Original Article

# Multifactorial analysis of renal anemia-associated substandard hemoglobin levels and prevalence of anemia in patients on maintenance hemodialysis in Liaoning Province: a cross-sectional study

**Shuhui Yin[1#^], Yinke Du[2#], Yadong Guo[1], Guangying Guo[2], Da Sun[2], Li Yao[2]**

[1]School of Public Health, China Medical University, Shenyang, China; [2]Department of Nephrology, The First Hospital of China Medical University, Shenyang, China

*Contributions:* (I) Conception and design: S Yin, Y Du; (II) Administrative support: Y Du, L Yao; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: S Yin, Y Guo; (V) Data analysis and interpretation: S Yin, Y Guo; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work and should be considered as co-first authors.

*Correspondence to:* Li Yao. Professor, Director of Nephrology, Member of the Nephrology Branch of the Chinese Medical Association, Chairman of the Nephrology Branch of Liaoning Province, The First Hospital of China Medical University, 155 Nanjing Street, Heping District, Shenyang 110001, China. Email: liyao_cmu@163.com.

**Background:** In hemodialysis (HD) patients, anemia is greatly improved due to regular weekly use of iron and erythropoietin (EPO), but a large number of patients still show persistent anemia. We do a survey to elucidate the influencing factors that contribute to the failure of hemoglobin (Hb) to meet the standard and provide epidemiological data reference for promoting the recognition of renal anemia and improving the treatment effect of renal anemia.

**Methods:** The clinical data of End-Stage Renal Disease (ESRD) HD patients in 22 tertiary hospital HD centers in Liaoning Province from September 2021 to June 2022 were collected by convenient sampling. According to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) anemia diagnostic criteria. The standard of Hb compliance: Hb ≥110 g/L is considered as Hb compliant, and Hb <110 g/L as Hb non-compliant. The factors influencing Hb up-to-standard in ESRD HD patients and their correlations were analyzed by comparison between the two groups.

**Results:** The results of this study showed that among the 1,652 ESRD patients investigated in Liaoning Province, the prevalence rate of anemia was 89.29% (1,475/1,652), and the Hb compliance rate was 46.25% (764/1,652). The Hb compliance rate in maintenance hemodialysis (MHD) patients with different primary diseases was statistically significant (P<0.05). Compared with the Hb non-standard group, the gender, dialysis access, HD frequency, concurrent infection, primary disease of ESRD patients, red blood cell (RBC) count, hematocrit (HCT), mean RBC Hb concentration, mean RBC Hb content, platelet (PLT), albumin (ALB), total protein (TP), serum creatinine (Cr), serum calcium (Ca), serum potassium (K), ferritin (Fer), serum iron (SI), and transferrin (TRE) saturation were significantly different between both groups (P<0.05). Adrenaline was an independent risk factor affecting Hb failure in ESRD patients (OR =1.001, 95% CI: 1.000–1.002); dialysis frequency (OR =0.726, 95% CI: 0.601–0.878), ALB (OR =0.959, 95% CI: 0.929–0.990), TP (OR =0.982, 95% CI: 0.968–0.996), serum Cr (OR =0.959, 95% CI: 0.929–0.999), and SI (OR =0.961, 95% CI: 0.940–0.982) were protective factors affecting Hb failure in ESRD patients (P<0.05). Pearson correlation analysis showed that ALB, TP, serum Cr, serum Ca, serum K, SI, and TRE saturation were positively correlated with Hb (P<0.05).

^ ORCID: 0000-0002-7716-5159.

**Conclusions:** The anemia rate of ESRD patients treated with MHD in Liaoning Province is high. Based on the results, increasing the frequency of dialysis can improve anemia. Parathyroid hormone levels need to be controlled.

**Keywords:** End-stage renal disease (ESRD); maintenance hemodialysis (MHD); renal anemia; hemoglobin standard

Submitted Oct 24, 2022. Accepted for publication Dec 19, 2022.
doi: 10.21037/apm-22-1348
**View this article at:** https://dx.doi.org/10.21037/apm-22-1348

## Introduction

Anemia is a common complication of chronic kidney disease (CKD), and as chronic renal failure progresses, the prevalence of anemia increases with CKD stage; as a 3-year-long prospective study showed, CKD stage 3 patients with anemia progress to CKD stage 4 more rapidly (1). Relevant study has shown that compared with patients without anemia, severe CKD patients with anemia have a 1.74-fold increased risk of acute hospital admission and a 1.82-fold increased risk of all-cause mortality (2). Research has found that patients with hemoglobin (Hb) <8.0 g/dL are 2 times more likely to die compared to those with Hb ≥11.0 g/dL at the start of hemodialysis (HD) (3). Renal anemia in dialysis patients is caused by a variety of causes, including erythropoietin (EPO) deficiency, absolute and functional iron deficiency, hyperparathyroidism, nutritional status, inflammation, etc. In HD patients, anemia is greatly improved due to regular weekly use of iron and EPO, but a large number of patients still show persistent anemia. The compliance rate of Hb in patients with end-stage renal disease (ESRD) is still not ideal (4). The results of the Dialysis Outcomes and Practice Patterns Study (DOPPS) showed that even with EPO treatment on a large scale (greater than 90%), more than 21% of dialysis patients in China had a Hb value of less than 9 g/dL, compared with 10.3% in Japan and 2.7% in the United States (5). In this study, we conducted a cross-sectional survey on the status of anemia in ESRD HD patients in Liaoning, and analyzed the factors that affect substandard Hb in HD patients. We aimed to perform a better and more comprehensive analysis of the causes of anemia in patients in order to elucidate the current situation of anemia, and provide a direction for improving its survival rate and quality of life. The findings would be helpful to guide the HD center to use drugs in a reasonable and standardized way, further reduce the number of blood transfusions in HD patients, avoid the occurrence of related complications, and provide a basis for the prevention and treatment of anemia in HD patients with ESRD. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1348/rc).

