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Higher Eosinophils Predict Death-Censored Technique Failure in Peritoneal Dialysis Patients

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Keywords
Eosinophil · Technique failure · Peritoneal dialysis · Biocompatibility · Gender heterogeneity

Abstract
Introduction: Eosinophilia (eosinophil fraction of leukocytes >5%), an indicative parameter for bioincompatibility in various circumstances, is well established in hemodialysis. However, change in eosinophil count (EOC) and its association with death-censored technique failure among peritoneal dialysis (PD) patients remain unclear. ***Methods:*** We compared eosinophils before and after PD initiation among 1,432 eligible continuous ambulatory PD patients regularly followed up in our PD center during 2007–2018. Risk factors of early-stage eosinophilia were examined by the logistic regression test. The relationship of early-stage eosinophilia and EOC with death-censored technique failure was examined using the Cox proportional hazards model for overall patients and for men and women separately. ***Results:*** After PD initiation, the EOC and percentage of patients with eosinophilia were significantly increased compared with baseline. Being male (odds ratio [OR]: 2.26; 95% confidence interval [CI]: 1.55–3.31; $p < 0.001$) and higher EOC at baseline (100 cells/μL increase, OR: 1.62; 95% CI: 1.45–1.82; $p < 0.001$) were risk factors of early-stage eosinophilia after PD initiation. During follow-up, 204 death-censored technique failures were recorded. In fully adjusted models, each with 100 cells/μL increase in EOC, the adjusted hazard ratios (HRs) of technique failure were 1.11 (95% CI: 1.03–1.20; $p = 0.009$) in the whole cohort, 1.29 (95% CI: 1.10–1.51; $p = 0.002$) in women, and 1.07 (95% CI: 0.97–1.17; $p = 0.196$) in men. Eosinophilia was significantly associated with the risk of technique failure for women (HR: 2.24; 95% CI: 1.07–4.70; $p = 0.033$), which was especially significant for women aged <55 years (HR: 7.61; 95% CI: 1.88–30.90; $p = 0.005$). ***Conclusion:*** EOC was increased significantly after PD initiation, and increased numbers of eosinophils were associated with higher death-censored technique failure in PD patients, especially women.

Introduction

End-stage renal disease (ESRD) is a leading cause of mortality and a global health burden. Peritoneal dialysis (PD) is a safe, effective, and home-based renal replacement therapy with increasing acceptance, especially in China and the United States [1, 2]. However, technique

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failure remains an important and frequent cause of PD cessation, which is the main reason for relatively poor PD retention rates worldwide [3].

Traditionally, eosinophils are associated with atopic conditions, such as allergic diseases, parasitic infections, autoimmune processes, and neoplastic disorders [4]. Current research has shown that elevated eosinophils are a predictor of cardiovascular disease (CVD) and cardiovascular mortality because of their active participation in inflammation [5–7]. Eosinophilia is common in hemodialysis (HD) patients in part because of the limited biocompatibility of the dialysis membrane [8, 9]. With the advancement of modern dialyzer membranes, the prevalence of hemodialysis-associated eosinophilia (HAE) has been significantly reduced, accounting for 4.7–23.4% HD patients in recent years [10, 11]. Even though the change in eosinophil count (EOC) is not serious, lower and higher eosinophils are associated with higher all-cause mortality in HD patients [11].

PD is a treatment methodology that makes use of the semipermeable function of the peritoneum and is more biocompatible with body membranes. Thus, the elevation of EOC in PD patients is less common and milder than that in HD patients [12]. Accordingly, eosinophilia in PD patients is rare and not a common concern for clinicians and researchers. Whether chemical and mechanical stimulations in PD therapy lead to changes in EOC and its possible influence on the prognostic outcomes of PD patients are unclear. Therefore, we conducted this prospective study in our PD center to determine the change of EOC and its association with prognostic outcomes in PD patients.

Methods

Participants

All patients undergoing catheterization surgery at the PD center of The First Affiliated Hospital of Sun Yat-sen University and who were followed up for at least 3 months from June 2007 to July 2018 were enrolled. Patients were included if they (1) were aged ≥18 years, (2) had signed an informed consent form, and (3) had at least one EOC at their baseline (records within 2 weeks before catheterization surgery). Patients were excluded if they (1) had a history of malignant tumor, (2) were transferred from failure renal transplantation, (3) were transferred from permanent HD, or (4) responded to identifiable allergens based on the medical history. During follow-up, patients with unavailable EOC at 1 and 3 months after PD initiation were also excluded. All patients in the study were treated according to standard PD prescriptions in our PD center (Dianeal 1.5, 2.5, or 4.25% dextrose; Baxter Healthcare, Guangzhou, China; exchanges 3–5 times daily).

