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ORIGINAL ARTICLE

Eosinophil count and mortality risk in incident hemodialysis patients

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ABSTRACT

Background. Eosinophils are traditionally known as moderators of allergic reactions; however, they have now emerged as one of the principal immune-regulating cells as well as predictors of vascular disease and mortality in the general population. Although eosinophilia has been demonstrated in hemodialysis (HD) patients, associations of eosinophil count (EOC) and its changes with mortality in HD patients are still unknown.

Methods. In 107 506 incident HD patients treated by a large dialysis organization during 2007–11, we examined the relationships of baseline and time-varying EOC and its changes (ΔEOC) over the first 3 months with all-cause mortality using Cox proportional hazards models with three levels of hierarchical adjustment.

Results. Baseline median EOC was 231 (interquartile range 155–339) cells/μL and eosinophilia (>350 cells/μL) was observed in 23.4% of patients. There was a gradual increase in EOC over time after HD initiation with a median ΔEOC of 5.1 (IQR −53–199) cells/μL, which did not parallel the changes in white blood cell count. In fully adjusted models, mortality risk was highest in subjects with lower baseline and time-varying EOC (<100 cells/μL) and was also slightly higher in patients with higher levels (≥550 cells/μL), resulting in a reverse J-shaped relationship. The relationship of ΔEOC with all-cause mortality risk was also a reverse J-shape where both an increase and decrease exhibited a higher mortality risk.

Conclusions. Both lower and higher EOCs and changes in EOC over the first 3 months after HD initiation were associated with higher all-cause mortality in incident HD patients.

Keywords: eosinophil, hemodialysis, mortality

INTRODUCTION

Peripheral eosinophil count (EOC) has been considered an objective marker of allergic reactions or parasitic infestation; however, recent advances in understanding EOC have revealed its novel role as a true immunoregulatory cell participating in antigen presentation and modulation of lymphocytes, mast cells and neutrophils [1, 2]. The levels of eosinophils in the body are tightly regulated and eosinophils account for only 1–3% of peripheral leukocytes [3]. Higher EOCs (eosinophilia) have been shown in patients with chronic kidney disease (CKD), with a prevalence of 16% in nondialysis-dependent CKD (NDD-CKD) [4, 5] and 4.7–52% in patients on hemodialysis (HD) [6–10]. The reasons for an elevated EOC in CKD patients are unclear and may be multifactorial. Suggested potential mechanisms include an increased turnover rate of eosinophils in bone marrow [11, 12], allergic reactions to extracorporeal processes [10] and associations with hepatitis or specific medications [10, 13]. However, none of these potential explanations were confirmed by further investigation.

Prior studies in the general population and patients with lung disease have also demonstrated that changes in EOC (both eosinophilia and eosinopenia) are associated with a higher mortality risk [14–17]. In NDD-CKD patients, an increase in EOC was independently associated with an increased risk of end-stage renal disease (ESRD) and mortality [4]. Eosinopenia in intensive care unit (ICU) patients was also reported as an independent marker of hospital stay and mortality [18].

However, the association of EOC and its changes over time with mortality in incident HD patients has not been previously studied. In a large nationally representative cohort of incident

HD patients in the USA, we investigated the predictors of EOC levels and the relationship of its levels and changes with all-cause mortality.

MATERIALS AND METHODS

Study population and data source

We examined data from a total of 208 820 patients with ESRD who initiated dialysis therapy from 1 January 2007 to 31 December 2011 in a large dialysis care organization in the USA, with a capture of baseline and longitudinal data on sociodemographics, comorbidities [ascertained from International Classification of Diseases, Ninth Revision (ICD-9) codes], laboratory tests, dialysis treatment characteristics, clinical events and vital status [19]. Patients were included if they were ≥18 years old, on dialysis for >60 days total, undergoing in-center thrice-weekly HD and had at least one EOC in their baseline quarter (i.e. first 91 days following the initiation of dialysis) at the start of the study. Patients were excluded if they were receiving peritoneal dialysis or home HD or had an outlier eosinophil value (<20 or >1318 cells/μL, corresponding to the <0.5th and >99.5th percentiles of observed eosinophil values, respectively). The final analytical cohort consisted of 107 506 incident HD patients (Supplementary data, Figure S1). Patients who were excluded due to unavailable EOC data or had outliers for baseline EOC were compared with the analytical cohort in Supplementary data, Table S1.

All data were obtained from electronic records of the dialysis organization. Blood samples were drawn using standardized techniques in all dialysis clinics and were transported to a central laboratory in Deland, FL, USA, typically within 24 h. All laboratory values were measured using automated and standardized methods. Serum creatinine, calcium, phosphorus, albumin, total iron-binding capacity and total lymphocytes were measured monthly. Serum intact parathyroid hormone (iPTH) and ferritin were measured at least quarterly. Hemoglobin was measured weekly to biweekly in most patients. Body mass index (BMI) was calculated as post-HD body weight in kilograms divided by height in meters squared. Residual kidney function (RKF) was calculated by renal urea clearance [20]. As eosinophils are routinely reported as a percent fraction of the total white blood cell (WBC) count, for the main analysis, absolute EOC was calculated by multiplying the WBC count in microliters (μL or 10^{-6} L) by the eosinophil fraction. Eosinophilia was defined as >350 cells/μL [3, 21]. In sensitivity analysis, eosinophil fraction (% of WBC) was used as a predictor and eosinophilia was defined as >5%.

To minimize variability, variables with repeated measures within each 3-month period (91-day intervals) were averaged to obtain a single quarterly mean value. Measurements taken during the first 91 days on dialysis therapy, referred to as the 'first patient quarter' (Q1), were used as baseline values.

The study was approved by the institutional review committees of the University of California, Irvine, CA, USA. The study was exempt from informed written consent due to its nonintrusive nature and anonymity of patients.

Exposure and outcome ascertainment

The primary exposures of interest were baseline and time-varying EOC. The outcome of interest was all-cause mortality. Patients were considered at risk for mortality from the date of dialysis initiation to death or censoring by one of the following events: kidney transplantation, transfer to another dialysis company or end of the study period.

Patients were divided into seven groups based on baseline mean EOC: <100 (9.6%), 100–<150 (14.0%), 150–<250 (31.8%), 250–<350 (21.3%), 350–<450 (reference, 11.3%), 450–<550 (5.7%) and ≥550 cells/μL (6.2%). In time-varying models, EOC was updated at each patient quarter over the entire follow-up period. EOC was carried forward to the next measurement for patients missing data in quarters subsequent to baseline (last observation carried forward). The proportion of missing time-varying EOC values was 5%. The same exposure categories were used for the time-varying model.

In the secondary analysis we examined the association of the changes in EOC (ΔEOC) between the baseline and second patient quarter (Q2, 92–182 days) with all-cause mortality in 97 616 patients with available eosinophil data in both Q1 and Q2 and who survived the baseline patient quarter. ΔEOC was stratified into six exposure categories: <−150 (7.0%), −150–<−50 (19.0%), −50–<0 (24.5%), 0–<+50 (reference, 23.3%), +50–<+150 (18.2%) and ≥+150 (8.1%).