### Highlight box

**Key findings**
- The prevalence of renal anemia remains high.
- The compliance rate of hemoglobin attainment is low.

**What is known and what is new?**
- Increasing the frequency of dialysis can improve anemia.
- We should focus on the patient's nutritional status and parathyroid hormone levels to improve anemia.

**What is the implication, and what should change now?**
- Renal anemia still needs attention. It is necessary to manage the patients general state.

## Methods

### *Patients*

The clinical data of ESRD HD patients in 22 tertiary hospital HD centers in Liaoning Province from September 2021 to June 2022 were collected by convenient sampling. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Medical Research Ethics Committee of the First Hospital of China Medical University approved the project (No. AF-SOP-07-1.1-01). The other 21 hospitals are informed and agreed with our study. Informed consent was taken from all the patients before collecting their data. The inclusion criteria were as follows: (I) meeting the diagnostic criteria

 

of ESRD (6); (II) aged ≥18 years; and (III) undergoing maintenance hemodialysis (MHD) treatment (dialysis months ≥3 months, dialysis frequency 2–3 times/week, dialysis 4 hours each time). The exclusion criteria were as follows: (I) combined with other diseases that can cause anemia, such as tumors, digestive tract diseases (peptic ulcer, hemorrhoids, acute gastric mucosal bleeding from anal fissure), blood system diseases (leukemia, aplastic anemia, thalassemia, haemophilia, thrombocytopenic purpura); (II) massive blood loss in the first 3 months of enrollment; and (III) having received immunosuppressant, blood transfusion, and hormone therapy in the past 3 months.

### *Questionnaire*

Basic information of patients is collected by special personnel. Laboratory indicators are measured by individual hospitals. The general information of patients (gender, age, ethnicity, marital status, education level, occupation, family annual income, type of medical payment), clinical data [whether they had been hospitalized in the past 3 months, smoking history, blood pressure, body mass index (BMI), age at dialysis, access to dialysis, frequency of HD, frequency of hemofiltration, complications, primary disease etiology], laboratory tests [red blood cell (RBC), Hb, hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular hemoglobin content (MCH), white blood cell (WBC) count, platelet (PLT), albumin (ALB), total protein (TP), prealbumin (PA), alkaline phosphatase (ALP), blood urea nitrogen (BUN), serum creatinine (Cr), fasting blood glucose (GLU), total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL-C), low density lipoprotein (LDL-C), uric acid (UA), bicarbonate (HCO3-), blood calcium (Ca), blood phosphorus (P), blood potassium (K), ferritin (Fer), serum transferrin (TRF), serum iron (SI), transferrin saturation (TSAT), parathyroid hormone (PTH)].

### *Criteria*

The diagnostic criteria for renal anemia stipulate that a patient meets the following conditions at the same time: (I) anemia caused by insufficient EPO production, shortened RBC lifespan, abnormal iron metabolism, and nutritional disorders due to chronic damage to renal structure and/or function; (II) according to the 2012K/DIGO anemia diagnostic criteria (6): male Hb <130 g/L, non-pregnant female Hb <120 g/L; (III) exclude anemia caused by other diseases except CKD. According to the Chinese expert consensus on the diagnosis and treatment of renal anemia, the clinical target of renal anemia is Hb ≥110 g/L, but not more than 130 g/L. The standard of Hb compliance: Hb ≥110 g/L is considered as Hb compliant, and Hb <110 g/L as Hb non-compliant (6).

### *Statistical analysis*

The software SPSS 26.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis, and the Kolmogorov-Smirnov (K-S) method was used to test the normality of measurement data. Measurement data with normal distribution or approximately normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$), and *t*-test was used for comparison between groups. The measurement data with skewed distribution were represented by as the mean {interquartile range; *M* [P25, P75]}, and comparisons between groups were performed by rank sum test; the count data were represented as the number of cases and the constituent ratio, and comparisons between groups were made using the $\chi^2$ test or Fisher's exact test. Logistic regression analysis was used to analyze the factors affecting Hb compliance in MHD patients, and Pearson correlation analysis was used to analyze the correlation between Hb and each index. When P<0.05, the difference was considered statistically significant. Missing data were filled in with multiple imputation.

## Results

### *Prevalence, awareness, and Hb compliance rate*

According to inclusion and exclusion criteria, a total of 1,652 ESRD patients treated with MHD were included in this study, including 1,027 males and 625 females, aged between 21 and 95 years, with an average age of (57.63±13.35) years. There were 1,475 ESRD patients with anemia and 177 without anemia. The prevalence of anemia was 89.29% (1,475/1,652). Among the ESRD patients, 701 were aware that they had anemia, comprising an anemia awareness rate of 42.43% (701/1,652). Among those with anemia, 1,367 patients were treated for anemia, and the treatment rate was 92.71% (1,367/1,475). There were 764 ESRD patients who reached the Hb standard, constituting a Hb compliance rate of 46.25% (764/1,652). Huludao City had the lowest Hb compliance rate, and Chaoyang City had

 