Study Protocol

Data were prospectively collected from the electronic medical database of our PD center. Before catheterization surgery for PD, the EOC was recorded and set as the baseline. EOCs were prospectively collected at 1, 3, 6, and 9 months after the start of PD therapy. Demographic and clinical data, which included age, gender, body mass index (BMI), presence of CVD (either coronary artery disease, peripheral vascular disease, stroke, or heart failure), diabetes mellitus (DM), and hypertension, cause of ESRD, and blood pressure, were collected at the initiation of PD therapy. Biochemical and dialysis parameters were also collected and measured in The First Affiliated Hospital of Sun Yat-sen University using an automatic chemistry analyzer (Hitachi 7180 or Abbott Aeroset).

Early-stage peripheral blood eosinophilia (PBE) was defined as an eosinophil fraction of leukocytes >5% at either 1 or 3 months after PD initiation. The outcome of interest was death-censored technique failure, defined as transferring to HD for more than 90 days, and this was censored for death, kidney transplantation, and spontaneous recovery of renal function [13]. All patients were regularly followed up to October 1, 2018, or until death-censored technique failure, death, kidney transplantation, transfer to other centers, or lost to follow-up. The study protocols were approved by the Ethics Committee of The First Affiliated Hospital of Sun Yat-sen University (2016) (No. 215).

Statistical Analysis

Data are presented as mean ± SD for normally distributed continuous variables, median and interquartile range for skewed continuous variables, and frequencies and percentages for categorical variables. Paired-sample Student's t test and χ^2 test were used to compare EOCs and eosinophilia percentages between different follow-up months and baseline. Differences between patients with or without eosinophilia were compared by Student's t test for approximately normally distributed continuous variables, the Kruskal-Wallis test for skewed continuous variables, and the χ^2 test for categorical variables. Logistic regression was used to classify the risk factors of eosinophilia in multivariate models including all covariates with near significance ($p < 0.1$) in the univariate logistic analysis and covariates with clinical significance.

The association of eosinophilia with death-censored technique failure rate was analyzed using Kaplan-Meier plots and log-rank tests. The Cox proportional hazards regression model was used to analyze the association of eosinophils with technique failure without adjustment and then with adjustment for several groups of covariates according to the following potential confounders: Model 1: univariate adjusted model; Model 2: gender, age, and BMI; and Model 3: Model 2 plus EOC at the baseline, 4-h dialysate-to-plasma creatinine ratio (D/PCr) of the peritoneal equilibration test, high-sensitivity C-reactive protein (CRP) level, systolic pressure, DM, CVD history, and cause of ESRD, which included all covariates with near-significance ($p < 0.1$) associated with technique failure in univariate analysis and covariates considered to be of clinical significance. The interaction between gender and eosinophilia on technique failure was also explored by the Cox regression model. Subsequent subgroup analyses were conducted in gender-specific and age-specific groups with the same defined models. Statistical analyses were performed using SPSS 24.0 software.

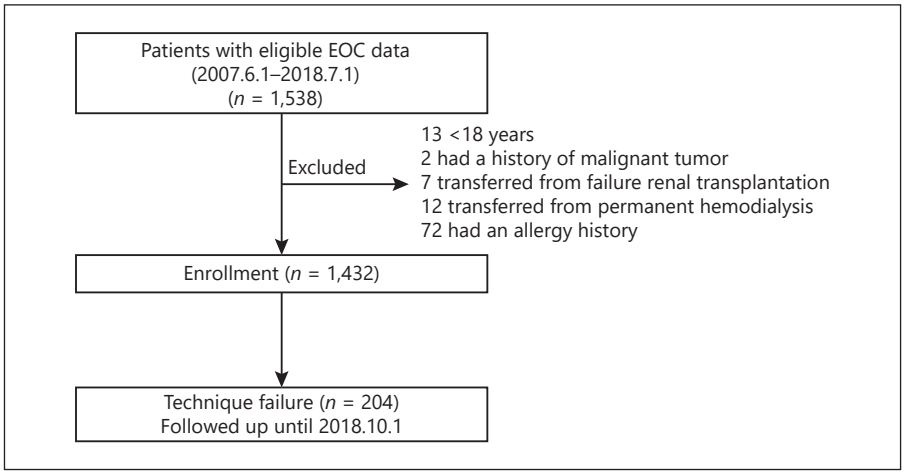

Fig. 1. Study flow of patient enrollment. EOC, eosinophil count.

Table 1. Characteristics of the study cohort and by classification of early-stage eosinophilia and noneosinophilia after PD initiation