Statistical analyses

Data were summarized using proportions, means [± standard deviation (SD)] for normally distributed variables or median [interquartile range (IQR)] for nonnormally distributed variables as appropriate and were compared using the test for trend. We analyzed the association of EOC groups with all-cause mortality using Kaplan–Meier plots, the log-rank test and Cox proportional hazards models for both baseline and time-varying models. The proportionality assumption was checked using plots of log [−log(survival rate)] against log(survival time). All models were examined across three levels of hierarchical multivariable adjustment, which included potential confounders based on theoretical considerations and distribution across baseline EOCs:

1. Unadjusted: included EOC as the primary exposure of interest;
2. Casemix: adjusted for demographic data (age and sex), race/ethnicity [non-Hispanic white (white), African American, Hispanic, Asian and other], comorbid conditions [diabetes, hypertension, congestive heart failure (CHF), arteriosclerotic heart disease, other cardiovascular disease (CVD), cerebrovascular disease, chronic obstructive pulmonary disease (COPD), liver disease, autoimmune disease (AID), history of malignancy, human immunodeficiency virus (HIV) antibody positive and infection], insurance type (Medicare, Medicaid and other), HD access type (central venous catheter, arteriovenous fistula, arteriovenous graft and other) and BMI]
3. Casemix + laboratory (fully adjusted model): adjusted for covariates in the casemix model as well as hemoglobin, total lymphocyte count, serum albumin, creatinine, calcium,

phosphorus, alkaline phosphatase (ALP), iPTH, ferritin and normalized protein equivalent of nitrogen appearance rate (nPNA).

Baseline laboratory measurements were also used as covariates in time-varying models to avoid the risk of adjusting for potential intermediates [22]. All mortality associations are reported as hazard ratios (HRs) and 95% confidence intervals (CIs).

To examine predictors of lower (<150 cells/μL) or higher (≥550 cells/μL) baseline EOC, we used multinomial logistic regression models. In addition, we illustrated trajectories of EOC, eosinophil fraction and WBC over time on HD patients using casemix-adjusted mixed-effects regression models.

For sensitivity analysis, we examined the association of eosinophil fraction and all-cause mortality to delineate the effect of eosinophil on mortality independent of WBC count. We additionally explored potentially nonlinear relationships between eosinophil exposures and mortality outcomes using restricted cubic spline models with four knots placed at the 5th, 35th, 65th and 95th percentiles. We also examined the association of lower (<150 cells/μL) and higher (≥550 cells/μL) EOC with mortality (reference 150–<550 cells/μL) across *a priori* selected subgroups in casemix-adjusted models. Statistical significance of potential effect modification by these covariates was tested with the Wald test, after including the interaction term between a given variable and three eosinophil groups.

To address missing covariate data, we implemented multiple imputation methods using five datasets. All covariates had <1% missing values except for BMI (1.4%), creatinine (4.6%), nPNA (1.5%) and RKF (66.8%). Due to the high percentage of missing values data, RKF was only included in subgroup analyses. All analyses were implemented using SAS version 9.4 (SAS Institute, Cary, NC, USA), Stata version 13.1 (StataCorp, College Station, TX, USA) and SigmaPlot version 12.5 (Systat Software, San Jose, CA, USA).

RESULTS

Study cohort description

Table 1 presents the baseline characteristics of the cohort according to the baseline EOC category. Among the 107 506 incident HD patients, the mean ± SD age was 63 ± 15 years and the cohort was 44% female, 59% diabetic and 32% African American. The mean ± SD baseline EOC and fraction in the overall cohort were 267 ± 161 cells/μL [median 231 (IQR 155–339)] and 3.6 ± 2.1% [median 3.2 (IQR 2.2–4.6)]. The prevalence of eosinophilia, defined as >350 cells/μL or >5% of total WBC count, was 23.4% and 21.2%, respectively.

Patients with higher EOC were more likely to be younger, male and non-African American and have higher BMI and comorbidities of diabetes or infection. Patients with lower EOC were more likely to have liver disease, AID, history of malignancy and be HIV positive. Patients with the highest levels of EOC tended to have an elevated serum albumin, creatinine and phosphorus and a lower level of ferritin. Prevalences of comorbid CVDs were comparable across seven eosinophil categories. The same tendency was also observed in seven eosinophil strata divided by baseline eosinophil fraction (Supplementary data, Table S2).

Predictor of baseline EOC

Predictors of baseline EOC adjusted for casemix and fully adjusted models similarly showed female sex, African American race/ethnicity, hypertensive nephrosclerosis comorbid AID, and chronic glomerulonephritis as the cause of ESRD while were associated with higher odds of lower EOC, whereas Asian race/ethnicity, comorbid infection and COPD were associated with higher odds of higher EOC. With respect to laboratory parameters, a higher nPNA predicted lower EOC, whereas higher phosphorus and ALP were associated with higher odds of higher EOC (Table 2). Higher albumin and phosphorus were inversely associated with odds of having a lower baseline EOC (Table 2).

All-cause mortality by baseline and time-varying EOC

There were 28 261 all-cause deaths during the median follow-up time of 495 (IQR 231–921) days, with a crude mortality rate of 155.6 deaths per 1000 patient-years (95% CI 153.8–157.4). The Kaplan–Meier survival curve demonstrated a worse survival in patients with lower baseline EOC (Supplementary data, Figure S2A). Patients with eosinophilia defined as >350 cells/μL had significantly lower mortality compared with patients without eosinophilia (Supplementary data, Figure S2B), with a crude mortality rate of 136.3 (95% CI 132.9–139.9) versus 161.4 (95% CI 159.3–163.5) deaths per 1000 patient-years, respectively.

Figure 1A shows the unadjusted and adjusted death HRs for baseline EOC groups. Compared with the reference EOC (350–<450 cells/μL), patients with a lower EOC had a higher mortality risk. The highest mortality risk was observed in patients with an EOC <100 cells/μL [HR 1.85 (95% CI 1.76–1.93)] in the unadjusted model (Figure 1A, Supplementary data, Table S3). This relationship was only slightly attenuated after covariate adjustment. A higher mortality risk was also found in patients with an elevated EOC (≥550 cells/μL), resulting in a reverse J-shaped relationship. A similar association was observed between the baseline eosinophil fraction and mortality with higher HR in patients with lower eosinophil fraction compared with the reference eosinophil fraction (4–<5%; Supplementary data, Figure S3), indicating that both absolute and percent EOC were associated with mortality in baseline models. In time-varying models, associations between time-varying EOC and mortality were even stronger, indicating a greater short-term association of EOC on the risk of death (Figure 1B, Supplementary data, Table S3). All-cause mortality associations in restricted cubic spline models of baseline and time-varying EOC similarly showed J-shaped relationships (Supplementary data, Figures S4 and S5). Sensitivity analysis using nonimputed covariates also showed the same association of baseline and time-varying EOC with mortality (Supplementary data, Table S4).

