Original Article

Long-term efficacy, safety, and medication compliance of roxadustat on peritoneal dialysis patients with renal anemia affected by the COVID-19 pandemic: a retrospective study

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Background: Current studies have limited data on long-term treatment safety and medication compliance of roxadustat for renal anemia in peritoneal dialysis (PD) patients. We aimed to analyze the long-term efficacy, safety, and medication compliance of roxadustat in the treatment of renal anemia in patients with PD who discontinued recombinant human erythropoietin (rhEPO) treatment due to the corona virus disease 2019 (COVID-19) outbreak.

Methods: We retrospectively collected patients who were switched from rhEPO to roxadustat in our hospital due to the pandemic. The criteria for subject inclusion: aged >18 years with a dialysis vintage >3 months, without malignant tumor, no severe cardiovascular and cerebrovascular diseases, and not combined hemodialysis. Patients were followed up until the end of December 2021. Hemoglobin (Hb), red blood cell (RBC) and hematocrit (Hct) were recorded at baseline, month 1–12 and month 20, and iron parameters at baseline, 3, 6, 9, 12, and 20 months were collected. The Morisky Medication Adherence Scale-8 (MMAS-8) was used to score medication compliance during rhEPO treatment and roxadustat treatment, and adverse reactions occurred during treatment were collected. The efficacy and medication compliance of roxadustat were analyzed using Wilcoxon rank sum test or *t*-test.

Results: The median follow-up time was 21.1 (20.6, 21.7) months. After 1 month of treatment, the Hb level was significantly increased by 9.4 g/L (95% CI: 6.0–12.8 g/L) compared with the baseline, follow up at 20 months showed the Hb level had remained stable, increased by 20.7 g/L (95% CI: 15.9–25.4 g/L) compared with before treatment. At the beginning of treatment, total iron binding capacity increased, transferrin saturation and serum ferritin decreased, serum iron remained stable during treatment. During roxadustat treatment, no patient discontinued treatment due to the pandemic, and the Morisky score was improved compared with that during rhEPO treatment [5.75 (4.25, 6.00) *vs.* 6.75 (5.75, 7.00), P=0.000]. There were no serious adverse events associated with roxadustat were observed.

Conclusions: Roxadustat can effectively improve anemia and had good tolerance in patients undergoing PD who have difficult using rhEPO, and the medication compliance was better than rhEPO during the COVID-19.

Keywords: Peritoneal dialysis (PD); renal anemia; COVID-19; roxadustat

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Introduction

Renal anemia is a common complication of end-stage renal disease (ESRD) in patients undergoing peritoneal dialysis (PD), with an incidence of 53.5% (1), and affects the quality of life and survival prognosis of patients (2). The condition is mainly due to the insufficiency of erythropoietin (EPO) caused by renal dysfunction and the relative or absolute iron deficiency caused by iron metabolism disorders. Recombinant human erythropoietin (rhEPO), as the main treatment for renal anemia, is administered intravenously or subcutaneously. As most PD patients are treated in medical institutions, the breakout of corona virus disease 2019 (COVID-19) at the end of 2019, especially the measures taken against the pandemic, such as traffic control, closed-off community management, and home quarantine, affected the use of rhEPO to treat renal anemia in PD patients.

Roxadustat as the first oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), has been applied clinically in the treatment of renal anemia by promoting endogenous physiological concentration of EPO production, increasing EPO receptors on the surface of bone marrow pre-red blood cells, and promoting iron absorption and reuse (3-5). Its oral administration is more suitable for home treatment than rhEPO, especially during the COVID-19 pandemic. Although previous phase 3 trials in China confirmed the efficacy of roxadustat in patients who are undergoing long-term dialysis, only 22 PD patients included, and was not analyzed separately (6). Another randomized controlled trial by Besarab *et al.* included 12 PD patients (7). Recently, a randomized controlled trial of roxadustat in PD patients by Hou *et al.* included 86 patients, but the follow-up time only 24 weeks (8), it's not long enough to observe long-term efficacy and safety. Furthermore, there are few studies on medication compliance of roxadustat in PD patients. Therefore, further studies are needed to evaluate the long-term efficacy, safety, and compliance of roxadustat in PD patients.