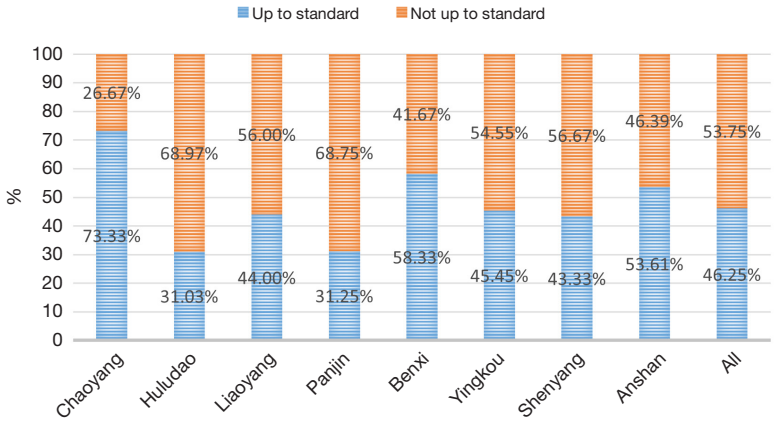


**Figure 1** Hb compliance in different cities in Liaoning Province. Hb, hemoglobin.

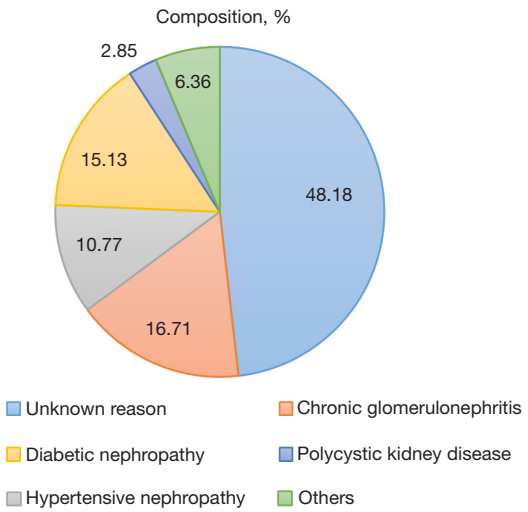


**Figure 2** The etiological composition of different primary diseases.

the highest Hb compliance rate (*Figure 1*).

### *Comparison of different primary disease*

Among the known primary diseases of MHD, chronic glomerulonephritis accounted for the highest proportion, followed by diabetic nephropathy, hypertensive nephropathy, others, and polycystic kidney disease (*Figure 2*). Patients with chronic glomerulonephritis exhibited the highest prevalence of anemia (*Figure 3*). Hypertensive nephropathy had the lowest Hb compliance rate, as shown in *Figure 4*. There was no significant difference in the prevalence of anemia in MHD patients with different primary diseases (P>0.05); the Hb compliance rates in MHD patients with different primary diseases had statistical significance (P<0.05) (*Table 1*).

### *Comparison of general data and clinical data*

Comparison of gender, dialysis access type, diastolic blood pressure, concurrent infection, primary disease etiology, RBC, HCT, MCHC, MCH, ALB, TP, Cr, Ca, K, Fer, SI, and TSAT between the Hb standard group and the Hb non-standard group showed that the difference was statistically significant (P<0.05) (*Tables 2,3*).

### *Logistic regression analysis of the influence*

In order to explore the relationship between Hb attainment and various factors, we included statistically significant and significant clinical variables in univariate analysis into the multivariate analysis model. For example, RBC, HCT, MCHC and MCH were not included in the regression model. PTH was included into the multivariate analysis. The results showed that: high ALB, high TP, high SI, dialysis frequency (3 times/week), and high Cr was a protective factor for Hb failure to reach the target (P<0.05), and high PTH was an independent risk factor for Hb failure to meet the target (P<0.05) (*Table 4*).

### *Correlation analysis of each laboratory index and Hb*

Pearson correlation analysis showed that ALB, TP, Cr, Ca, K, SI, and TSAT were positively correlated with Hb level (P<0.05), whereas Fer had no correlation with Hb level (P>0.05) (*Table 5*).

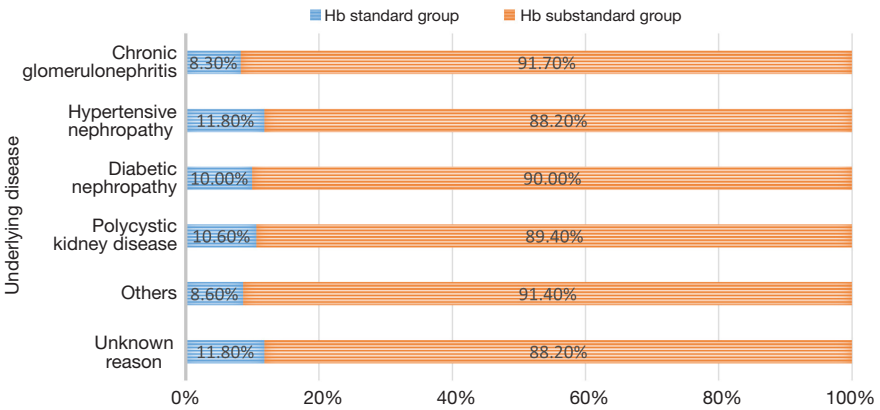


**Figure 3** Prevalence of anemia in MHD patients with different primary diseases. Hb, hemoglobin; MHD, maintenance hemodialysis.

