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RESEARCH ARTICLE

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High hemoglobin fluctuation was a protective factor for cardiovascular-related death in peritoneal dialysis (PD) patients: A retrospective analysis of 232 patients with PD

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Abstract

Objectives: This study aimed to investigate the effect of hemoglobin (Hb) fluctuation after dialysis on the prognosis of cardiovascular-related and all-cause deaths in peritoneal dialysis (PD).

Methods: According to the Hb fluctuation, patients were divided into low fluctuation group, moderate fluctuation group, and high fluctuation group, and then, the effects of Hb fluctuation after dialysis on the prognosis of cardiovascular-related and all-cause death in PD were analyzed by regression analysis.

Results: A total of 232 patients were selected in this study. Compared with the low Hb fluctuation group, the moderate and high fluctuation groups had lower body mass index (BMI), estimated glomerular filtration rate (eGFR), and baseline Hb, and the moderate fluctuation group had less erythropoietin (EPO) and dialysis dose. Compared with survivors, patients with cardiovascular-related and all-cause deaths had lower mean Hb and Hb fluctuation (all $p < 0.05$). Cox regression analysis showed that before and after adjusting for confounding factors, Hb fluctuation was still independently correlated with cardiovascular prognosis, and higher Hb fluctuation was still a protective factor for cardiovascular-related death in the Hb-substandard group, but there was no significant correlation between Hb fluctuation and all-cause death. Multivariate linear regression analysis revealed that Hb fluctuation was positively correlated with Kt/V and EPO dosage, but negatively correlated with the baseline Hb.

Conclusion: High Hb fluctuation was a protective factor for cardiovascular-related death in PD with substandard Hb. Compared with Hb fluctuation, correction of anemia timely and making Hb reaches the standard level had a greater impact on reducing cardiovascular-related death in PD.

KEYWORDS
all-cause death, cardiovascular-related death, chronic kidney failure, hemoglobin fluctuation, peritoneal dialysis

1 | INTRODUCTION

The number of patients with end-stage renal disease (ESRD) has increased significantly in the past 10 years. Patients with ERSD need renal replacement therapy, which has become a global public health burden.[1] Cardiovascular disease (CVD) is the leading cause of death in patients with ERSD, accounting for approximately 50% of cases.[2,3] Moreover, a large number of studies have shown that anemia is an important factor affecting the occurrence and development of CVD, and too high or low hemoglobin (Hb) may increase the incidence of CVD and the risk of death in peritoneal dialysis (PD) patients.[4,5,6]

In 2011, the "Dialysis Outcomes and Practice Pattern Study (DOPPS)" concluded that patients with greater Hb fluctuation had a higher risk of death.[7] A retrospective study by Taiwan scholars revealed that Hb fluctuation could not predict the prognosis of PD patients.[8] Subsequently, Altunoren et al.[9] expressed the same views. Another study reported that Hb fluctuation was an independent factor affecting all-cause and cardiovascular-related deaths in PD patients.[10,11]

Obviously, the impact of Hb fluctuation on the prognosis of PD patients, especially the prognosis of CVD, is controversial. The causes of disputes may be related to the following factors. Firstly, the economy, medical security, patient factors, regional diagnosis, and treatment level of each country or region may affect the correction of anemia degree and Hb fluctuation, so the baseline and fluctuation Hb in previous studies are different. Secondly, the race, sample size, inclusion, and exclusion criteria of populations in previous studies are different. All of the above may be important factors causing the controversy of the research results. Therefore, this study aimed to further explore the impact of Hb fluctuation on cardiovascular prognosis in PD patients under China's medical conditions, so as to provide clinical data for reasonably controlling anemia complications and reducing the risk of cardiovascular-related death in PD patients.