Table 1. Baseline characteristics in incident HD patients by baseline EOC (n = 107 506)

Variables	Total	EOC (cells/μL)							P-value
		<100 (n = 10 277)	100–<150 (n = 15 041)	150–<250 (n = 34 234)	250–<350 (n = 22 946)	350–<450 (n = 12 174)	450–<550 (n = 6124)	≥550 (n = 6710)	
EOC (cells/μL)	267.1 ± 160.9	72.3 ± 19.1	126.4 ± 14.4	198.9 ± 28.3	295.2 ± 28.6	393.7 ± 28.6	494.5 ± 28.8	696.2 ± 124.0	
Age (years)	62.7 ± 15.0	64.5 ± 15.8	64.4 ± 14.9	63.1 ± 14.9	62.0 ± 14.8	61.4 ± 14.9	61.4 ± 15.0	61.5 ± 15.4	<0.001
Female (%)	43.6	48.6	47	45.7	42.6	39.5	37.5	34.3	<0.001
Diabetes (%)	58.5	53.1	57.6	59.6	60.2	58.6	59.1	57.3	<0.001
Race/ethnicity (%)									<0.001
White	46.5	47.62	45.6	45.03	46.56	48.46	48.3	49.28	
African American	31.5	36.49	36.37	34.09	29.7	26.07	24.84	21.89	
Hispanic	14.8	10.39	12.62	14.63	16.13	17.02	17.26	17.12	
Asian	3.2	2.75	2.58	2.82	3.32	3.5	4.13	5.32	
Others	3.9	2.74	2.83	3.44	4.3	4.95	5.47	6.38	
Primary insurance (%)									<0.001
Medicare	53.7	55.8	55.5	53.9	52.6	52.1	52.8	52.8	
Medicaid	7.0	6.4	6.2	6.9	7.0	7.6	7.6	7.9	
Others	39.4	37.9	38.3	39.2	40.4	40.4	39.6	39.3	
Access type (%)									<0.001
CVC	77.5	80.4	77.3	77.1	77.0	77.2	79.0	77.4	<0.001
AVF	15.1	11.6	14.4	15.6	15.9	15.8	14.8	14.8	<0.001
AVG	4.2	4.1	4.6	4.4	4.2	3.9	3.6	3.5	<0.001
Others	3.3	4.0	3.7	2.9	3.0	3.2	2.6	4.4	<0.001
Comorbidities (%)									
Hypertension	51.2	50.5	51.6	51.9	51.1	50.1	50.7	50.9	<0.001
CHF	36.8	36.0	36.5	36.9	37.0	37.4	36.7	37.3	NS
Atherosclerotic heart disease	14.4	14.9	14.9	14.5	14.3	14.2	13.6	13.8	NS
Other cardiovascular disease	14.4	16.8	15.8	15.1	14.4	14.7	14.7	14.7	NS
CbVD	1.8	1.7	1.8	1.8	1.7	1.9	2.0	1.9	NS
COPD	5.1	5.4	4.8	4.8	5.2	5.2	5.4	5.6	<0.001
Liver disease	1.5	2.2	1.7	1.4	1.4	1.2	1.4	1.3	<0.001
Thyroid disease	9.5	10.0	9.8	9.6	9.6	9.1	8.9	9.3	NS
Dyslipidemia	25.3	25.5	25.3	25.1	25.4	25.3	25.1	25.8	NS
AID	1.9	4.4	2.1	1.6	1.6	1.3	1.5	1.5	<0.001
Malignancy	2.3	3.9	2.7	2.1	2.0	1.9	1.9	1.6	<0.001
HIV antibody positive	0.5	1.1	0.6	0.5	0.3	0.3	0.4	0.3	<0.001
Infection	79.6	76.6	78.0	79.7	80.4	80.1	80.9	81.8	<0.001
Alcohol abuse	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.4	NS
BMI (kg/m^2)	28.3 ± 7.4	26.5 ± 6.7	27.3 ± 6.9	28.4 ± 7.3	29.0 ± 7.6	29.0 ± 7.6	28.7 ± 7.7	28.0 ± 7.4	<0.001
RKF (mL/min)	4.07 ± 3.55	3.85 ± 3.94	4.01 ± 3.52	4.07 ± 3.56	4.18 ± 3.69	4.11 ± 3.33	4.11 ± 3.34	3.95 ± 3.15	<0.001
nPNA (g/kg/day)	0.79 ± 0.22	0.79 ± 0.24	0.78 ± 0.22	0.79 ± 0.21	0.80 ± 0.21	0.80 ± 0.21	0.79 ± 0.21	0.79 ± 0.21	<0.001
Laboratory parameters									
Albumin (g/dL)	3.51 ± 0.48	3.38 ± 0.53	3.48 ± 0.49	3.52 ± 0.47	3.54 ± 0.46	3.54 ± 0.46	3.52 ± 0.46	3.52 ± 0.47	<0.001
Creatinine (mg/dL)	5.9 ± 2.4	5.4 ± 2.2	5.6 ± 2.3	5.8 ± 2.4	6.0 ± 2.4	6.1 ± 2.4	6.1 ± 2.4	6.2 ± 2.4	<0.001
Hemoglobin (g/dL)	11.1 ± 1.2	10.9 ± 1.3	11.1 ± 1.2	11.1 ± 1.2	11.2 ± 1.1	11.2 ± 1.1	11.2 ± 1.2	11.1 ± 1.2	<0.001
WBC (10^9/μL)	7.8 ± 2.5	7.1 ± 3.0	7.1 ± 2.4	7.5 ± 2.3	7.9 ± 2.3	8.4 ± 2.4	8.8 ± 2.7	9.3 ± 2.9	<0.001
Lymphocyte (%WBC)	20.7 ± 7.4	19.5 ± 9.2	20.8 ± 7.8	21.2 ± 7.4	21.0 ± 7.0	20.7 ± 6.8	20.2 ± 6.7	19.8 ± 6.7	<0.001
iPTH (pg/mL)	393.1 ± 328.4	375.1 ± 326.2	394.6 ± 345.7	405.4 ± 334.4	399.2 ± 333.8	385.1 ± 302.6	374.6 ± 307.0	373.0 ± 310.4	<0.001
ALP (U/L)	103.7 ± 73.6	108.1 ± 82.2	105.2 ± 78.7	102.6 ± 70.6	101.5 ± 66.0	102.7 ± 68.2	105.2 ± 88.4	108.8 ± 87.6	<0.001
Calcium (mg/dL)	9.10 ± 0.56	9.12 ± 0.57	9.12 ± 0.56	9.10 ± 0.56	9.08 ± 0.55	9.09 ± 0.56	9.10 ± 0.55	9.09 ± 0.55	<0.001
Phosphorus (mg/dL)	4.9 ± 1.1	4.6 ± 1.1	4.7 ± 1.1	4.9 ± 1.1	5.0 ± 1.1	5.1 ± 1.2	5.1 ± 1.2	5.1 ± 1.2	<0.001
Ferritin (ng/mL)	385.4 ± 385.1	510.9 ± 559.9	397.6 ± 406.4	369.8 ± 344.1	362.7 ± 341.6	360.1 ± 331.5	375.6 ± 359.9	386.1 ± 431.3	<0.001
TIBC (mg/dL)	225.0 ± 49.0	213.9 ± 53.7	222.6 ± 51.0	225.7 ± 48.9	227.8 ± 47.5	228.4 ± 46.4	225.1 ± 46.8	225.4 ± 47.6	<0.001

Data are presented as mean ± SD unless stated otherwise and compared across groups with tests for trend.
CVC, central venous catheters; AVF, arteriovenous fistula; AVG, arteriovenous graft; CbVD, cerebrovascular disease; TIBC, total iron binding capacity; CHF, congestive heart failure; NS, nonsignificant.