Clinical index	Total (*N* = 1,432)	Eosinophilia[a] (*n* = 440)	Noneosinophilia[a] (*n* = 992)	*p* value[b]
Age, years	45 (35, 57)	46 (36, 57)	45 (35, 56)	0.339
Male gender, *n* (%)	856 (59.8)	330 (75.0)	526 (53.0)	<0.001[c]
BMI, kg/m^2	21.5 (19.5, 23.6)	22.0 (19.8, 24.1)	21.3 (19.4, 23.4)	<0.001[c]
DM, *n* (%)	241 (16.8)	80 (18.2)	161 (16.2)	0.362
CVD, *n* (%)	660 (46.1)	227 (51.6)	433 (43.7)	0.005[d]
Cause of ESRD, *n* (%)				
Glomerulonephritis	900 (63.0)	285 (64.8)	614 (62.1)	0.013[e]
Diabetic nephropathy	272 (19.0)	85 (19.3)	187 (18.9)	
HPN	107 (7.5)	40 (9.1)	67 (6.8)	
Others	150 (10.5)	30 (6.8)	120 (12.1)	
EOC at baseline, cells/μL	170.0 (92.1, 280.0)	260.0 (160.0, 434.2)	140.0 (80.0, 220.0)	<0.001[c]
WBC at baseline, ×10^9/μL	6.6 (5.2, 8.1)	6.5 (5.3, 8.3)	6.4 (5.1, 7.9)	0.033[e]
Neutrophils at baseline, %WBC	67.3±21.2	68.9±13.1	66.6±23.9	0.059
Lymphocytes at baseline, %WBC	21.8±8.3	20.5±8.2	22.4±8.2	<0.001[c]
Monocytes at baseline, %WBC	7.7±4.8	7.7±5.1	7.7±4.7	0.828
Systolic pressure, mm Hg	133 (121, 145)	135 (124, 147)	132 (120, 145)	0.028[e]
Diastolic pressure, mm Hg	85 (76, 95)	85 (77, 95)	85 (76, 94)	0.945
eGFR, mL/(min·1.73 m^2)	5.00 (3.82, 6.55)	5.20 (3.85, 7.10)	4.92 (3.81, 6.34)	0.068
Hemoglobin, g/L	105.8±18.5	105.5±18.1	106.0±18.7	0.600
Serum albumin, g/L	37.5 (34.0, 40.3)	37.0 (33.6, 40.0)	37.6 (34.3, 40.5)	0.112
Cholesterol, mmol/L	5.0 (4.2, 5.8)	5.0 (4.2, 5.9)	5.0 (4.3, 5.8)	0.374
Triglyceride, mmol/L	1.46 (1.06, 2.06)	1.37 (1.01, 2.09)	1.48 (1.09, 2.03)	0.139
hs-CRP, mg/L	1.61 (0.58, 4.39)	1.71 (0.65, 4.31)	1.53 (0.55, 4.41)	0.286
Uric acid, μmol/L	415±88	421±84	412±90	0.078
Serum calcium, mmol/L	2.25±0.21	2.24±0.22	2.26±0.20	0.103
Serum phosphorus, mmol/L	1.32 (1.10, 1.55)	1.32 (1.11, 1.55)	1.32 (1.10, 1.55)	0.752
D/PCr	0.71±0.11	0.72±0.11	0.70±0.11	0.004[d]
Total, Kt/V	2.44±0.53	2.47±0.60	2.42±0.49	0.576
HbA_{1c}	5.1 (4.6, 6.0)	5.10 (4.7, 6.0)	5.2 (4.6, 6.0)	0.543

Data are presented as mean ± SD for normally distributed continuous variables, median and interquartile range for skewed continuous variables, and frequencies and percentages for categorical variables. BMI, body mass index; CVD, cardiovascular disease; ESRD, end-stage renal disease; HPN, hypertensive nephropathy; WBC, white blood cell; EOC, eosinophils count; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; D/PCr, dialysate-to-plasma ratio of creatinine at 4 h of peritoneal equilibration test; HbA_{1c}, glycated hemoglobi; PD, peritoneal dialysis. [a] Early-stage eosinophilia was defined as eosinophils fraction of leukocytes >5% at 1 or 3 months after PD initiation. [b] Compared between eosinophilia and noneosinophilia with tests for trend. [c] $p < 0.001$. [d] $p < 0.01$. [e] $p < 0.05$.