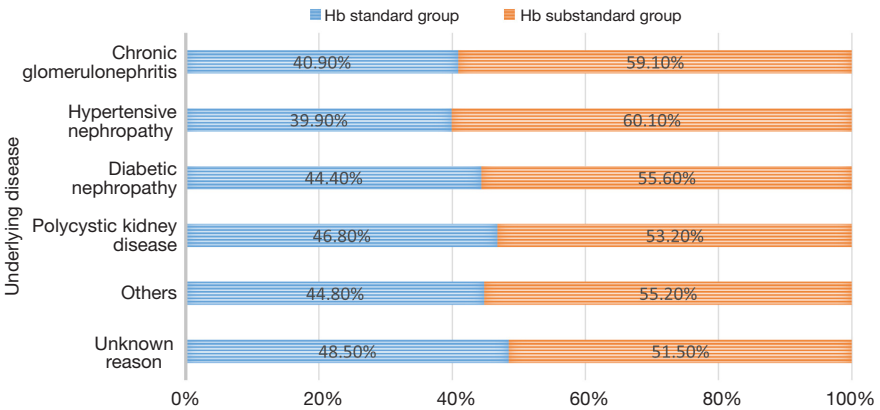


**Figure 4** Hb compliance in MHD patients with different primary diseases. Hb, hemoglobin; MHD, maintenance hemodialysis.

**Table 1** Comparison of the prevalence of anemia and the rate of Hb compliance in MHD patients with different primary diseases [n (%)]

| Underlying disease | n=1,652 | Anemia prevalence | Hb compliance rate |
|---|---|---|---|
| Chronic glomerulonephritis | 276 (16.71) | 253 (91.67) | 113 (40.94) |
| Hypertensive nephropathy | 178 (10.77) | 157 (88.20) | 71 (39.89) |
| Diabetic nephropathy | 250 (15.13) | 225 (90.00) | 111 (44.40) |
| Polycystic kidney disease | 47 (2.85) | 42 (89.36) | 25 (53.19) |
| Others | 105 (6.36) | 96 (91.43) | 58 (55.24) |
| Unknown reason | 796 (48.18) | 702 (88.19) | 386 (48.49) |
| $\chi^2$ | | 3.489 | 12.304 |
| P | | 0.625 | 0.031 |

Hb, hemoglobin; MHD, maintenance hemodialysis.

**Table 2** Comparison of general data and clinical data between ESRD patients with Hb compliance group and Hb non-compliance group [n (%), ($\bar{x} \pm s$)]

| Items | n | Hb standard group (n=764) | Hb substandard group (n=888) | $\chi^2/t/Z$ | P |
|---|---|---|---|---|---|
| Sex (%) | | | | | |
| Male | 1,027 | 495 (48.20) | 532 (51.80) | 4.159 | 0.041* |
| Female | 625 | 269 (43.04) | 356 (56.96) | | |
| Age (years) | | 57.27±13.24 | 57.99±13.46 | –1.011 | 0.312 |
| Nationality (%) | | | | | |
| Han nationality | 1,560 | 720 (46.15) | 840 (53.85) | 0.098 | 0.755 |
| Others | 92 | 44 (47.83) | 48 (52.17) | | |
| Marital status (%) | | | | | |
| Married | 1,431 | 673 (47.03) | 758 (52.97) | 3.787 | 0.285 |
| Unmarried | 123 | 54 (43.90) | 69 (56.10) | | |
| Divorced | 44 | 18 (40.91) | 26 (59.09) | | |
| Widowed | 54 | 19 (35.20) | 35 (64.80) | | |
| Education status (%) | | | | | |
| Junior high school and below | 763 | 355 (46.53) | 408 (53.47) | 0.095 | 0.954 |
| High school and secondary school | 455 | 211 (46.37) | 244 (53.63) | | |
| College and above | 434 | 198 (45.62) | 236 (54.38) | | |
| Profession (%) | | | | | |
| On-the-job | 864 | 419 (48.50) | 445 (51.50) | 4.096 | 0.129 |
| Leave (retire) | 636 | 282 (44.34) | 354 (55.66) | | |
| Unemployed | 152 | 63 (41.45) | 89 (58.55) | | |
| Annual household income 10,000 yuan (%) | | | | | |
| <0.3 | 123 | 48 (39.02) | 75 (60.98) | 5.082 | 0.166 |
| 0.3≤ income <8 | 1,109 | 523 (47.16) | 586 (52.84) | | |
| 8≤ income <15 | 333 | 147 (44.14) | 186 (55.86) | | |
| ≥15 | 87 | 46 (52.87) | 41 (47.13) | | |
| Types of medical payments (%) | | | | | |
| Resident medical insurance | 207 | 87 (42.03) | 120 (57.97) | 2.951 | 0.399 |
| Employee medical insurance | 1,354 | 636 (46.97) | 718 (53.03) | | |
| Other medical insurance | 65 | 27 (41.54) | 38 (58.46) | | |
| At own expense | 26 | 14 (53.85) | 12 (46.15) | | |
| Hospitalization in the past 3 months (%) | | | | | |
| Yes | 401 | 177 (44.14) | 224 (55.86) | 0.946 | 0.331 |
| No | 1,251 | 587 (46.92) | 664 (53.08) | | |

