Original Article

Comparison of risk of peritoneal dialysis-associated peritonitis between roxadustat and recombinant human erythropoietin in peritoneal dialysis patients: a retrospective comparative cohort study

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Background: Roxadustat and recombinant human erythropoietin (rhuEPO) have been approved for the treatment of renal anemia in patients undergoing dialysis. The comparison of risk of peritoneal dialysis (PD)-associated peritonitis between roxadustat and rhuEPO in PD patients remains uncertain. We aimed to compare the risk of PD-associated peritonitis between roxadustat and rhuEPO and examine possible modifiers for the comparison in PD patients.

Methods: A total of 437 PD patients with renal anemia (defined as hemoglobin ≤10.0 g/dL) from 4 centers were selected. Participants were scheduled for follow-up every 1–3 months at each center. We compared differences in baseline characteristics by medication group and 1:1 matching group based on propensity scores. PD-associated peritonitis was defined according to the International Society for Peritoneal Dialysis guidelines. Univariable and multivariable Cox proportional hazard analyses were performed to compare the risk of PD-associated peritonitis between roxadustat and rhuEPO in PD patients. Propensity score matching method was used to examine the robustness of results.

Results: A total of 437 participants, including 291 in roxadustat group and 146 in rhuEPO group, were included in the current study, respectively. During a median follow-up of 13.0 (25th–75th, 10.0–15.0) months, PD-associated peritonitis occurred in 68 patients, including 26 of 291 (0.10 episodes per patient-year) patients in the roxadustat group and 42 of 146 (0.27 episodes per patient-year) patients in the rhuEPO group. Overall, compared to patients in the rhuEPO group, the roxadustat group (hazard ratio, 0.345; 95% confidence interval: 0.202–0.589) was associated with a lower risk of PD-associated peritonitis with adjustment of use of roxadustat medication, age, sex, hypertension status, diabetes status, dialysis vintage, serum potassium, hemoglobin, and albumin. Furthermore, the results were consistent with the propensity score analysis. None of the variables, including age, sex, body mass index, PD vintage, presence of residual renal function, hemoglobin, albumin, serum potassium, and C-reactive protein levels, significantly modified the associations.

Conclusions: Our study demonstrated that compared with rhuEPO, roxadustat may reduce the risk of PD-associated peritonitis in PD patients, highlighting the importance of roxadustat for the prevention of PD-associated peritonitis in PD patients.

Keywords: Roxadustat; peritoneal dialysis-associated peritonitis; peritoneal dialysis (PD)

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Introduction

Peritoneal dialysis (PD) is an important therapy for patients with end-stage kidney disease (ESKD) (1). PD-associated peritonitis is a common and severe complication of PD (2) and can result in technique failure (3), hospitalization (4), a switch to hemodialysis (5), increased mortality (6,7), and limited utilization of PD. PD-associated peritonitis was associated with impaired host peritoneal, reduced mesothelial defense capacity and microbial invasion into the peritoneum. Previous study found that various factors such as contamination of dialysis manipulations, exit site and/or catheter tunnel infection, basal gastrointestinal lesions, constipation, hypoproteinemia, hypokalemia, and hypokalemia were associated with higher risk of PD-associated peritonitis (8). The peritonitis rates varied between countries, ranging from 0.26 episodes/patient-year in the United States to 0.40 episodes/patient-year in Thailand (9). Although multiple strategies have been developed to reduce the risk of PD-associated peritonitis (10,11), it remains a serious problem for PD patients. Therefore, it is important to identify more strategies for preventing PD-associated peritonitis in PD patients.

Hypoxia-inducible factor (HIF), a regulator for detecting and adapting to cellular oxygen levels, can transcriptionally activate genes modulating oxygen homeostasis and metabolic activation (12). HIF has also been reported to be implicated in the regulation of inflammation (13) and to be protective in inflammation of intestinal (14), pulmonary (15), and kidney injuries (16,17). Roxadustat, an oral HIF prolyl hydroxylase inhibitor (HIF-PHI) that can reversibly inhibit degradation and induce stabilization and transcription of HIF, stimulate erythropoiesis, and regulate iron metabolism (18), has been approved for the treatment of renal anemia in patients with chronic kidney disease (CKD) who are either dialysis-dependent (DD) (19,20) or are not DD (21,22). Thus, it is speculated that roxadustat may protect against PD-associated peritonitis in PD patients via regulation of inflammatory response. However, no studies have demonstrated the association between roxadustat and the risk of PD-associated peritonitis in PD patients. One single-center, retrospective study of 60 initial PD patients with renal anemia found that C-reactive protein (CRP) levels in the roxadustat group were significantly lower than in the recombinant human erythropoietin (rhuEPO) group after 40 weeks of treatment (23). However, another single-center, self-controlled study of 55 continuous ambulatory PD patients with renal anemia and erythropoietin (EPO) hyporesponsiveness showed that the median high-sensitivity CRP level and other inflammation-related indicators were not significantly different from baseline values after 12 weeks of roxadustat treatment (24).