2 | MATERIALS AND METHODS

2.1 | Study population

A total of 232 PD patients had stable dialysis and regular follow-up in the PD center of the First affiliated Hospital of Wannan Medical College were retrospectively selected for study enrollment. Patients received stable PD treatment for more than 3 months and regularly followed up every 1–3 months in our center for at least 1 year were included. Patients with hemorrhagic, hemolytic diseases, leukemia, malignant tumors, pregnancy, and incomplete Hb data were excluded. The study was conducted in accordance with the Declaration of Helsinki and was approved by the First affiliated Hospital of Wannan Medical College Ethics Committee.

2.2 | Measure grouping method

All patients were divided into different groups according to the Hb fluctuation which was measured by Hb periodic fluctuation method.[12] The mean Hb fluctuation = ($|Hb_1 - Hb_0| + |Hb_2 - Hb_0| + \ldots + |Hb_n - Hb_0|$)/ n, Hb_0 was the baseline Hb, and Hb_1, Hb_2... Hb_n were the level of Hb detected at different time points. When the study endpoint reached, patients with the mean Hb fluctuation value less than 10 g/L were defined as the low fluctuation group, patients with the mean Hb fluctuation value between 10 and 20 g/L were defined as the moderate fluctuation group, and patients with the mean Hb fluctuation value more than 20 g/L were defined as the high fluctuation group. According to the 2012 Organizational Guidelines for Improving the Prognosis of Global Renal Diseases and related studies,[13,14,15] patients were divided into the Hb standard group (Hb ≥110 g/L) and the Hb substandard group (Hb <110 g/L).

2.3 | Data extraction

The clinical data such as gender, age, height, weight, body mass index (BMI), primary disease, dialysis age, dialysis dose, erythropoietin (EPO) dosage, Hb, ferrum (Fe), blood urea nitrogen (BUN), serum creatinine (Scr), blood calcium (Ca), phosphorus (P), intact parathyroid hormone (iPTH), albumin (ALB) and other laboratory indexes were collected through electronic medical records of PD patients.

2.4 | Calculation index

CKD-EPI formula was used to measure baseline estimated glomerular filtration rate (eGFR). $eGFR = a \times (Scr \text{ concentration} / b)^{c} \times 0.993^{age}$, the a (female = 144, male = 141), and b (female = 0.7, male = 0.9) value were adopted according to gender, the c value was adopted according to gender and Scr.[16] Weekly urea clearance index Kt/V (Krpt/V) = 7×(Krt/V + Kpt/V) = 7×[D/P(mmol/L)×dialysis drainage volume (L) + U/P (mmol/L)×Urine Volume (L)]/ V. Krt/V was the residual kidney urea nitrogen clearance index, Kpt/V was the peritoneal urea nitrogen clearance index, V was the distribution volume of urea nitrogen, and D, P, U represented the solute concentration in the dialysis drainage fluid, plasma and urine, respectively.

2.5 | Definition

All-cause death was defined as death caused by any factor. Cardiovascular-related death was defined as death caused by myocardial infarction, cardiac arrest, heart failure, cerebrovascular accident, and other heart diseases.[17] The deadline for follow-up was defined as the end of the study until the patient received hemodialysis or renal transplantation.

2.6 | Basic treatment plan

All patients used the PD-2 dual system which was produced by Baxter Medical Products Co (United States). The peritoneal

dialysate was PD2 and PD4 lactate dialysate, and the exchange of peritoneal dialysate was 6–8 L per day. According to the "Chinese Expert Consensus on the Diagnosis and Treatment of Renal Anemia (2018 Revised Edition),"[18] iron agents and erythropoiesis-stimulating agents (ESA) were used for treatment.

2.7 | Statistical analysis

SPSS 16.0 was used to establish a database. The continuous variables of normal distribution were presented as the mean ± standard deviation (SD) and compared with Student's *t* test. Non-normal distribution data compared with Mann–Whitney U test were presented as the median and interquartile range (IQR). The categorical variables were presented as counts (percentage) and compared with chi-squared test. The Kaplan–Meier (K-M) survival analysis method was used to compare the survival rates among different fluctuation groups. Cox regression analysis was used to evaluate the relationship between Hb fluctuation and cardiovascular-related death or all-cause death. Multivariate linear regression was used to analyze the related factors of Hb fluctuation in PD patients. $p < 0.05$ meant the difference was statistically significant.

