 18 to 101, including 959 males and 597 females. Among them, 308 patients had EOS, while 1248 patients did not (Fig. 1).

2.2 Data collection

The demographic characteristics, such as name, age, and sex, were collected for all enrolled patients. Additionally, data on smoking, drinking, hypertension, diabetes, coronary heart disease, arthritis, and other underlying diseases were recorded. The use of angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor antagonist (ARB), exogenous erythropoietin (EPO), calcium-free phosphate binders (lanthanum carbonate tablets/thinking lamb tablets), and active vitamin D (VitD) were documented. Details such as dialysis time and dialysis membrane materials were noted for HD patients. Various blood parameters, including leukocytes, hemoglobin, CRP, serum creatinine, urea nitrogen, uric acid, estimated glomerular filtration rate (eGFR), and PBE, were collected from each patient. The eGFR was calculated using the CKD-EPI formula.

Initially, 1870 CKD patients were collected, with 314 patients excluded and 1556 patients ultimately enrolled. The prevalence of EOS was calculated for patients in CKD stages 1-2, CKD stages 3-4, CKD stage 5, and CKD stage 5 dialysis (CKD5D).

The study employed binary logistic regression to analyze the correlation between EOS and various

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factors, including sex, age, smoking, drinking, hypertension, diabetes, coronary heart disease, arthritis, the use of ACEI/ARB, EPO, phosphorus binders without calcium, Vitamin D, primary disease (chronic glomerulonephritis, hypertensive renal impairment, diabetic nephropathy), white blood cell count, hemoglobin level, CRP, serum creatinine, urea nitrogen, uric acid, estimated glomerular filtration rate (eGFR), and other influencing factors.

Furthermore, a historical cohort study involving 270 CKD5D patients was conducted. This group was divided into an HD group (n = 234) and a PD group (n = 36) to investigate the differences in EOS between HD and PD patients before and after dialysis.

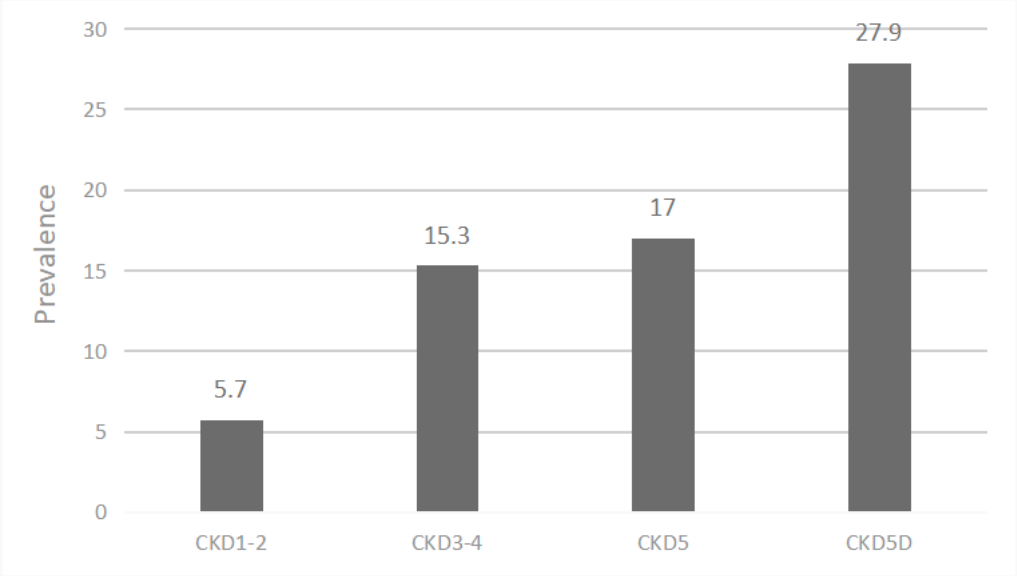
For the HD group (n = 234) included in the cohort study, binary logistic regression analysis was performed to assess the association between EOS and HD in one month or less and the composition of the dialysis membrane.