This study retrospectively analyzed PD patients in our center who discontinued rhEPO treatment due to the COVID-19 pandemic and switched to roxadustat treatment. Follow up was for 20 months. The study evaluated the therapeutic efficacy and medication compliance to explore new alternatives and modalities for renal anemia treatment during the COVID-19 pandemic. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-555/rc).

Methods

Study design and patient selection

PD patients who were switch to roxadustat from rhEPO due to the impact of COVID-19 in the Department of Nephrology, Ningbo First Hospital from January 2020 to March 2020 were retrospectively reviewed. A total of 29 patients aged >18 years with a dialysis vintage >3 months were selected and followed up to Dec. 31, 2021. Patients with malignant tumor, severe cardiovascular and cerebrovascular diseases, or who combined hemodialysis were excluded. An increase in hemoglobin (Hb) >10 g/L from baseline is considered effective. Adverse events regarding roxadustat were collected from medical records. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Ningbo First Hospital (No. 2022RS076) and individual consent for this retrospective analysis was waived.

Study methods

Data collection

Demographic and clinical data, such as sex, age, height, weight, dialysis vintage, and primary disease, were collected, as were PD-related indicators such as weekly total urea clearance rate (t-Kt/V), total creatinine clearance rate (Ccr), and other PD-related indicators at baseline. During the follow-up process, termination of PD, discontinuation of medication for 1 week, or a change in the drugs under observation were regarded as the end point, and the data were treated as truncated data.

Laboratory indicators such as Hb, red blood cell (RBC) and hematocrit (Hct) were collected at baseline, 1 to 12, and 20 months, and iron parameters at baseline, 3, 6, 9, 12, and 20 months were collected. The Morisky Medication Adherence Scale-8 (MMAS-8) (9) was used to score medication adherence before and after treatment, with the full score of the scale as 8, a score of <6 is poor, and 6-8 is moderate, while scores of 8 points show good compliance.

Treatment

The starting dose of roxadustat [Fibrogen (China) Pharmaceutical Technology Development Co., Ltd.] was determined according to body weight and previous rhEPO dosage, 100 mg (45–60 kg) or 120 mg (≥60 kg) each time, and orally, three times per week (TIW). Medication was

Table 1 Clinical characteristics of peritoneal dialysis patients

Characteristic	Value
Male, n (%)	16 (55.2)
Age, years	51.6±13.4
BMI (kg/m^2)	22.18±2.61
Dialysis vintage, months	32.0 (12.0, 52.5)
Primary disease, n (%)	
Chronic glomerulonephritis	15 (51.7)
Diabetic kidney disease	9 (31.0)
Hypertensive kidney lesion	2 (6.9)
Other	3 (10.3)
Dialysis form	
CAPD	25
IPD	4
Systolic blood pressure (mmHg)	143±21
Diastolic blood pressure (mmHg)	81±12
t-Kt/V	2.05±0.38
Total Ccr (mL/min/1.73 m^2)	60.59±17.16
Serum creatinine (μmol/L)	968.9±350.1
Urea nitrogen (mmol/L)	18.7±5.3
Uric acid (μmol/L)	386.0±91.8
hsCRP (mg/L)	0.71 (0.50, 218)
Albumin (g/L)	34.8±3.6
Total cholesterol (mmol/L)	4.44±1.30
Triglyceride (mmol/L)	1.52±0.82
LDLC (mmol/L)	3.14±1.06
HDLC (mmol/L)	1.11±0.25
Glucose (mmol/L)	4.95 (4.19, 5.69)
PTH (pg/mL)	194.3 (146.2, 459.3)
Serum potassium (mmol/L)	4.2±0.6

The data are shown as mean ± SD or median with the 25–75% range. BMI, body mass index; CAPD, continuous ambulatory peritoneal dialysis; t-Kt/V, total dialysis clearance; Ccr, creatinine clearance rate; IPD, interrupted peritoneal dialysis; hsCRP, high sensitivity C reactive protein; LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; PTH, parathyroid hormone.

taken on an empty stomach or with food. Hb levels were monitored at monthly follow-up visits, and the dose of roxadustat was adjusted based on this. Whether or not to use iron therapy was determined according to the iron metabolism index and Hb level of the patient.