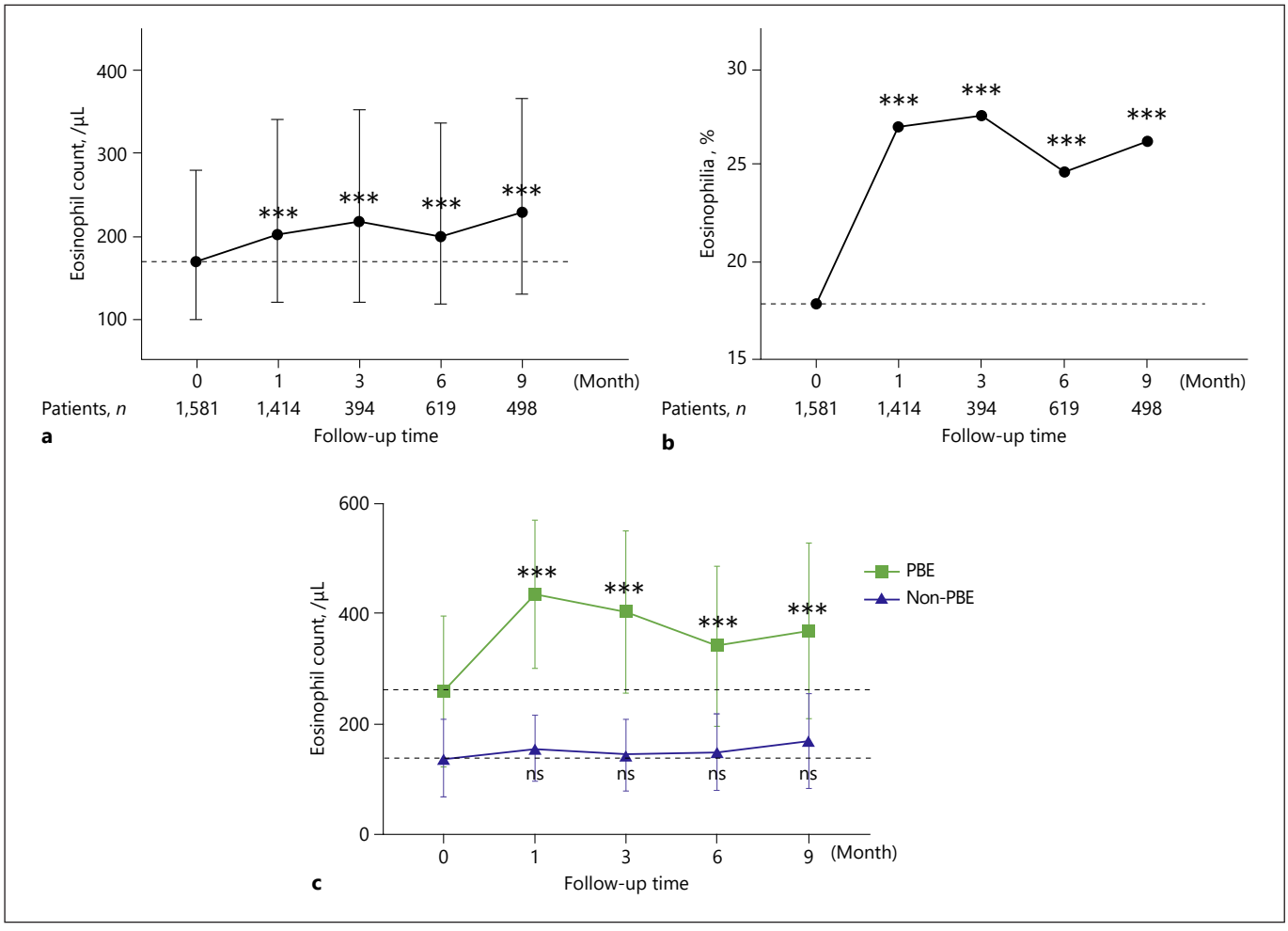

Fig. 2. Eosinophil count and eosinophilia (%) before catheterization and over 9 months in PD patients. Trajectories of median and interquartile range of eosinophil counts in all patients (**a**) and in early-stage PBE and non-PBE patients (**c**). **b** Percentage of eosinophilia in PD patients over time. The paired-sample *t* test and χ^2 test were used for comparisons of different follow-up months with the baseline. *** $p < 0.001$. The eosinophil count and eosinophilia percentage of patients at 0 months represent the baseline indicated by the horizontal line. PBE, peripheral blood eosinophilia, defined as eosinophil fraction of leukocytes >5% at 1 or 3 months after PD initiation; ns, not significant.

Results

Participant Characteristics

Overall, 1,432 eligible continuous ambulatory PD (CAPD) patients were enrolled and regularly followed up until October 1, 2018 (Fig. 1). Demographic and clinical characteristics of the cohort are shown in Table 1. The median age of the population was 45 (35, 57) years. Among them, 59.8% patients were male, 16.8% had DM, 46.1% had a history of CVD, and the leading cause of ESRD was glomerulonephritis (63.0%) followed by diabetes nephritis (19.0%).

Elevation of Peripheral Blood Eosinophils after Catheterization

The median EOC before catheterization (baseline) was 170.0 (92.1, 280.0)/μL and it became 201.4 (120.2, 341.5)/μL, 218.3 (120.8, 359.2)/μL, 199.8 (117.6, 336.6)/μL, and 229.9 (130.8, 378.0)/μL at 1, 3, 6, and 9 months after catheterization, respectively. There was a significant increase (paired-sample *t* test, $p < 0.001$) in EOC at different follow-up months compared with that before catheterization in the whole cohort and in patients with early-stage eosinophilia (Fig. 2a, c). Furthermore, 17.84% PD patients had PBE before catheter insertion and the percent-

Table 2. Death-censored technique failure for early-stage eosinophilia and EOC in total cohort