To address the discrepancies mentioned above, the present study was conducted to compare the risk of PD-associated peritonitis between roxadustat and rhuEPO in patients undergoing PD through a multicenter cohort study in China. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5050/rc).

Methods

Study population and design

The current multicenter, retrospective comparative cohort study was performed in 4 centers (Nanfang Hospital, Southern Medical University, Shunde Hospital, Southern Medical University, Nanhai People's Hospital of Foshan, and the Affiliated Donghua Hospital of Sun Yat-sen University). All patients undergoing PD ≥3 months with renal anemia [defined as hemoglobin (Hb) ≤10.0 g/dL] at the above centers between January 1, 2019 and May 30, 2022 were recruited. Patients were excluded if they were under 18 years of age, lost to follow-up, complicated with chronic infection or malignant tumor, combined with hemodialysis, or lost to follow-up more than 3 times per year during the study period.

Patients were divided into 2 groups according to the antirenal anemia medication they were taking at baseline: roxadustat group (n=291) and rhuEPO group (n=146). Patients in the roxadustat group had not received roxadustat previously and must not have received rhuEPO treatment within 1 week of enrollment. The patients in the rhuEPO group were only recruited from Shunde Hospital, Southern

Medical University. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the research ethics committee of Shunde Hospital, Southern Medical University (No. 20201215) and informed consent was taken from all individual participants.

The starting dose of roxadustat, taken 3 times a week orally, was 100 mg in patients weighing 45 to <60 kg and 120 mg in patients weighing ≥60 kg. The follow-up dose was adjusted according to the patient's Hb level at that time and degree of Hb change over the past 4 weeks to maintain Hb levels at 10–12 g/dL. Patients in the rhuEPO group continued with their existing dose. The follow-up dose of rhuEPO was adjusted based on the patient's Hb level, rhuEPO dose at that time, and treatment response to maintain Hb levels at 10–12 g/dL. PD training was conducted by experienced and educated physicians and nurses.

Data collection, measurements, and follow-up

All data, which were obtained from a review of medical records, were collected at enrollment by a group of experienced doctors and research nurses. Potential confounders that were known to be traditional or suspected PD-associated peritonitis risk factors were recorded, including demographic information (center, age, sex, height, weight, hypertension status, and diabetes status), medication records, dialysis vintage, ultrafiltration volume, blood pressure (BP), 24-hour urine volume, urea clearance index (KT/V), and biochemical data. Laboratory parameters included serum creatinine, blood urea nitrogen, uric acid, CRP, white blood cell count, hemoglobin, neutrophil count, potassium, intact parathyroid hormone (iPTH), albumin, prealbumin, serum iron, ferritin, fasting glucose, total cholesterol, triglycerides, and B-natriuretic peptide (BNP). BP measurement was taken before PD sessions after 10 minutes of rest in a supine decubitus position. Height and weight were measured following a standard procedure with calibrated instruments. Body mass index (BMI) was calculated as weight (kg) by height squared (m^2). Fasting venous serum specimens were sampled before PD sessions. Presence of residual renal function (RRF) was defined as 24-hour urine volume ≥100 mL/24 hours.

Participants were scheduled for follow-up every 1–3 months at each center and provided biological samples and latest demographic information. The patients were asked to report back if they experienced cloudy effluent or abdominal pain. Previous study indicated that the peritonitis rates ranged from 0.26 episodes/patient-year in the United States to 0.40 episodes/patient-year in Thailand (9), therefore we had a sufficient sample size to observe between-group variance. Patient follow-up data were collected until PD-associated peritonitis occurred or until May 30 2022 or PD withdrawal.

Study outcomes

The study outcome was PD-associated peritonitis. According to the International Society for Peritoneal Dialysis (ISPD) guidelines (8), the diagnosis of PD-associated peritonitis requires any 2 of the following features: (I) clinical features consistent with peritonitis, i.e., abdominal pain and/or cloudy dialysis effluent; (II) dialysis effluent white cell count >100/μL or $>0.1\times10^9$/L (after a dwell time of at least 2 hours), with >50% polymorphonuclear cells; and (III) positive dialysis effluent culture.

Statistical analysis

Baseline characteristics are presented as means ± standard deviations (SDs) or median [interquartile range (IQR)] for continuous variables, and proportions for categorical variables. Two-sample *t*-test, Kruskal-Wallis rank sum test, or chi-square tests were used to compare differences in baseline characteristics by medication group and 1:1 matching group based on propensity scores.