3. Statistical analysis

The statistical analysis was conducted using SPSS 22.0 software. Initially, the normality of the data was assessed through the Kolmogorov–Smirnov test. For normally distributed data, measurement results were expressed as mean ± standard deviation, and group comparisons were made using the t-test. Medians represented skewed distributions, and the Mann–Whitney U test was used for group comparisons. Enumeration data were expressed as percentages, and $\chi 2$ tests were used for statistical analysis. Binary logistic regression was used to analyze the influencing factors of EOS and its correlation with eGFR in CKD patients. The significance level for all analyses was set at $p < 0.05$.

4. Results

The prevalence of EOS increased across different stages of CKD: 5.7% (11/192) in CKD1-2, 15.3% (41/268) in CKD3-4, 17% (78/459) in CKD5, and 27.9% (178/639) in CKD5D. The overall prevalence of EOS in CKD patients was 19.8%, indicating a significant increasing trend with advancing renal dysfunction, with statistically significant differences (Fig. 2).



Notes: CKD chronic kidney disease; CKD5D CKD5 dialysis.

Figure 2: Comparison table of the prevalence of EOS in the physical examination population and different stages of CKD.

Binary logistic regression analysis revealed a positive association between the decline in eGFR and the presence of EOS. The prevalence of EOS increased by 12.7% for every 1 ml/min decrease in eGFR after adjusting for various factors, including demographic information, medical history, medication use, primary diseases, and blood parameters. Male patients with chronic glomerulonephritis as the primary disease and those who do not consume alcohol were found to be more likely to develop EOS. The occurrence of EOS was also associated with an increased white blood cell count (Table 1).

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Table 1: Binary logistic regression analysis of related influencing factors of EOS

Influencing factors	OR and 95%CI	P
Gender (male/female)	3.339(1.997~5.581)	<0.001
Age	1.006(0.989~1.023)	0.486
Smoking (Yes/No)	0.917(0.474~1.772)	0.796
Alcohol (Yes/No)	0.470(0.229~0.963)	0.039
Hypertension (Yes/No)	1.199(0.652~2.204)	0.559
Diabetes mellitus (Yes/No)	1.308(0.737~2.321)	0.359
Coronary heart disease (Yes/No)	1.006(0.542~1.866)	0.985
Uarthritis (Yes/No)	1.219(0.662~2.244)	0.525
ACEI/ARB (Yes/No)	0.893(0.524~1.522)	0.677
EPO (Yes/No)	0.962(0.595~1.556)	0.875
Calcium free phosphate binders (Yes/No)	1.274(0.778~2.087)	0.336
Active VitD (Yes/No)	1.184(0.699~2.005)	0.529
Chronic glomerulonephritis (Yes/No)	0.521(0.305~0.893)	0.018
Hypertensive kidney disease (Yes/No)	0.562(0.240~1.317)	0.185
Diabetic nephropathy (Yes/No)	0.675(0.345~1.320)	0.250
WBC ($\times10^9$/L)	1.426(1.272~1.600)	<0.001
HB (g/L)	0.996(0.988~1.005)	0.394
CRP (mg/dL)	0.988(0.971~1.006)	0.189
sCr (μmol/L)	0.998(0.997~0.999)	0.003
BUN (mmol/L)	0.998(0.972~1.026)	0.910
UA (μmol/L)	0.999(0.997~1.000)	0.153
eGFR (ml/min)	0.873(0.822~0.927)	<0.001

Notes: ACEI angiotensin-converting enzyme inhibitor; ARB angiotensin receptor antagonist; EPO exogenous erythropoietin; VitD active vitamin D; WBC white blood cell; HB hemoglobin; CRP c-reactive protein; sCr serum creatinine; BUN urea nitrogen; UA uric acid;eGFR estimated glomerular filtration rate

The prevalence of EOS after HD was 27.6%, significantly higher than the 14.2% observed before HD, with a statistically significant difference. Although there was no significant difference in the prevalence of EOS between PD patients before and after dialysis (11.1% vs. 13.9%), the PBE count increased after HD or PD compared to the counts before dialysis (Table 2).