3 | RESULTS

3.1 | Clinical characteristics of participants

A total of 232 patients were selected in this study, of which 146 were male (62.93%), 86 were female (37.07%), the average age was 51.23 years old, ranging from 36 to 76, and the median dialysis time was 42 months. The primary diseases were chronic glomerulonephritis (109 cases, 46.98%), diabetic nephropathy (58 cases, 25.00%) and hypertensive renal damage (44 cases, 18.97%). The patient's baseline Hb (before dialysis) was 86.08 ± 10.10 g/L, and the end point of Hb was 103.31 ± 14.08 g/L.

3.2 | Comparison of clinical data among different Hb fluctuation groups

As shown in Table 1, no difference was found in age, sex composition and dialysis time among different groups (all $p > 0.05$). Compared with the low fluctuation group, the moderate and high fluctuation groups had lower BMI, eGFR, baseline Hb, and the moderate fluctuation group had less EPO and dialysis dose ($p < 0.05$). Compared with the moderate fluctuation group, the

TABLE 1 Comparison of clinical data, laboratory inspection indicators and calculation index among different fluctuation groups

Baseline data	Low fluctuation group (<10 g/L, *n* = 23)	Moderate fluctuation group (10–20 g/L, *n* = 47)	High fluctuation group (>20 g/L, *n* = 162)	F/χ^2	*p*-Value
Gender (male / female)	14/9	31/16	101/61	0.250	0.882
Age (years)	53.97 ± 14.23	52.14 ± 16.62	50.59 ± 13.78	0.667	0.514
Dialysis time (month)	43 (22–56)	41 (23–60)	42 (24–53)	0.668	0.514
BMI (kg/m^2)	24.16 ± 0.58	23.59 ± 0.68[a]	22.98 ± 0.33[a,b]	89.430	0.000
eGFR[ml·min^{-1}·(1.73 m^2)$^{-1}$]	7.66 ± 2.54	5.58 ± 1.97[a]	5.33 ± 2.50[a]	9.442	0.000
Kt/V	1.82 ± 0.62	1.79 ± 0.51	2.10 ± 0.49[b]	8.561	0.000
Scr (μmol/L)	824.54 ± 321.47	936.32 ± 259.62	897.21 ± 317.33	1.025	0.360
BUN (mmol/L)	25.23 ± 8.92	27.86 ± 9.34	31.22 ± 10.25[a]	4.943	0.008
ALB (g/L)	35.24 ± 7.96	33.19 ± 8.12	32.96 ± 7.33	0.918	0.401
Ca (mmol/L)	2.15 ± 0.65	2.24 ± 0.59	2.13 ± 0.63	0.566	0.568
Blood phosphorus (mmol/L)	1.75 (1.02–2.14)	1.96 (1.12–2.27)	1.99 (1.16–2.31)	0.868	0.421
iPTH (ng/L)	174.57 ± 82.57	196.82 ± 94.36	185.33 ± 79.55	0.616	0.541
Fe (μmol/L)	12.36 ± 5.86	11.97 ± 6.94	12.78 ± 7.32	0.247	0.781
Dialysis dose (L/d)	6.45 ± 0.86	6.02 ± 0.71[a]	6.44 ± 0.93	4.262	0.015
EPO (IU/ week)	8952.33 ± 1636.54	7657.42 ± 1798.25[a]	8346.57 ± 2021.33	3.875	0.022
Baseline Hb (g/L)	95.37 ± 9.54	88.26 ± 8.57[a]	84.13 ± 10.12[a,b]	14.790	0.000
Mean Hb (g/L)	98.56 ± 8.32	99.52 ± 9.17	106.33 ± 9.33[a,b]	14.730	0.000
Mean Hb fluctuation value (g/L)	8.34 ± 9.52	15.97 ± 8.59[a]	29.36 ± 8.88[a,b]	85.000	0.000

Abbreviations: ALB, albumin; BMI, body mass index; BUN, blood urea nitrogen; Ca, blood calcium; eGFR, estimated glomerular filtration rate; EPO, erythropoietin; Fe, ferrum; Hb, hemoglobin; iPTH, intact parathyroid hormone; Kt/V, urea clearing index; Scr, serum creatinine.