	Events/ 1,000 patient-years	Model 1[a] HR (95% CI)	*p* value	Model 2[b] HR (95% CI)	*p* value	Model 3[c] HR (95% CI)	*p* value
Noneosinophilia	10.34	(Ref.)	–	(Ref.)	–	(Ref.)	–
Eosinophilia[d]	13.87	1.57 (1.10, 2.08)	0.001[e]	1.54 (1.11, 2.13)	0.010[f]	1.40 (0.94, 2.16)	0.100
EOC,[g] per 100 cells/μL increased	Overall 10.47	1.13 (1.07, 1.18)	<0.001[h]	1.11 (1.06, 1.18)	<0.001[h]	1.11 (1.03, 1.20)	0.009[e]

Sex and eosinophilia interaction: Model 1: β = −0.644; $p = 0.033$*; Model 2: β = −0.844; $p = 0.013$*; Model 3: β = −0.659; $p = 0.121$. CI, confidence interval; HR, hazard ratio; PET, peritoneal equilibration test; CVD, cardiovascular disease; ESRD, end-stage renal disease; D/PCr, dialysate-to-plasma ratio of creatinine; CRP, C-reactive protein; DM, diabetes mellitus; EOC, eosinophil count; PD, peritoneal dialysis. [a] Univariate model. [b] Adjusted for age, gender, and body mass index. [c] Adjusted for Model 2 covariates and EOC at baseline, 4-h D/PCr of the PET, high-sensitivity CRP, systolic pressure, CVD history, DM, and cause of ESRD. [d] Early-stage eosinophilia was defined as eosinophil fraction of leukocytes >5% at 1 or 3 months after PD initiation. Models for eosinophilia with noneosinophilia as the reference group. [e] $p < 0.01$. [f] $p < 0.05$. [g] Models for each 100 cells/μL increased in EOC. [h] $p < 0.001$.

age significantly increased to 26.89, 27.41, 24.56, and 26.10% at 1, 3, 6, and 9 months after PD initiation, respectively (χ^2 test, $p < 0.001$; Fig. 2b).

Early-Stage Eosinophilia after PD Initiation

Overall, 30.7% patients had eosinophilia at 1 or 3 months after PD initiation, and the characteristics between the groups are shown in Table 1. Patients with early-stage eosinophilia tended to have higher EOC and lower lymphocyte count before PD therapy and were more likely to be male, with CVD history, higher BMI, higher systolic pressure, and higher 4-h D/PCr by the peritoneal equilibration test. Considering the robust difference in gender between the groups, the patients were subsequently stratified into groups of men or women. Comparisons by gender demonstrated male patients with eosinophilia tended to have higher BMI (22.4 [20.2, 24.2] vs. 21.6 [19.9, 23.6]; $p = 0.011$) and CVD history (51.2 vs. 43.3%; $p = 0.025$), whereas systolic pressure (134 [124, 146] vs. 130 [119, 140]; $p = 0.013$) tended to be higher in female patients with eosinophilia (see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000509085). With respect to potential risk factors of early-stage eosinophilia after PD initiation, the fully adjusted multivariate model demonstrated that being male (OR: 2.26; 95% CI: 1.55–3.31; $p < 0.001$) and higher EOC at baseline (with 100 cells/μL increase, OR: 1.62; 95% CI: 1.45–1.82; $p < 0.001$) were associated with eosinophilia after adjustment for all the potential risk factors of eosinophilia with near-significance ($p < 0.1$) in the univariate model (online suppl. Table 2).

Eosinophils and Death-Censored Technique Failure in the Whole Cohort

Overall, 204 (14.2%, 10.47/1,000 patient-years) patients developed death-censored technique failure with a median follow-up time of 38.3 (18.4, 77.3) months. The causes of technique failure were peritonitis (92 patients, 45.1%), decrease or failure of ultrafiltration (22 patients, 10.8%), inadequate dialysis (21 patients, 10.3%), catheter dysfunction (4 patients, 2.0%), PD complications (24 patients, 11.8%), patient or doctor choice (21 patients, 10.3%), and other reasons (20 patients, 9.7%).

Association of eosinophils with technique failure was subsequently analyzed with defined models, in which Model 3 was the maximally adjusted model. With each 100 cells/μL increase in EOC at the first month, the adjusted HR (hazard ratio) of technique failure was 1.11 (95% CI: 1.03–1.20; $p = 0.009$) in the whole cohort, after adjustment of EOC at the baseline, age, gender, BMI, 4-h D/PCr, high-sensitivity CRP level, systolic pressure, DM, CVD history, and cause of ESRD (Table 2). Technique failure rates were 13.87/1,000 patient-years and 10.34/1,000 patient-years in patients with and without early-stage eosinophilia, respectively, which were significantly different (log rank = 10.267, $p = 0.001$; Fig. 3a) between the groups. Early-stage eosinophilia was significantly associated with technique failure in Model 2 with adjustment of age, gender, and BMI (HR: 1.54; 95% CI: 1.11–2.13; $p = 0.010$), while in Model 3, the association was attenuated (HR: 1.40; 95% CI: 0.94–2.16; $p = 0.100$).