The patients in the rhuEPO group were only recruited from Shunde Hospital, Southern Medical University, thus analysis was additionally conducted among the patients only recruited in this center using propensity score matching method. The propensity score was generated using a multivariable logistic-regression model, with the medication taken by patients as the dependent variable and variables that might affect medication selection or incident PD-associated peritonitis as covariates, including age, sex, dialysis vintage, hypertension status, diabetes status, BMI, presence of RRF, systolic BP (SBP), diastolic BP (DBP), serum CRP, serum potassium, serum hemoglobin, and albumin. Participants in the 2 groups with different treatment were matched 1:1 based on propensity scores. Nearest-neighbor matching with caliper distance of 0.02 was used for the matching. Kaplan-Meier curves were constructed to evaluate cumulative hazard of PD-associated peritonitis between the 2 groups, and group differences were assessed by log-rank tests in both the unmatched and matched cohorts. Univariate cox proportional hazard analysis was used to evaluate the risk factors for

PD-associated peritonitis in PD patients, including use of roxadustat medication. Covariates with P<0.05 on univariate analysis and conventional confounders related to PD-associated peritonitis were included in the multivariate regression model, including use of roxadustat medication, age, sex, hypertension status, diabetes status, dialysis vintage, serum potassium, hemoglobin, and albumin. We further explored through stratified analyses and interaction testing whether the comparison of risk of PD-associated peritonitis between roxadustat and rhuEPO varied by age, sex, PD vintage, BMI, presence of RRF, hemoglobin, albumin, serum potassium, and serum CRP levels.

To examine the robustness of our findings, we also conducted several sensitivity analyses. First, the analyses were repeated after propensity score matching. Second, to avoid reverse causation, we repeated the analyses after excluding participants who experienced PD-associated peritonitis within the first 3 months of follow-up.

All statistical analyses were performed using SPSS, version 24.0 (IBM, Armonk, New York, USA) and Rstudio software, version 4.2.0 (http://www.R-project.org/). Two-sided P values <0.05 were considered statistically significant.

Results

Characteristics of study participants

As shown in Figure S1, a total of 437 participants were included in the current study (roxadustat group, n=291; rhuEPO group, n=146). The mean age was 49.9±13.8 years, and median dialysis vintage was 31.0 (25th–75th, 17.0–54.5) months. A total of 250 (60.4%) of the participants were male. After propensity score matching, 246 patients (123 in each group) were included in the propensity score analysis.

Table 1 shows the baseline characteristics of patients from the roxadustat and rhuEPO groups before and after propensity score matching. Patients in the roxadustat group had higher CRP and fasting glucose levels and had lower hemoglobin, Ipth, albumin, prealbumin, and total cholesterol levels. In addition, patients in the roxadustat group had a higher prevalence of hypertension and diabetes at baseline. Generally, characteristics were well-balanced between the 2 groups after propensity score matching.

Comparison of risk of peritoneal dialysis-associated peritonitis between roxadustat and rhuEPO in PD patients

During a median follow-up of 13.0 (25th–75th, 10.0–15.0) months, PD-associated peritonitis occurred in 68 patients, including 26 of 291 (0.10 episodes per patient-year) patients in the roxadustat group and 42 of 146 (0.27 episodes per patient-year) patients in the rhuEPO group.

Kaplan-Meier analysis demonstrated that the cumulative incidence of PD-associated peritonitis in the roxadustat group was significantly lower than that of the rhuEPO group among all patients (log-rank P<0.001) (*Figure 1*). After propensity score matching, the roxadustat group continued to present a significantly lower risk of PD-associated peritonitis than the rhuEPO group (*Figure 2*). The univariate Cox proportional-hazards model showed that factors including the use of roxadustat medication, diabetes status, and serum albumin level were independent risk factors for PD-associated peritonitis. In the multivariate Cox proportional-hazards model, compared to the rhuEPO group, patients in the roxadustat group [hazard ratio (HR), 0.345; 95% confidence interval (CI): 0.202–0.589] was associated with a lower risk of PD-associated peritonitis (*Table 2*). After propensity score matching, similar results were also found (*Table 3*). In the sensitivity analyses, the results were similar after excluding incident cases that occurred within the first 3 months of follow-up (Table S1).

Stratified analyses by potential effect modifiers

We performed further stratified analyses to assess whether the comparison of risk of PD-associated peritonitis between roxadustat and rhuEPO in PD patients varied by other variables (*Figure 3*). None of the variables, including age (median, <50 *vs.* ≥50 years), sex (male *vs.* female), PD vintage (median, <30 *vs.* ≥30 months), BMI (<24 *vs.* ≥24 kg/m^2), presence of RRF (no *vs.* yes), hemoglobin (<11 *vs.* ≥11 g/dL), albumin (<35 *vs.* ≥35 g/L), serum potassium (<3.5 *vs.* ≥3.5 mmol/L), and serum CRP (<5.0 *vs.* ≥5.0 mg/L) significantly modified the comparison of risk of PD-associated peritonitis between roxadustat and rhuEPO in PD patients (*Figure 3*). Although the P value for interactions for diabetes (no *vs.* yes) was less than 0.05, this result may not have significant clinical implications given multiple testing and similar directionality of the associations.