[a]Compared with the low fluctuation group, $p < 0.05$.

[b]Compared with the moderate fluctuation group, $p < 0.05$.

TABLE 2 Comparison of Hb levels between surviving patients and dead Patients

Hb value	Survivors ($n = 145$)	Cardiovascular-related death group ($n = 38$)	t	p	All-cause death group ($n = 87$)	t	p
Baseline Hb (g/L)	86.82 ± 10.33	85.79 ± 9.72	0.553	0.581	84.84 ± 9.64	1.449	0.149
Mean Hb (g/L)	103.59 ± 8.13	96.12 ± 9.14	4.911	0.000	95.84 ± 9.66	6.543	0.000
Mean Hb fluctuation value (g/L)	25.57 ± 9.42	21.26 ± 8.73	2.548	0.012	22.87 ± 9.12	2.138	0.034

high fluctuation group had lower BMI, baseline Hb, but had higher Kt/V and mean Hb ($p < 0.05$).

3.3 | Analysis of Hb difference between survival and death patients

After a median follow-up of 42 months, 87 (37.50%) patients died, 38 cases died of CVD, which was the first cause of death. Compared with survivors, patients with cardiovascular-related and all-cause deaths had lower mean Hb and mean Hb fluctuation value (all $p < 0.05$), as shown in Table 2.

3.4 | Comparison of cumulative survival rate between different Hb fluctuation groups

The K-M survival analysis revealed that there was no significant difference in cumulative survival rate with cardiovascular-related death as the endpoint among different Hb fluctuation groups ($\chi^2 = 4.433$, $p = 0.109$, Figure 1). Similarly, there was no significant difference in cumulative survival rate with all-cause death as the endpoint among different Hb fluctuation groups ($\chi^2 = 4.534$, $p = 0.104$, Figure 2).

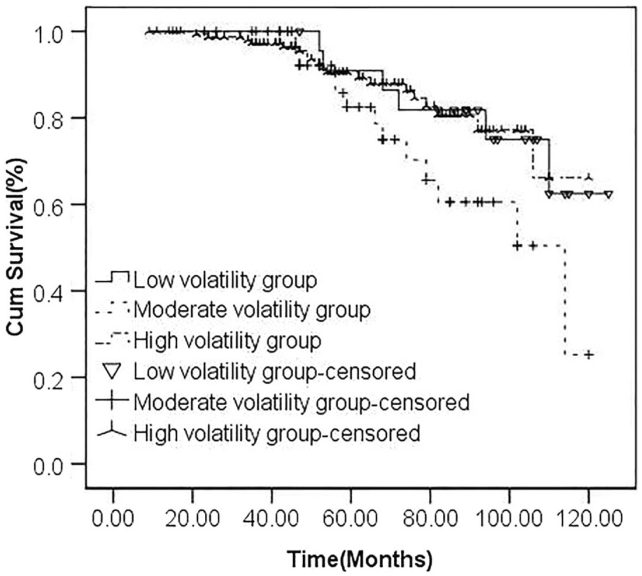

FIGURE 1 Comparison of cumulative survival rate with cardiovascular-related death as the endpoint among different Hb fluctuation groups