Eosinophils and Death-Censored Technique Failure in Subgroup Analyses

Considering the robust association of gender and early-stage eosinophilia, we tested the interaction between them on technique failure among all patients and observed a significant interaction in Model 1 (univariate analysis, β = −0.644; $p = 0.033$) and Model 2 (β = −0.844; $p = 0.013$), and a near-significant interaction was seen in Model 3 (β = −0.659; $p = 0.121$). Next, technique failure

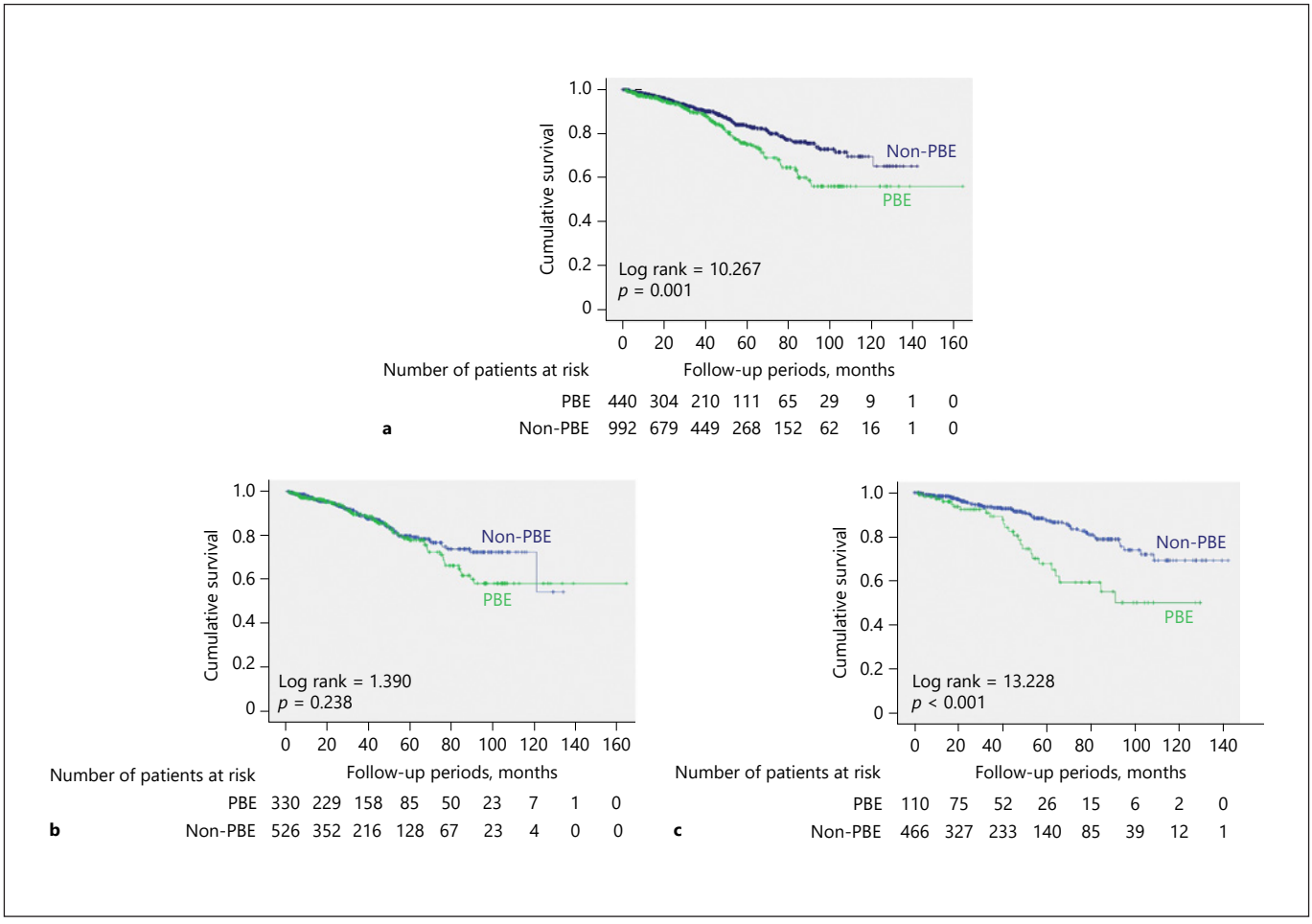

Fig. 3. Crude analyses of death-censored technique failure between early-stage eosinophilia and non-eosinophilia in the whole cohort and separately in men and women. Kaplan-Meier estimates of death-censored technique failure between eosinophilia and noneosinophilia in the whole cohort (**a**), men (**b**), and women patients (**c**). PBE, peripheral blood eosinophilia, defined as eosinophil fraction of leukocytes >5% at 1 or 3 months after PD initiation.

between early-stage eosinophilia and noneosinophilia was analyzed stratified by gender. There was a significant difference in women (log rank = 13.228, $p < 0.001$; Fig. 3b), which was not observed in men (log rank = 1.390, $p = 0.238$; Fig. 3c). In Model 3, with each 100 cells/μL increase in EOC at the first month, adjusted HRs of technique failure were 1.29 (95% CI: 1.10–1.51; $p = 0.002$) for women and 1.07 (95% CI: 0.97–1.17; $p = 0.196$) for men. Early-stage eosinophilia was significantly associated with the risk of technique failure for women even in the most powerfully adjusted Model 3 (HR: 2.24; 95% CI: 1.07–4.70; $p = 0.033$), while no association was indicated for men with any defined models (Table 3).