Statistical analysis

SPSS 24.0 software (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. The normality of the distribution of continuous variables was identified by the Kolmogorov-Smirnov test, and continuous variables are expressed as the mean ± SD (standard deviation) or median with the 25–75% range. The Wilcoxon rank sum test or *t*-test was used for pre-post comparisons, and the chi-square test was used to compare frequencies. A 2-sided P value <0.05 was considered to indicate statistical significance.

Results

Follow-up results and baseline clinical characteristics

A total of 29 patients were included, and as of December 31, 2021, the median follow-up time was 21.1 (20.6, 21.7) months. Among them, one patient was changed to hemodialysis because of ultrafiltration failure, one was changed to hemodialysis because of refractory peritonitis, one died because of myocardial infarction, and none of the other cases discontinued treatment or changed to rhEPO treatment. The baseline data are shown in *Table 1*.

Analysis of factors for changing to roxadustat treatment due to the pandemic

A total of 152 PD patients treated with rhEPO were followed up by our center before January 2020, and between January 2020 and March 2020, 29 patients were switched to roxadustat treatment. There were statistical differences in Hb level and residence between the roxadustat treatment group and continued rhEPO treatment group (P<0.05), but there was no statistical difference in educational level (P>0.05), as shown in *Table 2*.

Changes of Hb, RBC, and Hct before and after treatment

During treatment with rhEPO, the Hb level of 29 patients was 108±7 g/L (the average level in the 3 months before the interruption of rhEPO treatment), and the Hb level decreased to 95.1±10.1 g/L after the interruption of treatment due to the COVID-19 pandemic. After 1 month of roxadustat treatment, the Hb level was significantly increased by 9.4 g/L compared with the baseline (95% CI: 6.0–12.8 g/L, P=0.000), and the Hb level gradually

Table 2 Comparison of Hb level, residence, and education level between roxadustat group and continued rhEPO group

Variables	Roxadustat group, n (%)	Continued rhEPO group, n (%)	χ^2	P value
Hb level			9.005	0.003
≥100 g/L	9 (10.6)	76 (89.4)		
<100 g/L	20 (29.9)	47 (70.1)		
Residence			5.293	0.021
Rural	23 (25.0)	69 (75.0)		
City	6 (10.0)	54 (90.0)		
Education level			2.001	0.157
Below high school	19 (16.5)	96 (83.5)		
High school and above	10 (27.0)	27 (73.0)		

Hb, hemoglobin; rhEPO, recombinant human erythropoietin.

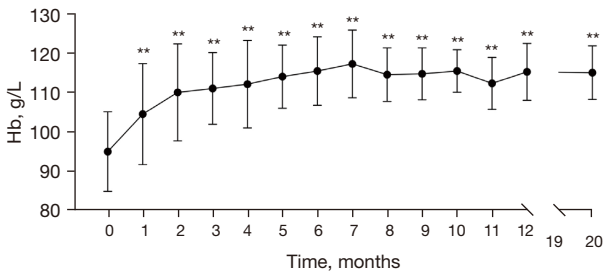

Figure 1 Changes in hemoglobin during roxadustat treatment. **, compared with the baseline, P<0.001. Hb, hemoglobin.

stabilized after 6 months of treatment. After 20 months of treatment, the Hb level increased by 20.7 g/L (95% CI: 15.9–25.4 g/L, P=0.000) compared with the baseline, and the RBC and Hct levels were increased compared with the baseline, as shown in *Figures 1*,*2*.

Changes of iron parameters during roxadustat treatment

After 3, 6, 9, 12, and 20 months of treatment, serum iron remained stable with an upward trend, but the difference was not statistically significant [12.9±4.7 μmol/L (0 m) *vs.* 14.5±9.8 μmol/L (20 m), P=0.440], while serum ferritin decreased compared with the baseline, and the difference was statistically significant [71.6 (25.1, 124.9) ng/mL (0 m) *vs.* 48.0 (13.2, 74.2) ng/mL (20 m), P=0.000]. While after 3 months of treatment, the transferrin saturation decreased, and the difference was statistically significant [18.5 (13.4, 23.4)% *vs.* 10.2 (8.2, 18.2)%, P=0.000], when the follow-up was continued for 6, 9, and 12 months, the transferrin saturation increased compared with the baseline, and the difference was not statistically significant. The total iron binding capacity increased from the baseline at 3 months of treatment (69.7±14.5 *vs.* 88.5±17.6 μmol/L, P=0.000), and there was no statistical difference from the baseline at 6, 9, 12, and 20 months of treatment (see *Table 3*).