Discussion

In this study, we found that roxadustat was associated with lower risk of PD-associated peritonitis in PD patients, and the results were consistent in the propensity scores analysis.

Table 1 Baseline characteristics of study participants by treatment group before and after propensity score matching*

Variables	Before propensity score matching			After propensity score matching		
	rhuEPO group (N=146)	Roxadustat group (N=291)	P value	rhuEPO group (N=123)	Roxadustat group (N=123)	P value
Age, years	50.0±14.4	50.3±13.5	0.792	50.0±14.5	49.4±13.2	0.751
Male, n (%)	79.0 (53.7)	179.0 (61.5)	0.119	64.0 (52.0)	61.0 (49.6)	0.702
BMI, kg/m^2	22.0±3.4	22.6±3.3	0.103	22.0±3.4	22.8±3.4	0.067
SBP, mmHg	140.2±18.8	141.2±18.1	0.605	136.6±11.6	134.3±14.9	0.739
DBP, mmHg	85.3±13.1	85.5±12.5	0.890	86.3±12.8	84.4±9.9	0.963
Diabetes, n (%)	23.0 (15.8)	69.0 (24.0)	0.048	20.0 (16.3)	31.0 (25.2)	0.084
Hypertension, n (%)	131.0 (89.7)	279.0 (96.9)	0.002	113.0 (91.9)	119.0 (96.7)	0.099
PD vintage, months	33.0 (18.8, 61.3)	30.0 (14.8, 50.0)	0.086	30.0 (18.0, 57.0)	32.0 (17.0, 53.0)	0.803
24-h urine volume, mL/24 h	300.0 (0.0, 800.0)	350.0 (20.0, 800.0)	0.398	300.0 (0.0, 800.0)	300.0 (0.0, 625.0)	0.965
KT/V	2.1 (1.7, 2.5)	1.8 (1.5, 2.1)	<0.001	2.0 (1.7, 2.4)	1.8 (1.6, 2.2)	0.039
UF volume, mL/24 h	600.0 (300.0, 900.0)	500.0 (300.0, 850.0)	0.684	566.4±536.3	531.0±467.5	0.604
Laboratory results						
Serum creatinine, μmol/L	1,015.5±351.9	1,039.9±334.5	0.425	1,026.0±352.8	1,005.3±324.9	0.632
Blood urea nitrogen, mmol/L	21.1±8.6	22.9±9.4	0.095	20.6±7.4	19.2±6.6	0.021
C-reactive protein, mg/L	7.4±12.1	12.1±25.3	0.010	7.0±10.9	4.3±4.7	0.356
White blood cells, 10^9/L	7.3±2.0	7.2±2.1	0.475	6.8±1.7	6.6±1.8	0.133
Hemoglobin, g/L	103.3±22.8	93.7±20.0	<0.001	100.8±22.2	101.7±19.9	0.715
Neutrophil, 10^9/L	4.9±1.7	4.7±1.7	0.286	4.5±1.5	4.3±1.5	0.150
Potassium, mmol/L	4.1±0.7	4.1±0.7	0.907	4.1±0.6	4.1±0.7	0.815
iPTH, pg/mL	413.1 (227.7, 757.9)	336.1 (179.3, 637.2)	0.016	444.8 (295.7, 1,062.3)	410.0 (271.2, 816.6)	0.338
Albumin, g/L	37.3±4.5	35.5±4.8	<0.001	36.9±4.4	37.7±4.5	0.466
Prealbumin, mg/L	361.2±85.6	328.1±117.6	0.032	358.2±88.8	361.2±108.1	0.830
Serum iron, μmol/L	12.1±5.6	12.4±7.4	0.646	12.9±6.4	12.8±6.3	0.159
Ferritin, μg/L	251.1±186.7	284.7±440.3	0.446	246.2±203.6	250.2±296.7	0.087
Fasting glucose, mmol/L	5.2±1.5	6.0±2.1	<0.001	5.3±1.4	5.6±1.5	<0.001
Total cholesterol, mmol/L	5.0±1.3	4.5±1.9	<0.001	5.2±1.2	4.7±1.4	0.018
Triglycerides, mmol/L	1.7±1.2	1.7±1.6	0.140	1.7±0.9	2.2±2.8	0.999
BNP, ng/L	950.3±4,686.3	284.9±528.0	0.462	212.3±350.1	206.1±371.4	0.226

*, continuous variables are presented as mean ± SD or median (25th percentile–75th percentile); category variables are presented as n (%). rhuEPO, recombinant human erythropoietin; BMI, body mass index; SBP, systolic BP; DBP, diastolic BP; BP, blood pressure; PD, peritoneal dialysis; KT/V, urea clearance index; UF volume, ultrafiltration volume; iPTH, intact parathyroid hormone; BNP, B-natriuretic peptide.