Table 2: Comparison of cohort study between HD and PD patients before and after dialysis

	HD group n=234			PD group n=36		
	Before HD	After HD	P	Before PD	After PD	P
EOS%	33(14.2)	64(27.6)	<0.001	4(11.1)	5(13.9)	0.722
PBE ($\times10^9$/L)	0.19(0.11~0.33)	0.20(0.13~0.54)	<0.001	0.15(0.11~0.27)	0.20(0.13~0.30)	<0.001
WBC ($\times10^9$/L)	6.46±1.83	6.33±1.66	0.299	5.68±1.47	6.49±1.58	0.016
HB (g/L)	83.0(70.0~96.3)	95.0(82.0~112.0)	0.018	81.0(71.3~90.5)	102.0(87.3~119.5)	0.892
CRP (mg/dL)	3.0(3.0~8.2)	5.0(3.0~10.4)	0.206	3.0(3.0~7.6)	3.0(3.0~5.1)	0.304
sCr (μmol/L)	718.0 (536.5~1002.5)	602.0 (438~813)	0.977	807.0 (584.8~1030.8)	959.0 (710.3~1161.8)	0.798
BUN (mmol/L)	27.9(20.2~35.7)	16.9(11.8~21.3)	0.004	31.1(22.6~37.1)	22.4(18.0~29.3)	0.759
UA (μmol/L)	448.6±140.8	329.5±122.0	<0.001	463.7±157.1	409.0±112.9	0.086
GFR (ml/min)	6.64±3.84	8.03±4.10	<0.001	6.05±2.45	5.47±2.81	0.278

Notes: HD Hemodialysis; PD Peritoneal dialysis; EOS Eosinophilia; PBE Peripheral blood eosinophil count; WBC white blood cell; HB hemoglobin; CRP c-reactive protein; sCr serum creatinine; BUN urea nitrogen; UA uric acid;eGFR estimated glomerular filtration rate

Binary logistic regression analysis showed that the risk of developing EOS was 3.053 times higher in patients with an HD duration exceeding to one month compared to those with an HD duration less than one month. Furthermore, the type of hemodialysis membrane material (synthetic cellulose membrane) was not associated with the risk of developing EOS (Table 3).

Table 3: Correlation of EOS with dialysis time and dialysis membrane in HD patients

Influencing factor	OR and 95%CI	P
Dialysis time≦1 month (Yes/No)	3.053(1.481~6.293)	0.002
Synthetic cellulose membrane (Yes/No)	2.036(0.890~4.657)	0.092

5. Discussion

CKD poses a significant threat to human health, particularly for ESRD patients who face a high mortality rate. Significantly, the prevalence of EOS exhibited a notable increase with advancing stages of renal dysfunction, consistent with previous reports [4,6,7]. The study found a decreased eGFR as an

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independent risk factor for EOS development. Moreover, EOS occurrence was more likely in male patients with chronic glomerulonephritis as their primary disease and those who do not drink alcohol. It is also consistent with Hildebrand et al. [8], who concluded that HD patients experience an increased prevalence of EOS compared with non-dialysis patients with CKD stage 5. He suggests that enhanced HD-induced cytokine production may play a role in the development of EOS and suggests that the majority of HD patients who experience EOS are subclinical effects of the dialysis process. Hildebrand et al. [8] also found that EOS is not uncommon in modern HD patients, with a prevalence of 4.7% in their cohort study, and dialysis patients who did not develop EOS had a better overall prognosis. Tariq et al. [9] analyzed 178 patients with renal biopsy and 65 patients had EOS (> 4% leukocytes), which was approximately 15-fold more associated with ESRD in patients with EOS compared with patients without EOS after adjusting for hypertension, proteinuria, and eGFR at the time of renal biopsy (OR 15.9 [1.9, 134.7]); and EOS was found to be significantly linearly associated with eosinophil positivity in renal tissue. Patients with PBE ≧ 10% had the fastest decline in renal function compared to patients with 4 - 10% PBE or no EOS. It points out that EOS is an independent predictor of subsequent progression to ESRD in CKD patients and that EOS may be an early biomarker of underlying inflammation and disease. Because the study by Tariq et al. included patients with renal impairment due to vasculitis, interstitial nephritis, systemic lupus erythematosus, malignant tumors, and other related diseases based on patients with renal biopsy, the prevalence of EOS was significantly higher than that in this study. However, it could provide us with a good idea that patients who had undergone renal biopsy could be screened on this study's inclusion criteria and exclusion criteria to analyze further the correlation between their PBE and renal tissue eosinophil count and the correlation between their counts and renal function.