Subgroup analysis of the association of lower or higher EOC with mortality

In subgroup analysis, lower baseline EOC was consistently associated with higher mortality across all patient strata in case-mix-adjusted analyses (Figure 2A). In baseline models, effect modification was observed by age (P for interaction = 0.030) and presence of infection (P for interaction = 0.014), where a higher mortality risk occurred for younger patients and those without infection comorbidity. The association between higher EOC and mortality was consistent across most strata, although only statistically significant for those who were diabetic, age <65 years, nonwhite race/ethnicity, had a history of CVD

Table 2. Likelihood of having lower (<150 cells/μL) and higher (≥550 cells/μL) EOC in 107 506 incident HD patients in casemix- and fully adjusted models

Variables	Casemix adjusted		P-value	Fully adjusted		P-value
	OR	95% CI		OR	95% CI	
Lower EOC						
Age (per 10 years)	1.013	(1.012–1.015)	<0.001	1.017	(0.994–1.040)	0.15
Female (versus male)	1.168	(1.134–1.202)	<0.001	1.178	(1.140–1.216)	<0.001
Race (versus white)						
African American	1.399	(1.353–1.447)	<0.001	1.395	(1.342–1.450)	<0.001
Asian	0.915	(0.837–1.000)	0.05	0.796	(0.725–0.874)	<0.001
Hispanic	0.911	(0.869–0.955)	<0.001	0.870	(0.828–0.915)	<0.001
Insurance (versus Medicaid)						
Medicare	0.996	(0.936–1.060)	0.90	0.979	(0.917–1.045)	0.56
Others	0.976	(0.946–1.007)	0.13	1.002	(0.969–1.035)	0.91
Vascular access (versus AVF)						
CVC	1.110	(1.068–1.153)	<0.001	1.025	(0.983–1.068)	0.25
AVG	1.035	(0.957–1.119)	0.39	0.990	(0.911–1.075)	0.80
ESRD causes (versus DN)						
Hypertensive NS	1.280	(1.221–1.341)	<0.001	1.290	(1.227–1.356)	<0.001
CGN	2.077	(1.012–1.015)	<0.001	1.904	(1.800–2.013)	<0.001
Comorbidities						
Diabetes	1.022	(0.989–1.057)	0.19	1.048	(1.012–1.086)	0.01
Hypertension	0.921	(0.885–0.958)	<0.001	0.935	(0.897–0.974)	0.001
CHF	1.015	(0.984–1.047)	0.34	1.045	(1.011–1.080)	0.01
ASHD	1.018	(0.972–1.066)	0.31	1.013	(0.965–1.063)	0.61
Other CVD	1.113	(1.062–1.167)	0.45	1.088	(1.036–1.143)	<0.001
AID	1.987	(1.778–2.220)	<0.001	1.911	(1.700–2.148)	<0.001
CbVD	0.861	(0.767–0.966)	0.01	0.842	(0.746–0.950)	0.01
Liver disease	1.082	(0.948–1.234)	0.24	0.964	(0.840–1.107)	0.61
Infection	0.884	(0.853–0.917)	<0.001	0.929	(0.869–0.962)	<0.001
COPD	0.832	(0.774–0.896)	<0.001	0.860	(0.797–0.928)	<0.001
BMI (per 1 kg/m^2)	0.968	(0.966–0.970)	<0.001	0.971	(0.968–0.973)	<0.001
nPNA (0.1 g/kg/1.73 m^2)	1.004	(0.997–1.010)	0.32	1.064	(1.056–1.073)	<0.001
Laboratory parameters						
Hemoglobin	0.920	(0.909–0.932)	<0.001	0.959	(0.945–0.972)	<0.001
Total lymphocyte	0.987	(0.985–0.989)	<0.001	0.992	(0.990–0.995)	<0.001
Creatinine	0.905	(0.898–0.913)	<0.001	0.943	(0.934–0.952)	<0.001
Albumin	0.691	(0.670–0.713)	<0.001	0.764	(0.737–0.792)	<0.001
Calcium	1.005	(0.979–1.032)	0.69	0.992	(0.964–1.021)	0.58
Phosphorus	0.812	(0.800–0.823)	<0.001	0.824	(0.810–0.839)	<0.001
ALP (per 50 U/L)	1.046	(1.037–1.056)	<0.001	0.989	(0.969–1.009)	0.75
iPTH (per 50 pg/mL)	0.994	(0.991–0.996)	<0.001	1.009	(1.006–1.011)	<0.001
Ferritin	1.018	(1.016–1.020)	<0.001	1.009	(1.007–1.011)	<0.001
Higher EOC						
Age (per 10 years)	1.017	(0.994–1.040)	0.15	0.989	(0.955–1.026)	0.56
Female (versus male)	0.706	(0.670–0.745)	0.001	0.725	(0.684–0.768)	<0.001
Race (versus white)						
African American	0.630	(0.590–0.673)	<0.001	0.660	(0.613–0.710)	<0.001
Asian	1.519	(1.351–1.708)	0.002	1.571	(1.388–1.777)	<0.001
Hispanic	0.967	(0.899–1.039)	0.36	0.996	(0.922–1.076)	0.92
Insurance (versus Medicaid)						
Medicare	1.053	(0.954–1.163)	0.30	1.027	(0.925–1.140)	0.62
Others	0.957	(0.906–1.010)	0.11	0.959	(0.906–1.015)	0.15
Vascular access (versus AVF)						
CVC	1.020	(0.956–1.089)	0.54	0.982	(0.916–1.052)	0.61
AVG	0.976	(0.844–1.129)	0.75	0.963	(0.827–1.122)	0.63
ESRD causes (versus DN)						
Hypertensive NS	1.058	(0.975–1.147)	0.17	1.054	(0.967–1.148)	0.23
CGN	1.121	(1.017–1.235)	0.02	1.103	(0.997–1.221)	0.07
Comorbidities						
Diabetes	0.944	(0.891–1.001)	0.05	0.945	(0.888–1.006)	0.07
Hypertension	1.014	(0.948–1.085)	0.68	1.002	(0.934–1.074)	0.96
CHF	1.006	(0.954–1.062)	0.82	0.996	(0.942–1.054)	0.90
ASHD	0.925	(0.853–1.004)	0.27	0.920	(0.845–1.002)	0.06
Other CVD	1.029	(0.947–1.118)	0.06	1.022	(0.938–1.114)	0.62