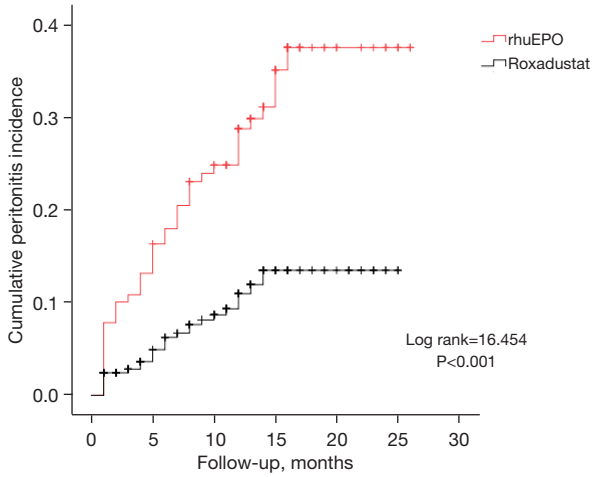

Figure 1 Kaplan-Meier curves of cumulative hazards of PD-associated peritonitis in PD patients by treatment (roxadustat *vs.* rhuEPO) before propensity score matching. PD, peritoneal dialysis; rhuEPO, recombinant human erythropoietin.

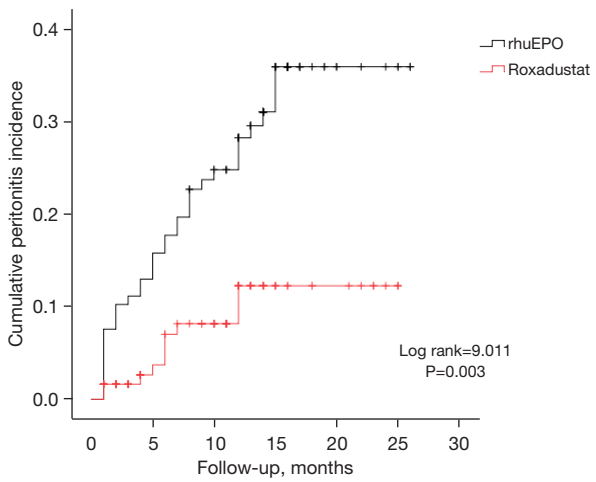

Figure 2 Kaplan-Meier curves of cumulative hazards of PD-associated peritonitis in PD patients by treatment (roxadustat *vs.* rhuEPO) after propensity score matching. PD, peritoneal dialysis; rhuEPO, recombinant human erythropoietin.

Previous studies have shown the role of HIF in regulating inflammatory response (12,13) and the benefit of roxadustat on renal anemia in dialysis patients as a type of HIF-PHI (18,25). However, no studies have demonstrated the association between roxadustat and the risk of PD-associated peritonitis in PD patients. One single-center, retrospective observational study of 60 initial PD patients with renal anemia found that CRP levels in the roxadustat group were significantly lower than in the rhuEPO group after 40 weeks of treatment (23). However, another single-center, self-controlled study of 55 continuous ambulatory PD patients with renal anemia and EPO hyporesponsiveness showed that the median high-sensitivity CRP level and other inflammation-related indicators, including white blood cell (WBC) counts, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio, were not significantly different from baseline values after 12 weeks of roxadustat treatment (24). Both studies were limited by a small sample size and short follow-up intervention period. Thus, whether roxadustat can protect against PD-associated peritonitis in PD patients remains unclear. Our study provided an opportunity to evaluate the association between roxadustat and the risk of PD-associated peritonitis in PD patients through a multicenter cohort study in China with a comprehensive stratified analysis of a number of important confounders.

Our study provided new insights. We firstly found that roxadustat was associated with lower risk of PD-associated peritonitis in PD patients. Previous studies have demonstrated the potential mechanisms that might explain the association between roxadustat and risk of PD-associated peritonitis in PD patients (12,13,26). Hypoxia is a common microenvironmental feature in the inflammatory process (26). HIF, a heterodimeric transcription factor composed of an oxygen dependent α subunit (HIF-1α, HIF-2α, and HIF-3α) and a constitutively expressed β subunit, is the master regulator of the adaptive response to hypoxia (12). HIF is also a significant regulator of the development, differentiation, and function of various types of immune cells and therefore plays an essential role in the development of infections (13). HIF-α can be activated through oxygen-dependent and oxygen-independent pathways, including cytokines, microorganisms, and bacterial components, ultimately leading to the transcription of genes implicated in the control of metabolism, angiogenesis, apoptosis, and cellular stress (13,27). HIF-1α increases macrophage aggregation, invasion, and motility and positively regulates cytokine production (28). Furthermore, HIF-1α increases intracellular bacterial killing by macrophages (29), stimulates the production of nitric oxide (12), and regulates the production of critical immune effector molecules, including granule proteases, antimicrobial peptides, and tumor necrosis factor α (TNF-α) (13). A previous study found that mice lacking HIF-1α in their myeloid cells showed decreased bactericidal activity and could not restrict the systemic spread of