Medication adherence before and after the COVID-19 pandemic

During rhEPO treatment, the Morisky score was 5.75 (4.25, 6.00), with no patient showing 8 points, while 8 patients showed 6–8 points, and 21 showed less than 6 points. After 6 months of roxadustat treatment, the Morisky score was 6.75 (5.75, 7.00) points, with 6 patients scoring 8 points, 15 with 6–8 points, and 8 patients had <6 points, and the difference was statistically significant (see *Figure 3*).

Serum lipids level and blood pressure before and after roxadustat treatment

After roxadustat treatment, total cholesterol and low-density lipoprotein cholesterol (LDLC) decreased compared with before treatment (3.14±1.06 *vs.* 2.32±0.62 mmol/L, P=0.000), but there was no statistical difference in triglyceride (1.52±0.82 *vs.* 1.20±0.67 mmol/L, P=0.284), high-density lipoprotein cholesterol (HDLC) (1.11±0.25 *vs.* 1.07±0.42 mmol/L, P=0.615), and blood pressure before and after treatment (143±21 *vs.* 139±21 mmHg, P=0.185; 79±12 *vs.* 80±11 mmHg, P=0.651) (see *Table 4*).

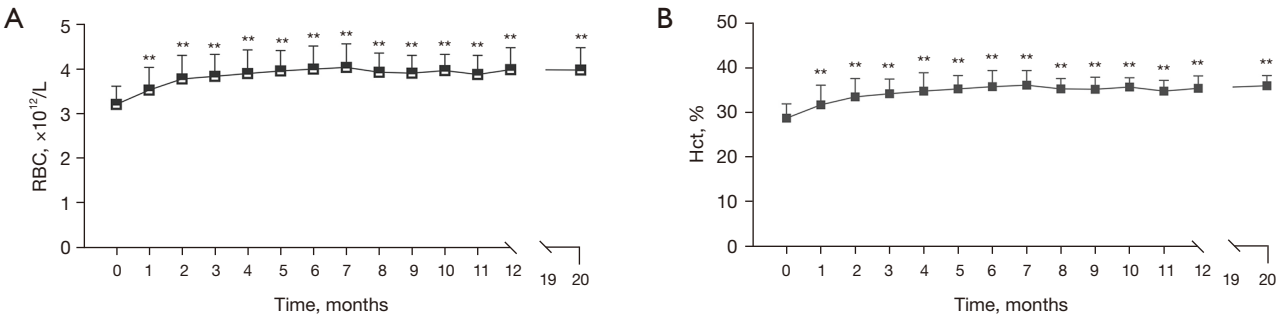

Figure 2 Changes in RBCs (A) and Hct (B) during roxadustat treatment. **, compared with the baseline, P<0.001. RBC, red blood cell; Hct, hematocrit.

Table 3 Changes in iron parameters

Month	Serum iron (μmol/L)	Serum ferritin (ng/mL)	Transferrin saturation (%)	Total iron binding capacity (μmol/L)
0	12.9±4.7	71.6 (25.1, 124.9)	18.5 (13.4, 23.4)	69.7±14.5
3	11.2±5.0	26.3 (12.7, 79.9)*	10.2 (8.2, 18.2)*	88.5±17.6*
6	14.4±6.5	37.1 (13.5, 136.1)	18.9 (14.0, 24.3)	71.3±15.0
9	13.2±5.3	42.2 (18.7, 111.0)*	20.5 (11.9, 27.6)	65.9±9.3
12	14.1±6.7	31.8 (14.5, 62.0)*	20.2 (12.7, 27.9)	69.4±9.9
20	14.5±9.8	48.0 (13.2, 74.2)*	15.6 (10.1, 31.8)	71.5±11.0

The data are shown as mean ± SD or median with the 25–75% range. *, compared with the baseline, P<0.001.