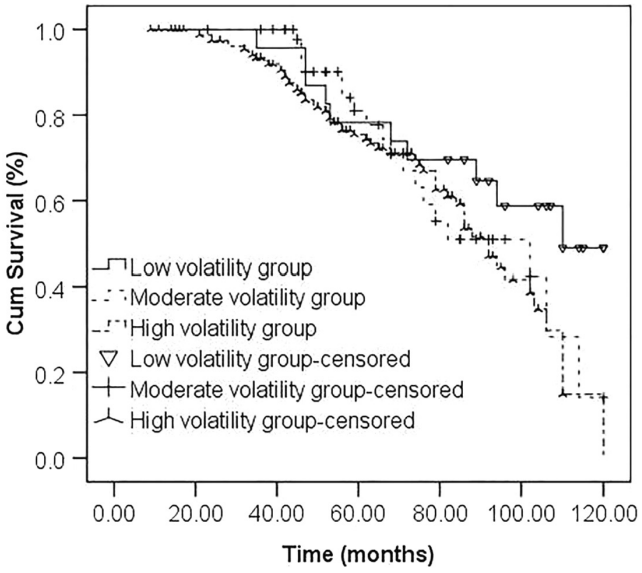

FIGURE 2 Comparison of cumulative survival rate with all-cause death as the endpoint among different Hb fluctuation groups

3.5 | Risk analysis of Hb fluctuation on cardiovascular-related and all-cause death

The Cox regression analysis revealed that the high fluctuation of Hb without adjusting for confounding factors was the protective factor for cardiovascular-related death in PD patients (HR = 0.942, 95% CI 0.915–0.992, $p = 0.038$). After adjusting for age, gender, Scr, and ALB, Hb fluctuation was still independently correlated with cardiovascular prognosis (HR = 0.958, 95%CI 0.918–0.997, $p = 0.043$). Before and after adjusting for confounding factors, there was no correlation between Hb fluctuation and all-cause death in PD patients, as shown in Table 3.

3.6 | Risk analysis of Hb fluctuation on cardiovascular-related death in standard and substandard groups

The Cox regression analysis revealed that the higher the Hb fluctuation, the better the prognosis of patients with cardiovascular in the substandard group (HR = 0.942, 95%CI 0.911–0.987, $p = 0.030$). After adjusting for age, gender, Scr, ALB, Fe, basic diseases, and other confounding factors, the conclusion was still valid (HR = 0.948, 95%

CI 0.909–0.992, $p = 0.040$). There was no correlation between Hb fluctuation and cardiovascular-related death in the standard group whether confounding factors were adjusted or not, as shown in Table 4.

3.7 | Factors related to Hb fluctuation in PD patients

The univariate linear regression analysis revealed that gender, BMI, Kt/V, baseline Hb, and EPO dosage were correlated with Hb fluctuation in PD patients (all $p < 0.05$). The multivariate linear regression analysis revealed that Hb fluctuation was positively correlated with Kt/V (B = 4.332, 95% CI 1.579–6.356, $p = 0.000$) and EPO dosage (B = 0.002, 95% CI 0.001–0.003, $p = 0.002$), but negatively correlated with the baseline Hb level (B = -0.545, 95% CI -0.651–-0.401, $p = 0.000$), as shown in Table 5.

4 | DISCUSSION

In this study, the relationship between Hb fluctuation and cardiovascular-related death, and Hb fluctuation and all-cause death in 232 patients with PD was investigated. The results showed that CVD was the leading cause of death in PD patients. Before and after adjusting for confounding factors, the high Hb fluctuation was still the protective factor of CVD in PD patients with substandard Hb, and Hb fluctuation was positively correlated with Kt/V and EPO dosage, but negatively correlated with the baseline Hb.

Many factors affect the occurrence and development of CVD, including anemia and Hb fluctuation during treatment.[19] There are still some disagreements about the impact of Hb fluctuation on the prognosis of PD patients. For example, Lacson et al.[20] found that Hb fluctuation increased the risk of death in hemodialysis patients, while Weiinhandl et al.[21] suggested that Hb fluctuation was not associated with the poor prognosis. Therefore, there is great value to make sure about the impact of Hb fluctuation on the prognosis of PD patients in China, so as to reduce the disease complications and death.