Table 2 Risk factors of PD-associated peritonitis in PD patients before propensity score matching

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)	1.015	0.997–1.032	0.095	1.003	0.985–1.020	0.775
Male	0.926	0.572–1.500	0.755	1.065	0.649–1.749	0.803
Use of roxadustat medication	0.376	0.229–0.617	<0.001	0.345	0.202–0.589	<0.001
Diabetes	1.773	1.050–2.995	0.032	1.489	0.841–2.635	0.172
Hypertension	0.786	0.316–1.956	0.605	1.008	0.389–2.610	0.987
PD vintage (months)	0.992	0.983–1.001	0.099	0.994	0.985–1.003	0.180
BMI (kg/m^2)	0.964	0.885–1.049	0.396			
24-h Urine volume (mL/24 h)	1.000	1.000–1.001	0.633			
Presence of RRF	0.699	0.471–1.657	0.699			
UF volume (mL/24 h)	1.000	1.000–1.001	0.175			
KT/V	1.152	0.849–1.564	0.364			
Serum creatinine (μmol/L)	1.000	0.999–1.000	0.278			
BUN (mmol/L)	0.991	0.964–1.019	0.522			
C-reactive protein (mg/L)	0.996	0.982–1.010	0.578			
White blood cell (10^9/L)	0.972	0.863–1.094	0.636			
Hemoglobin (g/L)	1.008	0.997–1.019	0.166	1.007	0.995–1.019	0.261
Neutrophil (10^9/L)	1.003	0.855–1.177	0.972			
Potassium (mmol/L)	0.838	0.590–1.192	0.326	0.859	0.592–1.245	0.422
iPTH (pg/mL)	1.000	1.000–1.001	0.913			
Albumin (g/L)	0.941	0.897–0.987	0.012	0.927	0.879–0.978	0.005
Prealbumin (mg/L)	1.000	0.998–1.003	0.886			
Serum iron (μmol/L)	0.983	0.944–1.022	0.385			
Ferritin (μg/L)	1.000	1.000–1.001	0.613			
Fasting glucose (mmol/L)	1.022	0.900–1.160	0.741			
Total cholesterol (mmol/L)	1.022	0.899–1.163	0.736			
Triglycerides (mmol/L)	1.069	0.912–1.253	0.409			

PD, peritoneal dialysis; HR, hazard ratio; CI, confidence interval; BMI, body mass index; RRF, residual renal function; UF volume, ultrafiltration volume; KT/V, urea clearance index; BUN, Blood urea nitrogen; iPTH, intact parathyroid hormone.

infection (30). HIF-1α can also influence T-cell-mediated inflammation by being involved in cluster of differentiation 4 (CD4) T cell and CD8 T cell polarization and activation (31-33). Moreover, HIF-2α deficiency impairs the ability of macrophages to respond and migrate to sites of inflammation *in vivo* (34). In addition, constipation has been reported to be associated with peritonitis in PD patients (35) due to the translocation of bacteria from the gut (36,37). The intestinal epithelium is in a continuous state of transient oxygen deprivation (38). HIF-PHI treatment ameliorated intestinal inflammation with reduction of inflammatory lesions and proinflammatory cytokines (14,39,40). However, future studies are warranted to further examine the underlying mechanisms of roxadustat and the

Table 3 Risk factors of PD-associated peritonitis after propensity score matching

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)	1.017	0.996–1.039	0.114	1.006	0.985–1.028	0.573
Male	1.133	0.626–2.047	0.680	1.165	0.637–2.131	0.621
Use of roxadustat medication	0.357	0.176–0.726	0.004	0.409	0.198–0.844	0.016
Diabetes	1.827	0.954–3.500	0.069	1.632	0.817–3.260	0.165
Hypertension	0.659	0.236–1.845	0.428	0.796	0.261–2.420	0.687
PD vintage (months)	0.991	0.979–1.003	0.123	0.993	0.981–1.006	0.284
BMI (kg/m^2)	0.954	0.862–1.056	0.364			
24-h Urine volume (mL/24 h)	1.000	1.000–1.001	0.296			
Presence of RRF	1.046	0.479–2.285	0.911			
UF volume (mL/24 h)	1.000	1.000–1.001	0.266			
KT/V	1.235	0.851–1.790	0.266			
Serum creatinine (μmol/L)	1.000	0.999–1.000	0.349			
BUN (mmol/L)	1.000	0.966–1.035	0.985			
C-reactive protein (mg/L)	1.015	0.995–1.035	0.134			
White blood cell (10^9/L)	0.898	0.756–1.066	0.218			
Hemoglobin (g/L)	1.001	0.987–1.015	0.935	0.922	0.860–0.989	0.023
Neutrophil (10^9/L)	0.927	0.740–1.162	0.513			
Potassium (mmol/L)	0.795	0.518–1.221	0.295	0.881	0.570–1.361	0.568
iPTH (pg/mL)	1.000	1.000–1.001	0.592			
Albumin (g/L)	0.906	0.850–0.965	0.002	1.005	0.990–1.020	0.491
Prealbumin (mg/L)	0.998	0.994–1.001	0.203			
Serum iron (μmol/L)	0.973	0.919–1.030	0.341			
Ferritin (μg/L)	1.001	0.999–1.002	0.277			
Fasting glucose (mmol/L)	1.045	0.899–1.215	0.567			
Total cholesterol (mmol/L)	0.987	0.840–1.161	0.879			
Triglycerides (mmol/L)	0.962	0.747–1.238	0.764			