Continued

Table 2. Continued

Variables	Casemix adjusted		P-value	Fully adjusted		P-value
	OR	95% CI		OR	95% CI	
AID	0.797	(0.630–1.008)	0.06	0.799	(0.510–1.253)	0.33
CbVD	1.068	(0.879–1.298)	0.51	1.051	(0.855–1.291)	0.64
Liver disease	0.855	(0.663–1.102)	0.23	0.773	(0.589–1.015)	0.06
Infection	1.132	(1.06–1.210)	0.03	1.138	(1.062–1.219)	<0.001
COPD	1.167	(1.037–1.313)	0.01	1.179	(1.043–1.334)	0.01
BMI (per 1 kg/m^2)	0.993	(0.990–0.997)	<0.001	0.995	(0.992–0.999)	0.02
nPNA (0.1 g/kg/1.73 m^2)	0.975	(0.964–0.987)	<0.001	0.954	(0.941–0.967)	<0.0001
Laboratory parameters						
Hemoglobin	0.990	(0.969–1.012)	0.37	1.009	(0.985–1.034)	0.46
Total lymphocyte	0.994	(0.991–0.998)	0.01	0.983	(0.979–0.987)	<0.001
Creatinine	1.046	(1.027–1.075)	0.002	1.032	(1.017–1.048)	<0.001
Albumin	0.91	(0.862–0.961)	<0.001	1.061	(0.952–1.183)	0.96
Calcium	1.067	(1.019–1.118)	0.01	1.048	(0.997–1.101)	0.06
Phosphorus	1.078	(1.054–1.102)	<0.001	1.113	(1.083–1.144)	<0.001
ALP (per 50 U/L)	1.054	(1.039–1.069)	<0.001	1.048	(1.032–1.063)	<0.001
iPTH (per 50 pg/mL)	0.992	(0.987–0.996)	<0.001	0.987	(0.982–0.992)	<0.001
Ferritin	1.007	(1.004–1.011)	<0.001	1.004	(1.000–1.008)	0.03

For laboratory parameters, the odds ratios (ORs) are per 1 unit increase of each variable unless specifically indicated.
AVF, arteriovenous fistula; CVC, central venous catheters; AVG, arteriovenous graft; DN, diabetic nephropathy; NS, nephrosclerosis; CGN, chronic glomerulonephritis; CHF, congestive heart failure; ASHD, atherosclerotic heart disease; CbVD, cerebrovascular disease; OR: odds ratio.

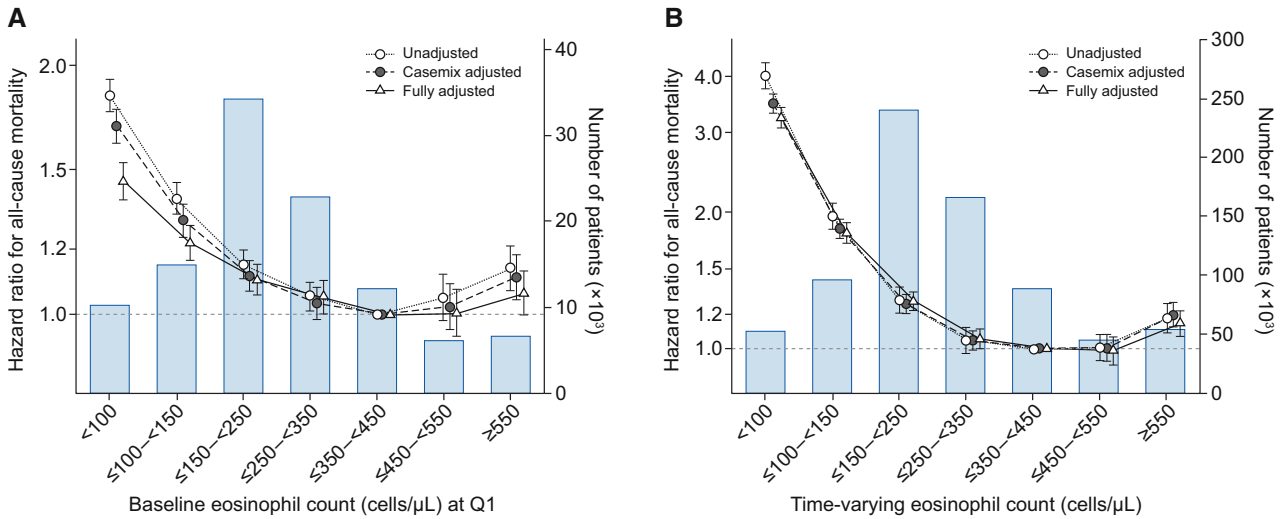

FIGURE 1: Association of (**A**) baseline and (**B**) time-varying EOC with all-cause mortality in 107 506 incident HD patients. Stratified by seven categories with three-level hierarchical adjusted models. Casemix adjusted for age, sex, race/ethnicity, vascular access, insurance type, diabetes, hypertension, congestive heart failure (CHF), atherosclerotic heart disease, other CVD, cerebrovascular disease, COPD, liver disease, AID, history of malignancy, HIV positive, infection and BMI. Fully adjusted for casemix + laboratory variables including hemoglobin, total lymphocyte, serum albumin, creatinine, calcium, phosphorus, ALP, iPTH, ferritin and nPNA.

and infection or had albumin <3.8 g/dL, nPNA <0.9 and WBC $<6.0 \times 10^9$/L.

In time-varying analysis, the association of lower and higher EOC with mortality was similar in most groups. Lower time-varying EOC was consistently and strongly associated with higher mortality across all patient strata in casemix-adjusted analyses. However, there was effect modification by race (P for interaction = 0.038), diabetes (P for interaction = 0.016) and WBC count (P for interaction <0.001), where whites, nondiabetics and patients with higher baseline WBC did not have a higher mortality risk with higher EOC (Figure 2B).

Changes in EOC during the first 3 months after HD initiation

Figure 3 shows the trajectories of quarterly mean EOCs and eosinophil fractions over 5 years in casemix-adjusted linear mixed-effects models. Overall, both eosinophil measurements increased over time after the initiation of HD. In contrast, the total WBC count decreased after initiation of HD up to quarter 10, followed by a gradual increase in the remaining quarters on HD.