Female patients aged ≥55 or <55 years were subsequently stratified into groups to distinguish between women with and without menopause. In Model 3, eosinophilia in women aged <55 years was significantly associated with technique failure. The HR was 7.61 (95% CI: 1.88–30.90; $p = 0.005$), which was more significant than that in all women even with fewer cases examined in the stratification analysis. In contrast, no associations were observed for women aged ≥55 years with any defined models (online suppl. Table 3).

Discussion

In the present study of 1,432 adult CAPD patients, we demonstrated that eosinophils were significantly elevated after PD initiation and that being male and higher EOC

Table 3. Death-censored technique failure for early-stage eosinophilia and EOC stratified by gender

	Model	Men HR (95% CI)	*p* value	Women HR (95% CI)	*p* value
Noneosinophilia	–	(Ref.)	–	(Ref.)	–
Eosinophilia[a]	Model 1[b]	1.23 (0.86, 1.75)	0.258	2.37 (1.47, 3.83)	<0.001[c]
	Model 2[d]	1.21 (0.82, 1.78)	0.331	2.73 (1.58, 4.71)	<0.001[c]
	Model 3[e]	1.22 (0.75, 1.99)	0.430	2.24 (1.07, 4.70)	0.033[f]
EOC,[g] per 100 cells/μL increased	Model 1[b]	1.09 (1.02, 1.16)	0.006[h]	1.20 (1.10, 1.30)	<0.001[c]
	Model 2[d]	1.09 (1.01, 1.16)	0.021[f]	1.22 (1.10, 1.35)	<0.001[c]
	Model 3[e]	1.07 (0.97, 1.17)	0.196	1.29 (1.10, 1.51)	0.002[h]

CI, confidence interval; HR, hazard ratio; PET, peritoneal equilibration test; CVD, cardiovascular disease; ESRD, end-stage renal disease; D/PCr, dialysate-to-plasma ratio of creatinine; CRP, C-reactive protein; DM, diabetes mellitus; EOC, eosinophil count; PD, peritoneal dialysis. [a] Early-stage eosinophilia was defined as eosinophils fraction of leukocytes >5% at 1 or 3 months after PD, initiation. Models for eosinophilia with noneosinophilia as the reference group. [b] Univariate model. [c] $p < 0.001$. [d] Adjusted for age and body mass index. [e] Adjusted for Model 2 covariates and EOC at baseline, 4-h D/PCr of the PET, high-sensitivity CRP, systolic pressure, CVD history, DM, and cause of ESRD. [f] $p < 0.05$. [g] Models for each 100 cells/μL increased in EOC. [h] $p < 0.01$.

at baseline were risk factors of early-stage eosinophilia after PD initiation. Our primary finding was that in the early stage of dialysis, higher eosinophils were associated with higher death-censored technique failure in PD patients independent of baseline EOC levels and other covariates. In the subgroup analysis, the association was observed in women, especially those aged <55 years, but not in men.

The results of this study indicated that eosinophils were significantly elevated after PD initiation and that the elevated EOC was continuous over 9 months. The long duration of increased EOC in PD patients indicated that in addition to allergic responses induced by injury from catheterization surgery or stimulation by dialysis equipment in the early stage, PD fluid and its additives (e.g., heparin and intraperitoneal antibiotics [14]) used in daily therapy also induced eosinophilic reactions. This explains why the biocompatibility of PD fluid has become the focus of research recently. Traditional lactate-based dialysates such as Dianeal have fewer biocompatible profiles compared with new products such as Physioneal, which has a more neutral pH, is partially bicarbonate-based, and is a low-glucose degradation product (GDP) concentration. The relatively low pH, hypertonicity, and GDP of traditional PD fluids might lead to the formation of advanced glycation end products (AGE), which can aggravate peritoneal toxicity [15]. Likewise, dialysate additives, plastics, or plasticizers from the PD catheter or dialysate bags deteriorate the nonphysiological situations [16, 17].