PD, peritoneal dialysis; HR, hazard ratio; CI, confidence interval; BMI, body mass index; RRF, residual renal function; UF volume, ultrafiltration volume; KT/V, urea clearance index; BUN, blood urea nitrogen; iPTH, intact parathyroid hormone.

risk of PD-associated peritonitis in PD patients.

Several potential limitations are worth mentioning. First, this was an observational study and our findings could not prove causality. Second, although a number of covariates had been included in the adjusted model, residual confounding effects from unmeasured or unknown factors could not be excluded. Third, the present study was conducted in Chinese PD patients, and therefore the generalizability of the results to other populations requires further consideration. Fourth, the patients in the rhuEPO group were only recruited from one center. Although sensitivity analysis was conducted using propensity score matching method, confounding effects from different centers cannot be completely avoided. Due to these limitations, additional studies are required to confirm our findings.

Conclusions

In summary, our study found that roxadustat was

Subgroups	Use of Roxadustat No. of events (%)	Use of rHuEPO No. of events (%)	Use of Roxadustat vs. Use of rHuEPO HR(95%CI)	P for interaction
Age, years				**0.386**
<50	10(8.2)	13(16.4)	0.414(0.129,1.323)	
≥50	15(13.7)	28(37.5)	0.383(0.149,0.986)	
Sex				**0.262**
Male	15(9.9)	23(29.6)	0.190(0.056,0.645)	
Female	11(11.2)	19(24.9)	0.799(0.305,2.092)	
Diabetes				**0.010**
Yes	9(17.0)	11(50.4)	0.434(0.104,1.808)	
No	17(8.7)	30(22.7)	0.456(0.192,1.082)	
PD vintage, months				**0.205**
<30	13(11.6)	21(27.8)	0.399(0.143,1.112)	
≥30	13(9.7)	20(25.5)	0.396(0.137,1.149)	
BMI, kg/m^2				**0.573**
<24	15(12.3)	23(22.1)	0.511(0.205,1.273)	
≥24	6(11.2)	7(18.7)	0.836(0.150,4.646)	
Presence of RRF				**0.854**
Yes	13(8.1)	19(20.2)	0.928(0.321,2.683)	
No	7(13.0)	7(17.2)	0.573(0.108,3.051)	
Hemoglobin, g/dL				**0.663**
<11	20(9.6)	26(27.5)	0.355(0.139,0.906)	
≥11	6(15.4)	14(24.5)	0.435(0.135,1.401)	
Albumin, g/L				**0.665**
<35	17(16.2)	15(38.9)	0.531(0.182,1.553)	
≥35	9(6.5)	25(22.1)	0.292(0.107,0.796)	
Potassium, mmol/L				**0.223**
<3.5	6(12.5)	7(29.8)	0.406(0.054,3.056)	
≥3.5	20(10.0)	33(25.7)	0.374(0.167,0.836)	
C-reactive protein, mg/L				**0.917**
<5.0	8(7.4)	25(25.2)	0.275(0.079,0.950)	
≥5.0	17(14.0)	14(27.6)	0.527(0.187,1.485)	

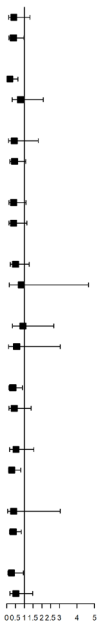

Figure 3 The relationship between roxadustat and the risk of PD-associated peritonitis in various subgroups[†]. [†], adjusted, if not stratified, for use of Roxadustat medication, age, sex, hypertension status, diabetes status, dialysis vintage, serum potassium, hemoglobin, and albumin at baseline. HR, hazard ratio; CI, confidence interval; PD, peritoneal dialysis; BMI, body mass index; RRF, residual renal function.

associated with lower risk of PD-associated peritonitis in PD patients. If further confirmed, our findings may provide some evidence for using roxadustat as a strategy for the prevention of PD-associated peritonitis in PD patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5050/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5050/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5050/coif). All authors report that this study was supported by the National Natural Science Foundation for Young Scholars of China (Grant No. 81800674), the Natural Science Foundation of Guangdong Province (Grant No. 2018A030310428), China Postdoctoral Science Foundation-funded project (Grant No. 2019M663006), the Science and Technology Project of Foshan (Grant No. 2020001005230), and the National Natural Science Foundation of China (Grant Nos. 81670647, 81873599, and 81900672). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the research

ethics committee of Shunde Hospital, Southern Medical University (No. 20201215) and informed consent was taken from all individual participants.