In 97 616 HD patients who had EOCs between 92 and 182 days after dialysis initiation, the mean ΔEOC between the baseline and the second patient quarter was 5.1 (95%

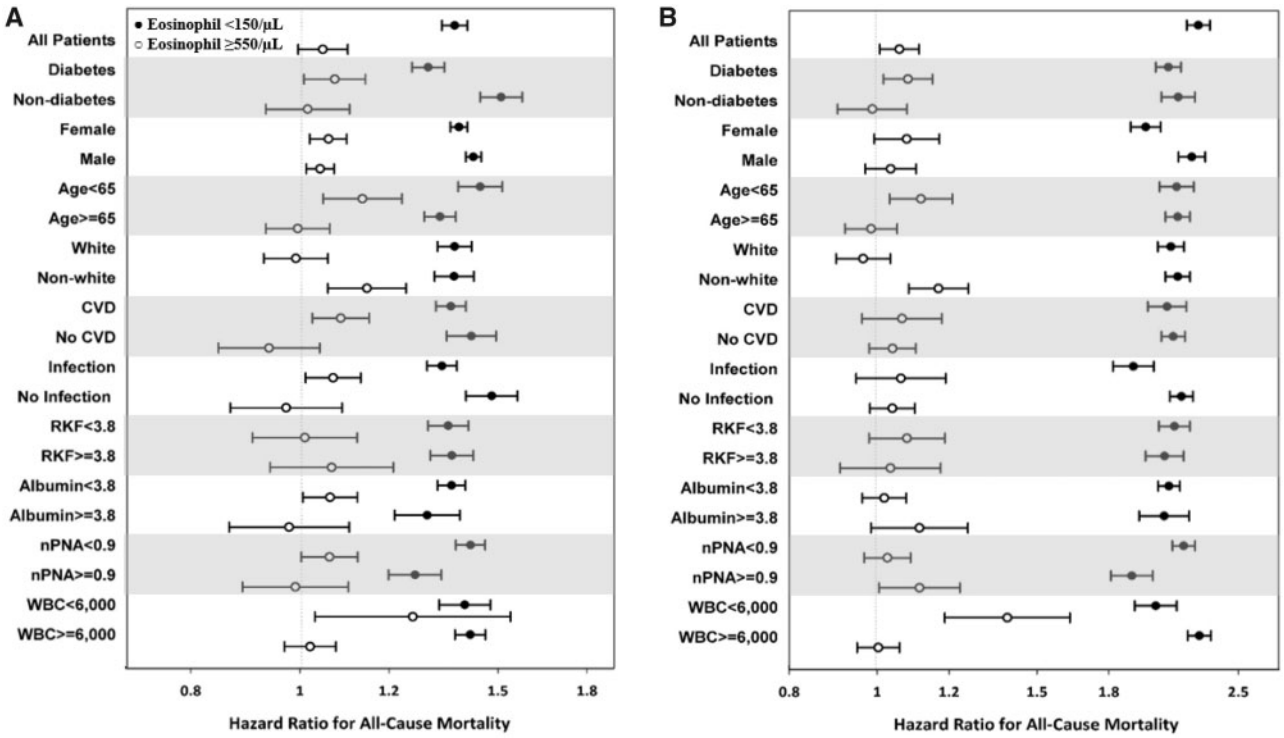

FIGURE 2: Overall and subgroup analysis of association of (**A**) baseline and (**B**) time-varying EOC with mortality. HR with 95% CI for the association of low (<150 cells/μL, closed circles) and high (≥550 cells/μL, open circles) (reference 150–<550 cells/μL) EOC with 5-year all-cause mortality in the casemix-adjusted models.

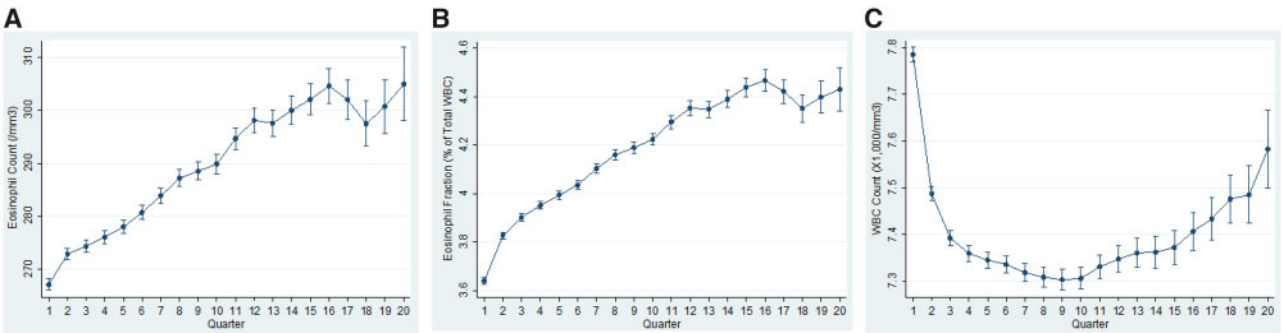

FIGURE 3: EOC, eosinophil fraction and WBC count per patient-quarter over 5 years in 107 506 incident HD patients. Trajectories of mean (**A**) EOC, (**B**) eosinophil fraction and (**C**) WBC over time in HD patients using casemix-adjusted mixed-effects regression models.

CI −53–199)/μL, equating to a mean 0.11% (95% CI −0.22–0.28) change from baseline EOC (ΔEOC/baseline EOC). Patient characteristics and the changes in laboratory parameters stratified across ΔEOC groups are described in Supplementary data, Table S5. Demographics, baseline and change in covariate laboratory measurements were clinically similar across groups of ΔEOC groups, with the exception of ΔWBC, where there was a direct linear relationship and larger decreases in WBC counts were observed for larger decreases in ΔEOC and a modest increase of ΔWBC was observed for the largest increase ΔEOC group. Baseline EOC tended to be higher in patients showing a decrease in EOC compared with ΔEOC 0–50 cells/μL. Both an increase and decrease in ΔEOC were associated with a higher mortality risk resulting in a reverse J-shaped relationship across all levels of adjustment and in restricted cubic spline models (Figure 4). Additionally, this association persisted after additional adjustment with baseline EOC (Supplementary data, Table S6).

DISCUSSION

In a large nationally representative cohort of 107 506 adult incident HD patients, our primary finding was a robust association between lower EOC and a higher risk of all-cause mortality in both baseline and time-varying models, independent of sex, age, comorbidity and laboratory parameters reflecting malnutrition and inflammatory status. Female sex, African American race/ethnicity, comorbid AID, low BMI and a low concentration of albumin and phosphorus were predictors of lower baseline EOC in this study. Patients with the highest baseline EOC (≥550 cells/μL) also had a higher mortality risk compared with patients with an EOC of 350–450 cells/μL. In addition, both a