**Table 2** *(continued)*

**Table 2** *(continued)*

| Items | n | Hb standard group (n=764) | Hb substandard group (n=888) | $\chi^2/t/Z$ | P |
|---|---|---|---|---|---|
| Smoking history (%) | | | | | |
| Yes | 287 | 143 (49.83) | 144 (50.17) | 1.838 | 0.399 |
| No | 1,069 | 488 (45.65) | 581 (54.35) | | |
| Quit | 296 | 133 (44.93) | 163 (55.07) | | |
| Blood pressure (mmHg) | | | | | |
| Systolic blood pressure | | 148.11±20.24 | 149.77±20.03 | 1.421 | 0.156 |
| Diastolic blood pressure | | 84.57±11.21 | 83.47±10.93 | –1.698 | 0.090 |
| BMI (kg/m$^2$) | | 22.58 (20.28, 25.26) | 23.14 (20.59, 25.43) | –1.431 | 0.152 |
| Dialysis age (months) | | 35.40 (14.16, 74.90) | 38.46 (17.22, 81.51) | –1.507 | 0.132 |
| Dialysis access (%) | | | | | |
| Arteriovenous fistula | 1,540 | 730 (47.40) | 810 (52.60) | 12.203 | 0.000* |
| Central venous catheter | 112 | 34 (30.36) | 78 (69.64) | | |
| Frequency of hemodialysis (%) | | | | | |
| 2 times/week | 155 | 62 (40.00) | 93 (60.00) | 13.024 | 0.001* |
| 3 times/week | 1,104 | 545 (49.37) | 559 (50.63) | | |
| 5 times/2 weeks | 393 | 157 (39.95) | 236 (60.05) | | |
| Frequency of hemofiltration (%) | | | | | |
| No | 1,054 | 490 (46.49) | 564 (53.51) | 0.590 | 0.964 |
| 1 time/week | 45 | 22 (48.89) | 23 (51.11) | | |
| 1 time/2 weeks | 90 | 43 (47.78) | 47 (52.22) | | |
| 1 time/month | 208 | 92 (44.23) | 116 (55.77) | | |
| Less than 1 time/month | 255 | 117 (45.88) | 138 (54.12) | | |
| Complication (%) | | | | | |
| Unknown | | | | | |
| Yes | 1,208 | 562 (46.52) | 646 (53.48) | 0.138 | 0.710 |
| No | 444 | 202 (45.50) | 242 (54.50) | | |
| Cerebrovascular disease | | | | | |
| Have | 74 | 36 (48.64) | 38 (51.36) | 0.356 | 0.551 |
| None | 370 | 166 (44.86) | 204 (55.14) | | |
| Cardiovascular disease | | | | | |
| Have | 170 | 72 (42.35) | 98 (57.65) | 1.097 | 0.295 |
| None | 274 | 130 (47.45) | 144 (52.55) | | |
| Renal bone disease | | | | | |
| Have | 180 | 84 (46.67) | 96 (55.33) | 0.167 | 0.628 |
| None | 264 | 118 (47.97) | 146 (55.30) | | |

**Table 2** *(continued)*

**Table 2** *(continued)*

| Items | n | Hb standard group (n=764) | Hb substandard group (n=888) | $\chi^2$/t/Z | P |
|---|---|---|---|---|---|
| Water and electrolyte disturbances and acid-base imbalances | | | | | |
| Have | 178 | 87 (48.88) | 91 (51.12) | 0.479 | 0.489 |
| None | 265 | 117 (44.15) | 148 (55.85) | | |
| Infection | | | | | |
| Have | 28 | 7 (47.18) | 21 (52.82) | 5.062 | 0.024* |
| None | 416 | 195 (46.88) | 221 (53.13) | | |
| Others | | | | | |
| Have | 9 | 5 (55.56) | 4 (44.44) | | 0.738 |
| None | 435 | 197 (45.29) | 238 (54.71) | | |

Compared with the Hb standard group and the Hb substandard group. *, P<0.05. Hb, hemoglobin; BMI, body mass index.

## Discussion

Various subgroups of CKD patients may be complicated with renal anemia, including ESRD patients, patients with cardiovascular and cerebrovascular diseases, and patients undergoing MHD treatment. One study has shown that the prevalence of anemia increases with the severity of CKD (7), ESRD patients are a high-risk group of renal anemia, and it is of practical significance to evaluate the impact of anemia in ESRD patients. The influencing factors of renal anemia are complex, and its mechanism is mainly related to the decrease of EPO level and the impairment of iron homeostasis caused by renal dysfunction caused by the primary disease (8). At present, the clinical treatment of renal anemia in ESRD patients is mainly based on EPO, iron supplementation, blood transfusion, and so on. Even if EPO and iron supplements are used on a large scale, there are still a considerable number of patients with low Hb, and they remain in a state of Hb substandard. This suggests that there may be other factors affecting the Hb level in ESRD patients. The purpose of this study was to investigate the current status of anemia and Hb compliance in ESRD patients treated with MHD, analyze the factors affecting the Hb level of patients, and provide epidemiological data reference for promoting the recognition of renal anemia and improving the treatment effect of renal anemia.

The results of this study showed that the prevalence of anemia in ESRD patients treated with MHD in Liaoning was 89.29%. Although most of the patients had received anemia treatment, the Hb compliance rate was only 46.25%. In recent years, different researchers have reported the related situation of renal anemia. From 2015 to 2017, the Hb compliance rate of MHD patients in Shanghai was 47.78% (9). A survey in Taiwan showed that the prevalence of anemia in non-dialysis patients with ESRD was 90.2% (10), which was slightly higher than in this study. Researchers such as Sofue *et al.* (11) have reported a prevalence of anemia in ESRD patients in Japan of 60.3%, which is far lower than the prevalence of anemia in this study. However, since some non-MHD patients were also included in this study, it is necessary to consider whether dialysis treatment should be performed. The reason for the difference between different studies is that dialysis treatment may be an important factor affecting the prevalence of anemia in ESRD patients. This study also found that there was a statistically significant difference in the Hb compliance rate of ESRD patients with different primary diseases, and the Hb non-compliance rate was the highest in ESRD patients with hypertension. Animal experiments have revealed that Hb and HCT in CKD rats were significantly negatively correlated with their blood pressure; the author asserted that EPO deficiency was related to blood pressure (12). Research by Kurniawan *et al.* (13) highlighted that in patients with CKD stage 3–5, diastolic blood pressure is an independent risk factor for the occurrence of anemia. In the multivariate results of this study, blood pressure was not an influencing factor for ESRD patients to reach the Hb standard, and there was no significant difference in blood pressure between the Hb standard group and the non-reach group. This difference may be related to the different grouping standards and included populations of each study. In the logistic regression analysis affecting the Hb standard of ESRD patients, the data of this study showed that PTH