This study revealed that the Hb fluctuated to a certain extent in PD patients. When grouping and comparing Hb fluctuations, we found that there was no statistically significant difference in the survival rate of cardiovascular-related death and all-cause death in each Hb fluctuation group, which was consistent with some studies.[22,23] However, the Cox regression analysis of the relationship between Hb fluctuation and cardiovascular-related death revealed that with the increase of Hb fluctuation, the risk of cardiovascular-related death decreased, but it had no significant impact on all-cause death. It is well known that Hb fluctuation is affected by many factors, such as race, drug dosage, mode of administration, complications, and so

TABLE 3 Risk analysis of Hb fluctuation on cardiovascular death and all-cause death in PD

	Cardiovascular-related death		All-cause death	
Model	**HR (95% CI)**	***p*-Value**	**HR (95% CI)**	***p*-Value**
Uncorrected model	0.942 (0.915–0.992)	0.038	0.978 (0.967–1.154)	0.341
Model 1	0.959 (0.920–0.996)	0.042	0.992 (0.975–1.160)	0.352
Model 2	0.958 (0.918–0.997)	0.043	0.992 (0.975–1.160)	0.354
Model 3	0.945 (0.924–0.998)	0.040	0.995 (0.983–1.210)	0.410
Model 4	0.962 (0.921–1.021)	0.158	1.001 (0.993–1.259)	0.583

Note: Model 1: Corrected age and gender; Model 2: Corrected serum creatinine, serum albumin, and influencing factors in model 1; Model 3: Corrected whether Hb met the standard and the influencing factors in model 2; Model 4: Corrected primary diseases, body mass index, urea clearance index, ferrum, erythropoietin dose, iron dosage, and the influencing factors in model 3.

Abbreviation: HR, risk ratio.

TABLE 4 Risk analysis of Hb fluctuation on cardiovascular death in standard and substandard groups

	Standard group		Substandard group	
Model	**HR (95% CI)**	***p*-Value**	**HR (95% CI)**	***p*-Value**
Uncorrected model	0.983 (0.944–1.025)	0.279	0.942 (0.911–0.987)	0.030
Model 1	0.983 (0.944–1.025)	0.281	0.952 (0.913–0.994)	0.036
Model 2	0.979 (0.937–1.021)	0.262	0.948 (0.909–0.992)	0.040
Model 3	0.975 (0.932–1.019)	0.254	0.969 (0.914–1.037)	0.397

Note: Model 1: Corrected age, gender, and diabetes; Model 2: Corrected serum creatinine, serum albumin, serum calcium, ferrum, whole blood parathyroid hormone, and influencing factors in model 1; Model 3: Corrected body mass index, urea clearance index, and influencing factors in model 2.

Abbreviations: HR, risk ratio.

TABLE 5 Factors related to Hb fluctuation in PD patients

	Univariate linear regression analysis		Multivariate linear regression analysis	
Baseline data	B (95% CI)	*p*-Value	B (95% CI)	*p*-Value
Gender (female /male)	3.332 (0.212–6.541)	0.038		
Age (years)	−0.049 (−0.183–0.057)	0.352		
Dialysis time (month)	−0.032 (−0.096–0.311)	0.349		
BMI (kg/m^2)	−0.792 (−1.147 to −0.339)	0.003		
eGFR	−0.366 (−0.933–0.212)	0.220		
Kt/V	4.121 (1.399–6.952)	0.006	4.332 (1.579–6.356)	0.000
EPO (IU/week)	0.001 (0.001–0.002)	0.000	0.002 (0.001–0.003)	0.002
Baseline Hb (g/L)	−0.539 (−0.644 to −0.395)	0.000	−0.545 (−0.651 to −0.401)	0.000
Fe (μmol/L)	0.005 (−0.212–0.262)	0.896		
Dialysis dose (L/d)	−0.038 (−1.535–1.626)	0.884		
Scr	−0.042 (−0.121–1.226)	0.534		
ALB (g/L)	−0.112 (−0.353–1.525)	0.679		
iPTH (ng/L)	0.002 (−0.003–0.007)	0.424		