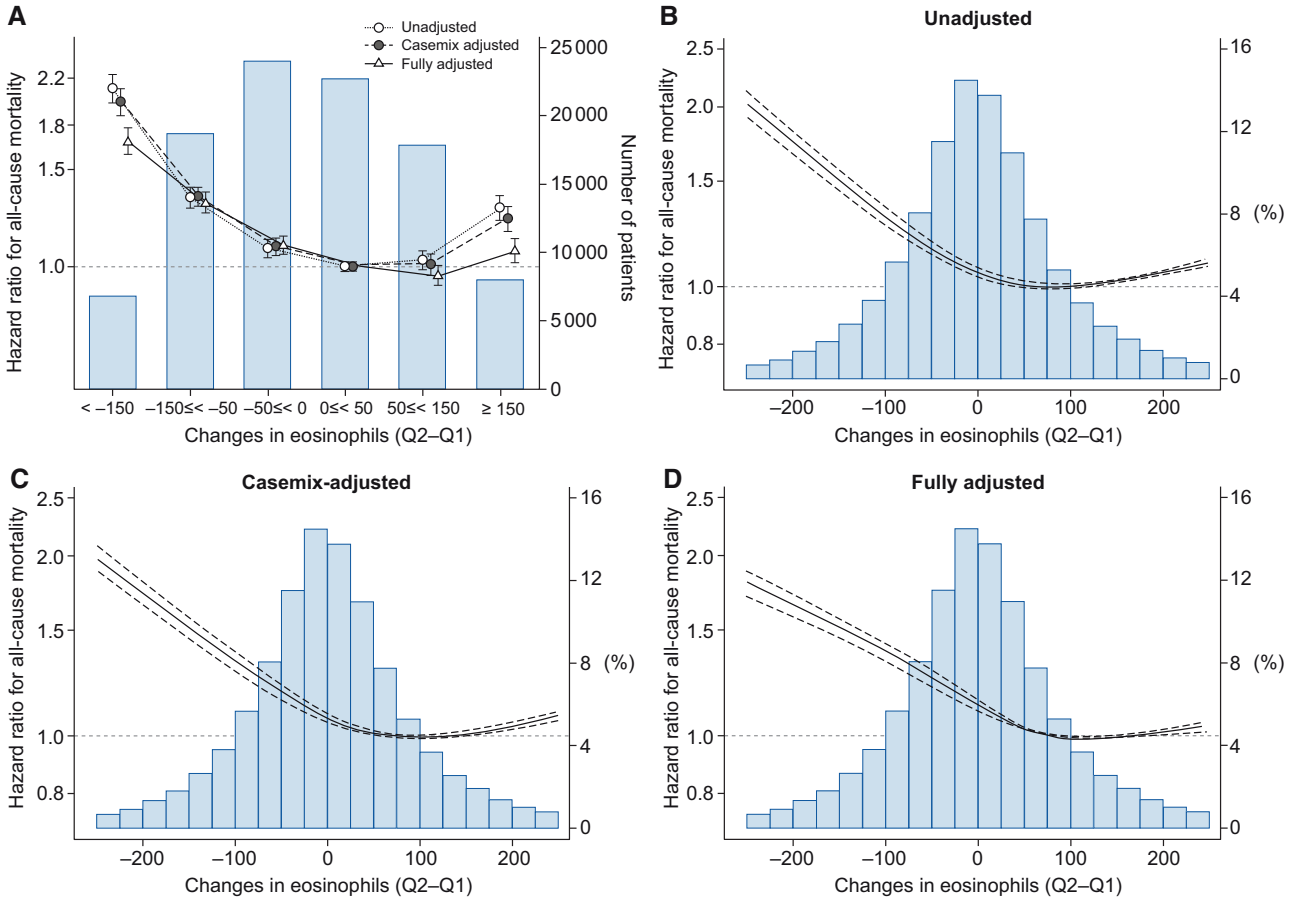

FIGURE 4: Frequency distribution and mortality risk according to the ΔEOC between Q1 and Q2: (**A**) stratified by six categories with three-level hierarchical adjusted model, (**B**) the unadjusted model with restricted cubic spline functions, (**C**) the casemix-adjusted and (**D**) fully adjusted models with restricted cubic spline function ($n = 97\,616$).

decrease and increase in EOC over the first 6 months of HD was associated with a higher mortality risk independent of baseline EOC levels and other covariates.

Our study demonstrated that eosinophilia was not uncommon in incident HD patients. Recent developments in the understanding of cytokines and chemokines released by eosinophils shed light on a new role of peripheral and tissue eosinophils as principal immunoregulatory and effector cells with roles in antigen presentation, T-cell regulation and polarization, B-cell priming as well as regulation of dendritic cells, mast cells and neutrophils [1–3]. Abnormal EOCs in peripheral circulation, in particular, eosinophilia, have been reported in CKD and HD patients, with a prevalence of 4.7–52% depending on different criteria of eosinophilia [6–11]. This prevalence is more common compared with the <1% prevalence of eosinophilia seen in the general population [3–5, 7, 23]. Mechanisms for an elevated EOC in HD patients are still unknown; however, they were often attributed to renal dysfunction per se or a hypersensitivity reaction to the dialysis process, which resulted in an increased turnover of eosinophil in bone marrow, increased peripheral sequestration and enhanced interaction with endothelial cells [6, 7].

In a previous study in 21 HD patients, the mean EOC was 490 ± 10 cells/μL (range 70–1710) with 43% of patients having eosinophilia (defined as >380 cells/μL). HD patients with eosinophilia showed a greater increase in production of interleukin (IL)-1 and IL-2 from peripheral mononuclear cells isolated before and after the HD session, with a significant correlation between EOC and cytokine production, suggesting that eosinophilia in HD patients may be a marker of exaggerated cytokine response [7]. However, other studies have found no relationship of EOC with dialyzer type, dialysis time or vascular access [5, 11]. In a recent article analyzing 1339 hospitalized patients referred to a nephrology consultation service, Diskin *et al.* [24] reported an increase in EOC in ESRD patients compared with NDD-CKD or acute kidney injury patients.

The prevalence of eosinophilia (>350 cells/μL) in 107 756 incident HD patients was 23.4% in our study. Most eosinophilia observed in our study was mild in its severity based on an arbitrary conventional classification (351–1500 cells/μL) and only 0.34% of HD patients showed moderate eosinophilia (>1500 cells/μL). Given the recent advances in modern dialyzer technology and its sterilization process and a decrease in HD-associated hypersensitivity reaction, the comparable prevalence of eosinophilia in HD patients in our study compared with previous studies from the era using less biocompatible dialyzers suggests mild eosinophilia in HD may not relate to dialyzer biocompatibility but instead may be a marker of immune competency, subclinical infection or endothelial dysfunction [25, 26]. Previous studies in HD patients have shown a higher prevalence

of eosinophilia in males, patients with lower high- sensitivity C-reactive protein or on angiotensin-converting enzyme inhibitors [10]. Our study showed male sex, Asian race and infection comorbidity predicted higher EOC in fully adjusted models; however, CVD was not associated with eosinophilia. On the other hand, there is no report specifically addressing the lower EOC in dialysis patients. A lower EOC (eosinopenia) can be associated with a viral or bacterial infection or sepsis [27, 28]. In this study, logistic regression analysis demonstrated female sex, African American race/ethnicity, comorbid AID, lower BMI and lower concentrations of albumin and phosphorus were predictors of lower EOC; however, patients with infection were less likely to have lower EOC, with marginal statistical significance in fully adjusted models.