The peritoneal cavity is a major reservoir of eosinophils under homeostatic and inflammatory states [18] and where eosinophils become activated and cause effects on the peritoneum. Hypersensitivity and intraperitoneal inflammatory reactions induced by PD drive the activation of Th2 cells and other inflammatory cells [19, 20], releasing cytokines including IL-5, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-3, which trigger eosinophil proliferation, activation, and chemotaxis to the peritoneum [21]. There are several possible changes to the peritoneum induced by activated eosinophils. (1) Direct damage: eosinophils cause marked damage to host tissues via a nonspecific mechanism determined by their ability to produce and release toxic granules, including eosinophil cationic proteins (ECP), major basic proteins (MBP), and eosinophil peroxidase (EP) [22, 23]. (2) Increased vascular permeability: eosinophils can activate mast cells through interactions of IgE-FceRI and subsequently release inflammatory factors in traditional allergic reactions. This might increase peritoneal vascular permeability leading to high peritoneal transport status. (3) Promotion of chronic inflammatory states: persistent PD can lead to chronic inflammation in the peritoneum [24]. Eosinophils function as immunoregulatory cells participating in the activation of T cells and monocytes, which can lead to a

deterioration of the inflammatory state. When combined, these effects might explain the association of higher numbers of eosinophils with higher technique failure observed in this study.

Interestingly, our study indicated gender heterogeneity related to the quantity and quality of eosinophils. We found that being male was a significant risk factor for eosinophilia after PD initiation and that before dialysis, the percentage of eosinophilia was also higher in men compared with women (19.9 vs. 14.1%, $p = 0.005$). EOC in men and women showed significant differences both before and after dialysis (190.0 vs. 130.0/μL, $p < 0.001$; 239.3 vs. 161.9/μL, $p < 0.001$, respectively) in our study. This is consistent with studies of eosinophils in a healthy population, predialysis CKD patients, and HD patients, all of which reported EOC was higher in men than in women [11, 25, 26]. These results indicate that gender itself contributes to the different domain value of EOC instead of the effect caused by PD therapy, suggesting gender should be considered when defining the "normal" values of EOC.

Our study also showed the association of increased EOC with technique failure in women but not in men even though the EOC in women was relatively lower than that in men both before and after PD initiation. This association with women suggests the potential effect of gender hormones in hypersensitive conditions. Furthermore, estrogens act as enhancers of humoral responses and mast cell reactivity, which further activate eosinophils [27]. In addition, estrogens enhance eosinophilic degranulation and increase the expressions of type 2 and type 3 histamine receptors [28], thus exacerbating direct damage of the peritoneum. Surprisingly, even though older age was a significant risk factor for technique failure in women (with each 1 year increase, HR: 1.021; 95% CI: 1.005–1.037; $p = 0.009$), the significant association of eosinophilia with technique failure was only observed in women aged <55 years but not in women aged ≥55 years. Similar results were reported for HD patients, which indicated that a higher EOC was more likely to be associated with mortality in younger patients [11]. Together, these data consolidate our hypothesis that estrogen has a role on the function of eosinophils and thus explains in part the differences observed between males and females with eosinophilia.

Furthermore, our data showed that D/PCr in male PD patients was significantly higher than that in female patients (0.73 vs. 0.68; $p < 0.001$), suggesting a higher peritoneal transport function in men, which is consistent with our previous study [29]. A previous study reported microinflammation of the peritoneum led to a higher peritoneal transport rate and that CRP was an indicator of microinflammation and therefore peritoneal transport function [30], which was similar between men and women in our study (1.82 vs. 1.26; $p = 0.211$). Interestingly, our data showed that male patients had a higher EOC and higher D/PCr compared with female patients, suggesting EOC might be a more sensitive indicator than CRP for predicting peritoneal transport function and intraperitoneal inflammation, which is further supported by the positive association between D/PCr and EOC ($r = 0.110$, $p = 0.001$) in the bivariate correlation test. Further studies are needed to confirm this.

The strengths of our study included the prospectively data-collected cohort having a large number of CAPD patients and the correlation between eosinophil level and technique failure was examined for both overall patients and those stratified by gender. This study had several limitations. First, because of the observational design of our study, the association does not suggest causality. Moreover, because we did not count eosinophils in PD fluid, the relationship between eosinophils in peripheral blood and in PD fluid could not be analyzed and the possible direct effect of eosinophils on the peritoneum could not be interpreted. In addition, we did not obtain data for IgE and estrogen levels, history of parasitic infections, and use of PD fluid additives or medications inducing changes in EOC.

In conclusion, our study found that higher EOC was associated with higher death-censored technique failure in PD patients, which was highly significant in women. This robust association suggests that early extreme elevations of eosinophils after PD initiation should be a concern, especially for female patients. Further studies are needed to fully understand the underlying mechanisms involved and the value of increased EOC as an indicator of intraperitoneal inflammation and as a prognostic marker for patient technique failure in PD therapy.

Statement of Ethics

All participants provided written informed consent. The study was approved by the First Affiliated Hospital of Sun Yat-sen University Institutional Review Boards (2016; No. 215).

Conflict of Interest Statement

On behalf of all authors, the corresponding author states that there are no conflicts of interest to declare.

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Author Contributions

X.W. and J.Y.Y. conceived and designed the study. J.Y.Y. was involved in analyses and interpretation of data and drafting manuscript. J.J.F., L.F., C.Y.Y., and J.X.L. performed data collection. X.W., H.P.M., and X.Y. were involved in manuscript revision and performed overall supervision.

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