Abbreviations: ALB, albumin; BMI, body mass index; eGFR, estimated glomerular filtration rate; EPO, erythropoietin; Fe, ferrum; Hb, hemoglobin. iPTH, intact parathyroid hormone; Kt/V, urea clearing index; Scr, serum creatinine.

on,[24] all of above may affect the analysis results, this may be one of the important reasons for the differences in different research. In previous studies, patients with high BMI had a high risk of coronary heart disease, heart failure, atherosclerosis, and so on.[25,26] This study also suggested that the correction of BMI eliminated the effect of Hb fluctuation on cardiovascular-related death and demonstrated that patients with a lower eGFR had a lower baseline Hb.

In this study, cardiovascular-related death accounted for 43.68% of PD deaths, which was the leading cause of death. In the substandard group, the higher Hb fluctuation, the lower risk of cardiovascular-related death, which might be related to the lower baseline Hb level and higher Hb fluctuation after anemia treatment. Compared with Hb fluctuation, making Hb to meet the standard had more important impact on the prognosis of PD patients. Therefore, treatments should be taken to make Hb to meet the standard first. However, some studies revealed that Hb more than 130 g/L will increase the risk of death in PD, the best level was between 120 and 130 g/L, and suggested that Hb should be controlled in an appropriate range.[27] Some anemia patients failed to meet the Hb standard after treatment, the reasons might be related to individual differences, dosage of EPO, medical insurance level and so on. In this study, PD patients used EPO at a dose of 6000 to 10,000 IU per week, which was lower than the domestic mean dose.[28] Therefore, from the perspective of medical staff, strengthening the standardization of anemia diagnosis and treatment process had important clinical value, which might reduce the adverse prognosis of PD patients. In addition, this study analyzed the factors related to Hb fluctuation in PD patients, and the results revealed that Hb fluctuation levels were negatively correlated with baseline Hb levels, but positively correlated with Kt/V and EPO dosage. The reasons might be related to the following: (1) After the anemia was corrected, the dosage of EPO would be reduced, causing Hb level to drop significantly; (2) toxin retention in the blood could inhibit bone marrow hematopoiesis and affected the production and functional integrity of red blood cells. Adequate dialysis could help PD patients to excrete more toxins in the blood[29]; in other words, patients with more dialysis had higher Hb fluctuation.

The purpose of this study was to investigate the effect of Hb fluctuation on cardiovascular prognosis during anemia treatment. At the same time, the Hb baseline was analyzed in patients with low baseline Hb, and the results showed that the greater Hb fluctuation, the stronger protection of cardiovascular, indicating the importance of achieving Hb standards. This study also had shortcomings, including the drawbacks of single-center and retrospective study. In addition, Hb fluctuation data at the time of patient registration required one-year follow-up, excluding patients who survived less than 1 year may lead to selection bias. Therefore, researches with multicenter, large sample, and more rigorous design are needed for further exploration.

5 | CONCLUSION

In patients whose Hb did not meet the standard, high Hb fluctuation was a protective factor to reduce the risk of cardiovascular-related death; in other words, patients who maintained low Hb fluctuation after dialysis had higher mortality. In addition, Hb fluctuation was negatively correlated with baseline Hb, and positively correlated with Kt/V and EPO dosage. This suggested that compared with Hb fluctuation factors, adopting a reasonable treatment to correct anemia in time to meet the standard level had a greater impact on reducing cardiovascular-related death in PD patients.

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CONFLICT OF INTEREST

The authors have declared that no conflict of interest.

DATA AVAILABILITY STATEMENT

The data are available upon reasonable request.

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