 

**Table 3** Relationship between different biochemical indexes and Hb compliance

| Biochemical indicators | Hb standard group (n=764) | Hb substandard group (n=888) | *t*/Z | P |
|---|---|---|---|---|
| RBC (10^12/L) | 3.95±0.43 | 3.24±0.47 | –31.464 | <0.001* |
| HCT (%) | 36.85±2.91 | 30.08±3.65 | –41.659 | <0.001* |
| MCV (fL) | 93.36±5.95 | 92.97±6.60 | –1.25 | 0.211 |
| MCHC (g/L) | 326.24±13.49 | 321.52±14.22 | –6.811 | <0.001* |
| MCH (pg) | 30.40±2.14 | 29.87±2.38 | –4.687 | <0.001* |
| WBC (10^9/L) | 6.28 (5.14, 7.71) | 6.10 (5.01, 7.59) | –0.174 | 0.862 |
| PLT (10^9/L) | 180.50 (145.25, 216.00) | 179.00 (138.00, 227.00) | –0.145 | 0.885 |
| ALB (g/L) | 39.61±3.56 | 38.67±4.50 | –3.457 | 0.001* |
| TP (g/L) | 67.58±10.15 | 65.81±8.03 | –2.082 | 0.038* |
| PA (mg/dL) | 35.14±12.61 | 31.83±10.98 | –0.665 | 0.098 |
| ALP (U/L) | 76.18 (64.00, 99.00) | 83.95 (65.00, 100.00) | –1.085 | 0.278 |
| BUN (mmol/L) | 25.33±7.06 | 24.78±7.31 | –1.416 | 0.157 |
| Cr (μmol/L) | 1074.39±332.3 | 1023.45±307.92 | –2.972 | 0.003* |
| GLU (mmol/L) | 6.09 (5.00, 8.19) | 5.99 (4.86, 7.82) | 0.717 | 0.473 |
| TC (mmol/L) | 4.05 (3.29, 4.97) | 3.91 (3.23, 4.50) | 1.327 | 0.185 |
| TG (mmol/L) | 1.68 (1.18, 2.56) | 1.435 (0.98, 2.51) | 1.375 | 0.083 |
| HDL-C (mmol/L) | 0.96 (0.79, 1.19) | 0.89 (0.79, 1.08) | 1.487 | 0.137 |
| LDL-C (mmol/L) | 2.24 (1.69, 3.01) | 2.285 (1.75, 2.90) | 0.399 | 0.690 |
| UA (μmol/L) | 449.00 (372.00, 511.05) | 437.00 (365.00, 514.00) | 0.831 | 0.406 |
| HCO3- (mmol/L) | 22.95±3.76 | 22.46±3.81 | –1.594 | 0.111 |
| Ca (mmol/L) | 2.19±0.28 | 2.15±0.30 | –2.802 | 0.005* |
| P (mmol/L) | 1.92±0.62 | 1.88±0.66 | –1.216 | 0.224 |
| K (mmol/L) | 4.87±0.86 | 4.74±0.90 | –2.517 | 0.012* |
| Fer (μg/L) | 148.4 (47.95, 359.54) | 193.40 (68.055, 411.1) | –2.786 | 0.005* |
| TRF (mg/dL) | 198.00 (149.00, 234.00) | 188.00 (154.00, 206.50) | –1.283 | 0.203 |
| SI (μmol/L) | 11.26±5.78 | 9.75±5.18 | –4.644 | <0.001* |
| TSAT (%) | 23.00 (18.86, 29.82) | 20.81 (14.96, 27.13) | –3.426 | 0.001* |
| PTH (pmol/L) | 32.83 (15.26, 63.57) | 35.15 (18.12, 66.45) | –1.797 | 0.072 |

Data are presented as mean ± standard deviation or median (range). Compared with the Hb standard group and the Hb non-standard group, *, P<0.05. Hb, hemoglobin; RBC, red blood cell; HCT, hematocrit; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; MCH, mean corpuscular content; WBC, white blood cell; PLT, platelet; ALB, albumin; TP, total protein; PA, prealbumin; ALP, alkaline phosphatase; BUN, blood urea nitrogen; Cr, creatinine; GLU, glucose; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UA, uric acid; HCO3, bicarbonate; Ca, calcium; P, phosphate; K, potassium; Fer, ferritin; TRF, serum transferrin; SI, serum iron; TSAT, transferrin saturation; PTH, parathyroid hormone.

was an independent risk factor affecting the Hb failure of ESRD patients, and dialysis frequency, ALB, TP, Cr, and SI were protective factors affecting ESRD patients' Hb failure to meet the standard. Moreover, correlation analysis also showed that ALB, TP, Cr, and SI were positively correlated with Hb. Among the protective factors, the lowest odds

 

**Table 4** Logistic regression analysis of the influence of ESRD hemodialysis patients not reaching the Hb standard

| Variables | B | Standard error | Wald $\chi^2$ | P | OR | 95% CI | |
|---|---|---|---|---|---|---|---|
| | | | | | | Upper | Lower |
| ALB (g/L) | –0.042 | 0.016 | 6.599 | 0.010 | 0.959 | 0.929 | 0.990 |
| TP (g/L) | –0.018 | 0.007 | 6.177 | 0.013 | 0.982 | 0.968 | 0.996 |
| SI (μmol/L) | –0.040 | 0.011 | 13.268 | <0.001 | 0.961 | 0.940 | 0.982 |
| PTH (pmol/L) | 0.001 | 0.001 | 4.062 | 0.044 | 1.001 | 1.000 | 1.002 |
| Dialysis frequency | –0.321 | 0.097 | 10.953 | 0.001 | 0.726 | 0.601 | 0.878 |
| Cr (μmol/L) | –0.042 | 0.016 | 6.599 | 0.013 | 0.959 | 0.929 | 0.999 |

ESRD, end-stage renal disease; Hb, hemoglobin; OR, odds ratio; CI, confidence interval; ALB, albumin; TP, total protein; SI, serum iron; PTH, parathyroid hormone; Cr, creatinine.