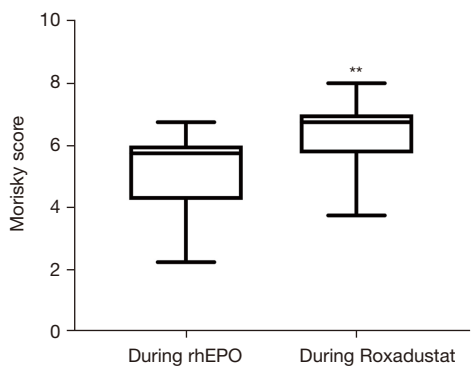

Figure 3 Morisky score before and after treatment. **, compared with the rhEPO treatment period, P<0.001. rhEPO, recombinant human erythropoietin.

Adverse effects during roxadustat treatment

During the treatment period, two patients were hospitalized due to PD-related peritonitis, of which one was cured after effective antibiotic treatment, and the other was switched to hemodialysis because of refractory peritonitis. The cause of peritonitis was analyzed as diarrhea. One patient developed pulmonary infection and recovered after treatment, and a gastrointestinal reaction occurred in another, which improved after gradual adjustment of the roxadustat dose. Two patients developed cardiac insufficiency, one of which was caused by ultrafiltration failure, and was later switched to hemodialysis. No serious adverse reactions related to roxadustat were observed.

Discussion

The repeated outbreaks of the COVID-19 pose challenges to the treatment of renal anemia in PD patients. Compared with hemodialysis (10), PD can be conducted at home, which is of benefit to patients who need to be quarantined during the pandemic. Some studies had recommended peritoneal dialysis as the preferred choice for renal replacement therapy during the COVID-19 pandemic (2,11,12). However, patients with renal anemia treated with rhEPO still require frequent visits to medical institutions for injections, which reduces the advantages of PD

Table 4 Serum lipids and blood pressure before and after roxadustat treatment

Variables	Before treatment	After treatment	P value
Blood pressure (mmHg)			
Systolic blood pressure	143±21	139±21	0.185
Diastolic blood pressure	79±12	80±11	0.651
Triglyceride (mmol/L)	1.52±0.82	1.20±0.67	0.284
Total cholesterol (mmol/L)	4.44±1.30	3.72±0.85	0.006
LDLC (mmol/L)	3.14±1.06	2.32±0.62	0.000
HDLC (mmol/L)	1.11±0.25	1.07±0.42	0.615

The data are shown as mean ± SD. LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol.

conducted in the home. During the most severe period of the pandemic, the anemia compliance rate of PD patients in our center was lower than before, and some patients had interruptions in treatment. This study analyzed the long-term efficacy and medication compliance of roxadustat treatment after rhEPO treatment was discontinued due to the pandemic, to explore a new model of renal anemia treatment in PD patients in the pandemic era.

The COVID-19 pandemic has had a profound impact on people's mental health (13,14). Fear of the virus and the impact of the quarantine measures were the main reasons for the reduction of follow-up of patients, and some discontinued rhEPO treatment. The Hb level of the 29 patients who discontinued rhEPO treatment in our center decreased by an average of 13±4 g/L compared with regular treatment, which significantly affected the anemia compliance rate. Compared with patients whose Hb level was still higher than 100 g/L after discontinuation of treatment and who lived in urban areas, the proportion of patients whose Hb level was lower than 100 g/L after discontinuation of treatment and who lived in rural areas, and these patients were more likely to switch to roxadustat. This is related to the greater inconvenience associated with rhEPO injection due to the pandemic in rural areas, and that patients with Hb levels below 100 g/L need more standardized treatment and have a greater fear of interruption of their treatment. Unlike rhEPO, which requires intravenous or subcutaneous injection and has the difficulty of cold chain storage, roxadustat has the advantages of oral administration and convenient storage, which explains why these patients are more willing to use it.