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Supplementary

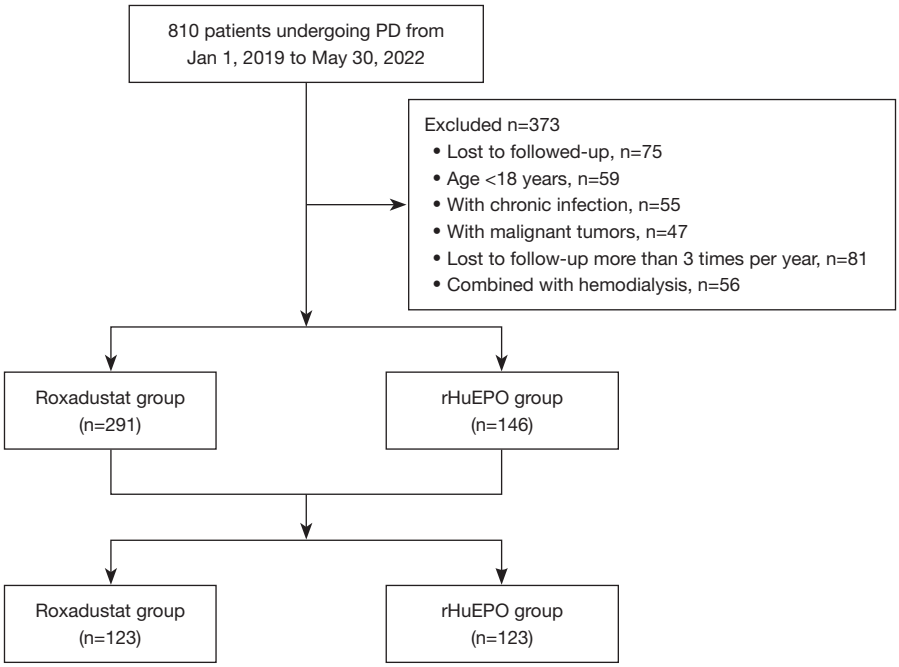

Figure S1 Flow chart of study participants.

https://dx.doi.org/10.21037/atm-22-5050

Table S1 Risk factors of PD-associated peritonitis before propensity score matching after excluding participants with PD-associated peritonitis within the first three months of follow-up

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Age (years)	1.018	0.999-1.036	0.063	1.008	0.985-1.032	0.494
Male	0.839	0.500-1.406	0.505	1.091	0.559-2.128	0.799
Use of Roxadustat medication	0.284	0.164-0.493	<0.001	0.375	0.177-0.793	0.010
Diabetes	1.715	0.974-3.021	0.062	1.877	0.895-3.935	0.096
Hypertension	0.853	0.309-2.357	0.759	0.834	0.239-2.917	0.777
PD vintage (months)	0.993	0.984-1.003	0.173	0.985	0.968-1.002	0.092
BMI (kg/m^2)	0.961	0.876-1.054	0.397			
24-h Urine volume (ml/24h)	1.000	1.000-1.001	0.388			
Presence of RRF	0.993	0.508-1.941	0.984			
UF volume (ml/24h)	1.000	1.000-1.001	0.147			
KT/V	1.175	0.874-1.579	0.286			
Serum creatinine (μmol/L)	1.000	0.999-1.000	0.316			
BUN (mmol/L)	0.988	0.959-1.018	0.442			
C-reactive protein (mg/L)	0.996	0.982-1.011	0.607			
White blood cell (10^9/L)	0.990	0.874-1.121	0.876			
Hemoglobin (g/L)	1.011	0.999-1.023	0.069	1.002	0.986-1.018	0.846
Neutrophil (10^9/L)	1.042	0.883-1.229	0.629			
Potassium (mmol/L)	0.791	0.544-1.151	0.220	0.883	0.531-1.471	0.634
iPTH (pg/ml)	1.000	1.000-1.001	0.695			
Albumin (g/L)	0.956	0.909-1.006	0.086	0.954	0.887-1.027	0.209
Prealbumin (mg/L)	1.000	0.997-1.003	0.999			
Serumiron (μmol/L)	0.987	0.947-1.028	0.516			
Ferritin (ug/L)	1.000	0.999-1.001	0.926			
Fasting glucose (mmol/L)	1.028	0.901-1.172	0.684			
Total cholesterol (mmol/L)	1.038	0.920-1.171	0.545			
Triglycerides (mmol/L)	1.108	0.943-1.302	0.214			

HR, hazard ratio; CI, confidence interval; PD, peritoneal dialysis; BMI, body mass index; RRF, residual renal function; UF volume, ultrafiltration volume; KT/V, urea clearance index; BUN, Blood urea nitrogen; iPTH, intact parathyroid hormone.

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