Moledina et al.[10] proposed the theory that eosinophils are mediated by specific T helper cells, leading to more cytokine production, including TNF-α and IL-9, leading to interstitial atrophy, irreversible fibrosis, and ultimately ESRD, as recent studies in the field of IgG4-related nephropathy point to peripheral and tissue EOS that can progress to irreversible fibrotic dysfunction or organ failure [11, 12]. Based on the above theory, the author speculates that early aggressive treatment of patients with persistent EOS can block renal interstitial fibrosis, which may achieve the efficacy of delaying renal function; there is no relevant literature support, and prospective case-control studies are needed to verify. However, Stevens et al.[5] suggested that EOS is one of the standard features of hypersensitivity caused by antigen-activated Th2 cells and continuous release of critical cytokines, in which IL-5 can trigger eosinophil proliferation, accumulation, and function. Any exogenous antigen can cause hypersensitivity reactions, which may affect renal function. Thus, hypersensitivity is one of the recognized causes of EOS in CKD patients. In this study, we observed that the majority of CKD patients developed transient EOS, which could not be intervened in such patients; however, whether hypersensitivity could be suppressed by active intervention, such as hormone and antihistamine treatment, in patients with persistent EOS to achieve PBE reduction while protecting renal function needs further confirmation.

Notably, CKD stage 5 patients undergoing hemodialysis (HD) exhibited a significantly higher prevalence of EOS after treatment compared to before HD initiation, and the risk of EOS was pronounced within the first month of commencing dialysis. Hildebrand's historical cohort study indicates an increasing prevalence of hemodialysis-related EOS over time, with most cases considered a subclinical effect of the dialysis process. Simon et al. [13] suggested that the increased prevalence of EOS in the HD population may be related to the dialysis membrane used, as synthetic membranes potentially trigger more anaphylactoid reactions than cellulose membranes, which can be replaced. Although most dialysis membranes used in our hemodialysis center are synthetic cellulose membranes, there is no significant difference in the risk of EOS compared to other membrane types.

Kang et al. performed a Cox proportional hazards model on 10,7506 patients newly started on HD. They found that both lower (<100 cells/lL) and higher PBE (≧550 cells/lL) and changes in PBE over the first three months after HD initiation were associated with higher all-cause mortality in incident HD patients [14]. Additionally, Hospers et al. and Diskin et al. suggested that EOS may serve as markers of vascular disease rather than uremia in patients with renal disease [15–17].

In conclusion, this study found that the prevalence of EOS in CKD patients increased with worsening renal function by retrospective analysis of a large sample of data, and there is sufficient evidence in combination with previous literature to demonstrate a mutually reinforcing effect between EOS and CKD progression. Although the causal relationship between EOS and CKD in this study cannot be clarified, it has great guiding significance for subsequent studies. Because studies have shown that EOS is also associated with cardiovascular disease, the effect of EOS on cardiovascular

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complications in CKD patients can also be further investigated.

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XC collected and analyzed the data and wrote the manuscript. JL and YN collected and analyzed the data. XC revised the manuscript. All the authors contributed to the article and approved the submitted version.

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