**Table 5** Correlation analysis between laboratory indicators and Hb

| Variables | r | P |
|---|---|---|
| ALB (g/L) | 0.177 | <0.001* |
| TP (g/L) | 0.162 | 0.001* |
| Cr (μmol/L) | 0.113 | <0.001* |
| Ca (mmol/L) | 0.102 | <0.001* |
| K (mmol/L) | 0.088 | 0.001* |
| Fer (μg/L) | –0.052 | 0.068 |
| SI (μmol/L) | 0.176 | <0.001* |
| TSAT (%) | 0.195 | <0.001* |

Compared with the Hb standard group and the Hb non-standard group, *, P<0.05. Hb, hemoglobin; ALB, albumin; TP, total protein; Cr, creatinine; Ca, calcium; K, potassium; Fer, ferritin; SI, serum iron; TSAT, transferrin saturation.

ratio (OR) value of dialysis frequency was 0.726 times that of those who received 3 times/week of dialysis/week than those who received 2 times/week of dialysis. In addition to insufficient EPO secretion, the shortening of RBC life span caused by uremic toxins and inflammatory factors is also an important pathological mechanism of renal anemia (14). Regular dialysis 3 times a week can better remove toxins, some inflammatory factors, and other harmful substances in ESRD patients. It can improve the living environment of RBCs and reduce negative impacts on the lifespan of RBCs, so it is beneficial to reduce the risk of renal anemia. Iron and EPO are important raw materials for RBC production, and patients with CKD may develop both functional and absolute iron deficiency (15). The SI has a good diagnostic value for the iron-deficiency erythropoiesis and iron-deficiency anemia stages of iron-deficiency anemia. When iron-deficient RBCs appear, the absorption of iron by small intestinal cells increases, and the level of transferrin in the body rises and accelerates. Iron is transported into cells, promoting the increase of EPO and the decrease of SI (15,16). Therefore, lower SI levels were associated with the risk of Hb non-attainment. In addition, the results of this study also showed that there is no correlation between Fer and Hb levels. One study has shown that compared with patients without malnutrition, patients with malnutrition have higher levels of inflammatory markers, including Fer and C-reactive protein (CRP) [(301.2±127.1 *vs.* 212.7±124.9 mg/dL, P<0.05); 63% *vs.* 33%, P<0.05] (17). An inflammatory state affects the development of renal anemia, CKD represents an enhanced inflammatory status with high cytokine activity, which can inhibit the generation of erythroid progenitor cells, leading to reduced responsiveness to erythropoiesis-stimulating agents (ESA) and poor treatment outcomes (18). Iron-deficiency anemia in ESRD patients is mostly the result of progressive iron storage depletion, and some patients receive iron supplementation therapy. Patients may present at any stage of the chronic progression of iron-deficiency anemia. Therefore, Fer and TSAT in some patients may be lower or may be normal. The study by Yu *et al.* (16) also pointed out that CKD patients with normal TSAT but low SI content are still at risk of anemia. The incidence of malnutrition in HD is 23–73%. Malnutrition can reduce renal glomerular filtration rate (GFR) and renal blood flow, further reduce residual renal function, and aggravate renal anemia (19). Nutritional indicators include serum biochemical indicators, body mass, muscle mass, and protein energy intake. In the logistic regression analysis of this paper, Cr was a protective

 

factor for Hb reaching the standard. Cr is a metabolite of creatine, and under normal daily protein intake, the production of Cr is relatively stable. The Cr concentration can be used as a nutritional index to reflect the muscle content of patients, and low Cr reflects low muscle content and protein energy consumption. Changes in ALB levels are related to nutritional status and inflammatory status (20,21). Another Study has shown that low ALB levels significantly increase the risk of inflammatory status, and ALB levels are closely related to renal function in CKD patients (22). The results of this study found that ALB was a protective factor for Hb failure to reach the target. People with low ALB levels have a poorer nutritional status, which also affects the efficacy of dialysis treatment and has a higher risk of anemia in renal function in ESRD patients, which indirectly affects RBC production and lifespan. Therefore, in clinical treatment of renal anemia, it is necessary to pay attention to the nutritional status of patients, and anemia can be improved by ensuring protein, calorie intake, and improving micro-inflammation. In this study, PTH was the only independent risk factor for Hb failure. High levels of PTH can directly inhibit the production of RBCs, increase their destruction and shorten their lifespan, factors which are involved in the occurrence and development of renal anemia, and also lead to poor response to recombinant human EPO therapy (23). There are also clinical studies showing that PTH can indirectly aggravate anemia by affecting serum leptin levels (24).

## Conclusions

ESRD patients treated with MHD in Liaoning Province generally have low Hb levels, higher rates of anemia, and Hb failure to reach the standard. In clinical treatment of renal anemia, the frequency of dialysis per week should be increased when the patient's time and economic conditions permit due to concerns about the patient's nutritional status, quality of life, and control of the patient's inflammatory status. Anti-cytokine and antioxidant therapeutic strategies that are beneficial to improve anemia in patients may be the future of pharmacological interventions aimed at treating inflammation-related ESA hyporesponsiveness.