In our mortality analysis, although both extremes of EOC were associated with a higher mortality risk, lower EOC showed a stronger and more consistent association with worse survival. The association between lower EOC and mortality, unexpected readmission or hospital stays has been previously reported in COPD and critically ill patients [17, 18, 27, 29]. Abidi *et al.* [18] demonstrated that absolute EOC was significantly lower in nonsurvivors in the ICU, and EOC <40 cells/μL was an independent predictor of 28-day mortality [18]. Another study reported eosinopenia at ICU discharge was associated with an increased risk of post-ICU mortality [29]. With regard to the relationship of higher EOC with mortality, there are two previous studies showing the association between eosinophilia and clinical outcomes in non-CKD patients. In a cohort of 5383 subjects with asthma and COPD, eosinophilia (>275 cells/μL) was associated with a higher mortality risk, independent of sex, age, smoking habits and pulmonary function (relative risk 1.43) after 30 years of follow-up [16]. This association was robust after the exclusion of asthma patients. Sweetnam *et al.* [15]. also showed that subjects with an elevated EOC had a higher incidence of ischemic heart disease. One study in NDD-CKD patients showed an association of spikes of EOC with the risk of ESRD and death [4]. However, in the only study that has previously examined the association of eosinophilia with mortality in 510 prevalent HD patients with 29 months of follow-up [10], no association of eosinophilia with dialysis vintage, hospital admission or mortality was reported. Our study results may have differed from this previous study due to the larger cohort size and focus on incident HD patients.

The other novel finding of this study was the change in EOC over time on HD and the relationship of this change over the first 3 months with subsequent mortality risk. The mean EOC increased over time after the transition into HD, whereas the mean total WBC counts significantly decreased in the first 10 quarters after HD transition. This finding suggested EOC increases might not reflect an increase in WBCs. In our cohort, patients with a modest increase in EOC over 6 months had a mean decrease in WBCs (Supplementary data, Table S4). An inverse correlation between WBC count and dialysis vintage has already been reported [30], which may be explained by an improvement of inflammatory reactions and normalization of the WBC turnover rate due to alleviation of uremia. The inverse relationship between ΔEOC and WBC count over time on HD may be explained by the role of the dialysis process itself, which may induce an alteration in eosinophil homeostasis and subclinical hypersensitivity (similar to an allergic reaction) and thereby increase EOC in incident HD patients. Further studies to investigate the potential impact of dialysis treatments on EOC are needed.

The mechanisms underlying the relationships of abnormal EOC and its change with mortality may be complex, particularly in HD patients with many comorbidities. A prior study showed a higher eosinophil fraction in patients with vascular complications such as cardiac or peripheral vascular disease and vascular access thrombosis compared with patients with no vascular problems, suggesting EOC could be a marker of vascular disease [14, 15, 24]. However, in our study there was no association of either an increase or a decrease in EOC with comorbid CVD. Nonetheless, a significantly elevated EOC may be harmful in HD patients due to a proinflammatory or pro-oxidant effect of eosinophils. Alternatively, the eosinophils may serve a protective function in maintaining immune competency, and a lower EOC may reflect subclinical infection or noncompetent immune status in HD patients. Recent studies also suggest the role of eosinophils in maintaining vascular health. The eosinophil in its resting state appears to provide an anti-contractile property to the vasculature (probably through nitric oxide on the perivasculature adipose tissue) that is lost in the absence of eosinophils, thereby resulting in tissue ischemia [31]. However, in the activated state, high numbers of eosinophils can cause vascular fibrosis, calcification and vasoconstriction from prostaglandin D2 and leukotrienes C4 and D4 [32]. Unfortunately, although we did not investigate the association of EOC and cardiovascular mortality, we speculate that CVD is the major cause of death in our incident HD patients.

In our study, mild eosinophilia (350–450 cell/μL) was associated with the lowest mortality in incident HD patients, with no significant difference in mortality risk compared with patients with upper-normal EOCs (250–350 cell/μL).

Due to limited knowledge of eosinophil kinetics in the bone marrow, the release of eosinophils into the peripheral circulation and the function of eosinophils in HD patients, the interpretation of the association of EOC with mortality is still unclear. At this time it is certain that eosinophils function as both a marker of allergic reactions and immune regulatory functions [2]. Moreover, previous studies suggest that eosinophils may be markers of endothelial damage in disease progression [15, 24]. Future studies that are able to capture data on immune function, subclinical inflammation and endothelial dysfunction should explore the precise mechanisms of eosinophil changes and their association with mortality risk.

The strengths of this study include the large sample size, thorough adjustment for common markers of malnutrition and inflammation and refined eosinophil categories that allowed us to examine nonlinear relationships. However, several limitations should be noted, including the possibility of residual confounding and our inability to infer causality due to our retrospective observational study design. We do not have data on a number of comorbidities such as allergy, asthma, adrenal insufficiency, hepatitis, parasitic infection and medications

inducing changes in EOC. We also lacked data on potential confounders and other inflammatory markers such as C-reactive protein and proinflammatory cytokines. Data on comorbidities were based on ICD-9 codes provided by a large dialysis organization and we are unable to validate the presence of the comorbidity; however, we believe that this is a nondifferential misclassification and that accurate capture of the comorbidity is not related to a patient's eosinophil level. Although the data are sourced from a large representative US dialysis population, generalizability to non-US dialysis patients may be limited.

In a large national cohort of incident HD patients in the USA, mild-degree eosinophilia was not uncommon in incident HD patients and was also associated with the lowest risk of mortality. While both lower and higher EOC were associated with a higher risk of all-cause mortality, the risk was significantly worse for patients with lower EOC, in particular those with EOC <100 cells/μL. Additionally, a ΔEOC >150 cells/μL during the first 6 months after HD initiation was also associated with a higher mortality risk, where mortality risk was worse in patients whose EOC decreased. Additional studies with data on inflammatory markers and inflammation-related comorbidities are needed to confirm our findings. Further studies are also needed to understand the pathophysiology underlying this association and the value of EOC and its changes as a prognostic marker for patients' survival after initiation of HD.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

D.-H.K. contributed to the research idea and study design. E.S. and K.K.-Z. contributed to data acquisition. D.-H.K., Y.K.L., C.E.K., E.S. and K.K.-Z. contributed to data analysis and interpretation. D.-H.K., Y.L., J.-T.H. and C.P. contributed to statistical analysis. E.S., C.P.K., C.M.R. and K.K.-Z. were responsible for supervision or mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

K.K.-Z. has received honoraria and/or support from Abbott, AbbVie, Alexion, Amgen, American Society of Nephrology, AstraZeneca, AVEO, Chugai, DaVita, Fresenius, Genetech, Haymarket Media, Hospira, Kabi, Keryx, National Institutes of Health, National Kidney Foundation, Relypsa, Resverlogix, Sanofi, Shire, Vifor and ZS Pharma. C.P.K. has received honoraria from Sanofi-Aventis, Relypsa and ZS Pharma.

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