This study demonstrates that roxadustat is feasible and effective in the treatment of renal anemia during the COVID-19 pandemic. As an oral HIF-HPD inhibitor, roxadustat inhibits the degradation of HIF, enables the body to transcribe related genes under conditions of hypoxia, downregulates hepcidin levels, increases EPO, and increases erythropoietin receptor and transferrin receptors, playing an important role in improving anemia (4,5,15,16). Current studies have shown that roxadustat has a good effect on correcting anemia in both dialysis and non-dialysis patients (6,17). Zhu *et al.* conducted a self-controlled study on 113 patients with renal anemia on PD who were treated with roxadustat, and found their Hb levels at 1, 2 and 3 months were 97.6±18.4, 105.5±20.4, and 110.6±16.6 g/L, respectively. When the Hb was reviewed in the first month, the average increased 20.1±13.9 g/L (18). In addition, a randomized controlled trial of roxadustat in the treatment of PD patients with anemia by Hou *et al.* showed the Hb level in the roxadustat group was 11.5 g/dL after 24 weeks of treatment, an average increase of 2.5 g/dL from baseline (8). However, the follow-up time in these studies was not long, not exceeding 6 months. In our study, after 1 month of treatment, the Hb level increased significantly from baseline by 9.4 g/L (95% CI: 6.0–12.8 g/L), and after 12 months of treatment, the Hb level increased by 20.2 g/L (95% CI: 16.1–24.3 g/L) compared with the baseline. Followed up to 20 months, the Hb level remained stable, increased by 20.7 g/L (95% CI: 15.9–25.4 g/L) compared with the baseline, indicating roxadustat could correct anemia quickly and effectively, and the long-term effect is positive. However, it should be noted that during our follow-up, six patients had Hb levels higher than 130 g/L, which mainly occurred in the early follow-up period. This suggests greater attention should be paid to avoid rapid increases in Hb level during the roxadustat treatment, especially when adjusting the dose in the early stage.

Roxadustat can down-regulate hepcidin levels and

improve iron metabolism. A study by Hirai *et al.* of the treatment of anemia and iron metabolism in PD patients showed it reduced serum ferritin and transferrin saturation (19), while Akizawa *et al.* used roxadustat in PD patients and analyzed the iron metabolism after treatment and found serum iron, transferrin saturation, and ferritin decreased (20). However, one study showed that during roxadustat treatment in patients undergoing PD, compared with the baseline, serum iron, transferrin, transferrin saturation increased, and serum ferritin decreased, while another showed the serum iron level was stably maintained, the total iron binding capacity increased significantly, and transferrin saturation was basically stable with some slight decreases (8). In our study, serum iron remained stable and increased from baseline at 20 months of follow-up, but the difference was not statistically significant. Both transferrin saturation and serum ferritin decreased at the beginning of treatment and total iron binding capacity increased, which may be related to the increase in iron utilization, erythropoiesis, and iron requirements after roxadustat treatment (21).

In addition, the present study also showed a decrease in total cholesterol and LDLC after treatment, indicating a cardiovascular protective effect. The cholesterol-lowering effect may be regulated by the reduction of fatty ceramide levels. ACER2, which is the gene encoding alkaline ceramidase 2, was identified as a novel target gene of HIF-2α, triggering ceramide catabolism, and over expression of ACER2 in adipose tissue can improve atherosclerosis caused by HIF-2α deficiency in adipocytes. Furthermore, a study has shown the HIF prolyl hydroxylase inhibitor FG-4592 activates adipose HIF-2α to produce protective effects on atherosclerosis, and is accompanied by a decrease in adipose, plasma ceramide, and plasma cholesterol levels (22), although the mechanism requires further research.

The Morisky medication compliance survey we conducted among patients showed the compliance of patients after switching to roxadustat treatment was significantly better than when using rhEPO treatment, and there was no interruption of the patient's medication when the pandemic recurred during the follow-up process. This is an important reason for maintaining good control of Hb in patients.

In conclusion, during the COVID-19 pandemic, roxadustat has a good effect on improving anemia in ESKD patients undergoing PD who have difficult using rhEPO, with fast onset of effect, good long-term treatment effect, and patient medication compliance. While this may be a better choice for PD patients during special periods such as a pandemic, it is worth noting that Hb is prone to rise too quickly, and should be carefully monitored, especially at the beginning of treatment. This study has limitations such as a small sample size, single-center, and retrospective study design. However, we consider the results reflect real-world clinical experience during the pandemic, and may provide new insight into the treatment of renal anemia in PD patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-555/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-555/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-555/coif). All authors report that this study was supported by the Medical Health Science and Technology Project of Zhejiang Provincial Health Commission (Nos. 2022KY299 and 2022KY1105). XB is the director of the Professional Committee of Renal Disease Prevention and Control, Ningbo Preventive Medical Association, and the vice director of the Ningbo Nephropathy Society of Traditional Chinese and Western Medicine. 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 Ethics Committee of the Ningbo First Hospital (No. 2022RS076). Individual consent for this retrospective analysis was waived.

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