### *Limitation*

Some missing data in the questionnaire may have caused bias.

## Acknowledgments

*Funding*: The study was supported by the Special Fund for Renal Anemia of the China International Medical Exchange Foundation.

## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1348/rc

*Data Sharing Statement:* Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1348/dss

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1348/coif). The authors have no 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). Medical Research Ethics Committee of the First Hospital of China Medical University approved the project (No. AF-SOP-07-1.1-01). The other 21 hospitals are informed and agreed with our study. Informed consent was taken from all the patients before collecting their data.



## References

1. Portolés J, Gorriz JL, Rubio E, et al. The development of anemia is associated to poor prognosis in NKF/KDOQI stage 3 chronic kidney disease. BMC Nephrol 2013;14:2.
2. Toft G, Heide-Jørgensen U, van Haalen H, et al. Anemia

 

and clinical outcomes in patients with non-dialysis dependent or dialysis dependent severe chronic kidney disease: a Danish population-based study. J Nephrol 2020;33:147-56.
3. Karaboyas A, Morgenstern H, Waechter S, et al. Low hemoglobin at hemodialysis initiation: an international study of anemia management and mortality in the early dialysis period. Clin Kidney J 2019;13:425-33.
4. Li Y, Shi H, Wang WM, et al. Prevalence, awareness, and treatment of anemia in Chinese patients with nondialysis chronic kidney disease: First multicenter, cross-sectional study. Medicine (Baltimore) 2016;95:e3872.
5. Zuo L, Wang M, Hou F, et al. Anemia Management in the China Dialysis Outcomes and Practice Patterns Study. Blood Purif 2016;42:33-43.
6. National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. Am J Kidney Dis 2012;60:850-86.
7. George C, Matsha TE, Erasmus RT, et al. Haematological profile of chronic kidney disease in a mixed-ancestry South African population: a cross-sectional study. BMJ Open 2018;8:e025694.
8. Ni Z, Jin H, Jiang G, et al. A Telemedicine-Based Registration System for the Management of Renal Anemia in Patients on Maintenance Hemodialysis: Multicenter Study. J Med Internet Res 2019;21:e13168.
9. Zhao X, Niu Q, Gan L, et al. Baseline data report of the China Dialysis Outcomes and Practice Patterns Study (DOPPS). Sci Rep 2021;11:873.
10. Tsai SF, Tarng DC. Anemia in patients of diabetic kidney disease. J Chin Med Assoc 2019;82:752-5.
11. Sofue T, Nakagawa N, Kanda E, et al. Prevalence of anemia in patients with chronic kidney disease in Japan: A nationwide, cross-sectional cohort study using data from the Japan Chronic Kidney Disease Database (J-CKD-DB). PLoS One 2020;15:e0236132.
12. Phillips JK, Boyd R, Krockenberger MB, et al. Progression of anemia and its relationship with renal function, blood pressure, and erythropoietin in rats with chronic kidney disease. Vet Clin Pathol 2015;44:342-54.
13. Kurniawan AL, Yang YL, Hsu CY, et al. Association between metabolic parameters and risks of anemia and electrolyte disturbances among stages 3-5 chronic kidney disease patients in Taiwan. BMC Nephrol 2021;22:385.
14. Fishbane S, Coyne DW. How I treat renal anemia. Blood 2020;136:783-9.
15. Gafter-Gvili A, Schechter A, Rozen-Zvi B. Iron Deficiency Anemia in Chronic Kidney Disease. Acta Haematol 2019;142:44-50.
16. Yu PH, Lin MY, Chiu YW, et al. Low serum iron is associated with anemia in CKD stage 1-4 patients with normal transferrin saturations. Sci Rep 2021;11:8343.
17. Prakash J, Raja R, Mishra RN, et al. High prevalence of malnutrition and inflammation in undialyzed patients with chronic renal failure in developing countries: a single center experience from eastern India. Ren Fail 2007;29:811-6.
18. Gluba-Brzózka A, Franczyk B, Olszewski R, et al. The Influence of Inflammation on Anemia in CKD Patients. Int J Mol Sci 2020;21:725.
19. Riobó Serván P, Moreno Ruiz I. Nutrition in chronic kidney disease. Nutr Hosp 2019;36:63-9.
20. Bomholt T, Adrian T, Nørgaard K, et al. The Use of HbA1c, Glycated Albumin and Continuous Glucose Monitoring to Assess Glucose Control in the Chronic Kidney Disease Population Including Dialysis. Nephron 2021;145:14-9.
21. Mukai H, Villafuerte H, Qureshi AR, et al. Serum albumin, inflammation, and nutrition in end-stage renal disease: C-reactive protein is needed for optimal assessment. Semin Dial 2018;31:435-9.
22. Jiang C, Wang B, Li Y, et al. U-shaped association between serum albumin and development of chronic kidney disease in general hypertensive patients. Clin Nutr 2020;39:258-64.
23. Tanaka M, Komaba H, Fukagawa M. Emerging Association Between Parathyroid Hormone and Anemia in Hemodialysis Patients. Ther Apher Dial 2018;22:242-5.
24. Hoang D, Broer N, Sosa JA, et al. Leptin Is Produced by Parathyroid Glands and Stimulates Parathyroid Hormone Secretion. Ann Surg 2017;266:1075-83.

**Cite this article as:** Yin S, Du Y, Guo Y, Guo G, Sun D, Yao L. Multifactorial analysis of renal anemia-associated substandard hemoglobin levels and prevalence of anemia in patients on maintenance hemodialysis in Liaoning Province: a cross-sectional study. Ann Palliat Med 2022;11(12):3743-3754. doi: 10.21037/apm-22-1348

 