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NEPHROLOGY - ORIGINAL PAPER

Determinants of hemoglobin variability in stable peritoneal dialysis patients

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Abstract
Purpose Significant within-patient hemoglobin (Hb) level variability is well recognized in particularly hemodialysis patients. Several factors such as hospitalizations, intercurrent diseases and IV iron therapy are found to be related to Hb variability (Hb-var). In this observational study, we aimed to identify predictors and outcome of Hb-var in peritoneal dialysis (PD) patients without hospitalization, intercurrent disease and IV iron therapy during the study period.
Methods All patients were in the maintenance phase of short-acting erythropoiesis-stimulating agents (ESAs) therapy. The target range of Hb was 11–12 g/dL according to KDOQI Guidelines in 2007. The desired range of Hb was 11–12.5 g/dL. Patients' demographic and laboratory data were collected at baseline. Atherosclerotic disease was assessed using carotid intima-media thickness (CIMT). We assessed Hb variability with various methods using SD Hb_{mean}, SD Hb_{range} and the velocity of Hb change. Hb $deflect_{positive}$, Hb $deflect_{negative}$, Hb values and ESA dosing were recorded monthly for 6 months.
Results This study included 50 prevalent PD patients (mean age 46.9 ± 13.7 years, 25 women). The mean velocity of Hb change was negatively correlated with age and positively correlated with frequent ESA dose changes. Higher albumin and residual renal function (RRF) were also positively correlated with Hb $deflect_{positive}$. Patients with CIMT ≥0.7 cm had lower SD Hb range compared to CIMT <0.7 cm. Cumulative survival was better in patients with Hb levels consistently ≥10 g/dL compared to patients who had Hb <10 g/dL for at least 1 month. However, Hb-var was not associated with mortality.
Conclusions In PD patients without hospitalization, intercurrent disease(s) or IV iron therapy, young age, higher albumin or RRF and lower CIMT were associated with greater oscillations in response to ESA therapy. Careful and appropriate ESA dose changes considering these parameters could minimize Hb variability in these patients.

Keywords Hemoglobin variability · Peritoneal dialysis · ESA therapy · Mortality

Introduction

Hemoglobin variability (Hb-var) has been recognized as an important factor in anemia management of dialysis patients in the last decade and it is well recognized in especially hemodialysis (HD) patients treated with erythropoiesis-stimulating agents (ESA) [1–5].

Hb-var can be defined as a continuous rise and fall in indulations or cycles in Hb levels. Early reports from United States showed that Hb-var predicted mortality in a large HD population [1], whereas this association was not present in a cohort from Europe [2].

Factors associated with Hb-var in dialysis patients were erythropoiesis-stimulating agents (ESA) dose changes, hospitalizations, intercurrent illness such as infections, iron status, blood transfusions, IV iron therapy, serum albumin, lower age and BMI [2, 4–6]. The extent of Hb-var could also be affected by the type of ESA used. There are some data showing that lower dose

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changes with ESAs which have a longer mode of action could reduce Hb-var [7, 8].

Limited number of studies investigating Hb-var in peritoneal dialysis (PD) patients revealed that this entity is also frequent in PD patients [8–10]. However, we know that some factors which could affect Hb-var in HD patients such as dialysis access type is not present in PD patients.

In the present study, we evaluated Hb-var and related factors as well as the outcome of Hb-var in prevalent PD patients who were in the maintenance phase of ESA treatment. We included only stable chronic PD patients without IV iron therapy or blood transfusion, intercurrent disease and hospitalizations. In this way, we could eliminate the effects of these main confounding factors and evaluate the impact of ESA dosing and related changes on Hb-var.

Methods

Study population

We included patients who had been on continuous peritoneal dialysis therapy for at least 3 months in Marmara University PD Unit. We excluded patients who had active inflammatory disease, malignancy, chronic infection or chronic liver disease. Seventy-six PD patients met these criteria. Subsequently, patients who had active infection including peritonitis, inflammatory disease, blood transfusion(s), hospitalization or hemorrhage as well as those on IV iron therapy during 6 months were also eliminated from analysis. Patients who received a kidney transplant or who had been transferred to HD were also excluded from the study. In addition, only patients who have taken short-acting ESA (epoetin alpha and beta) were included in our study. All the patients were in the maintenance phase of ESA therapy.

Ultimately, 50 PD patients without any PD modality change during 6 months of follow-up period were found to be eligible for the study. The study was approved by the Ethics Committee of Marmara University Medical School and was carried out in accordance with the Declaration of Helsinki.

Study protocol

In all patients, serum ferritin levels and transferring saturation were measured at baseline. The target range of Hb was to 11–12 g/dL according to the Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines in 2007 [11]. The "desired" range of Hb was determined as 11–12.5 g/dL in parallel to previous reports which investigated Hb variability in HD patients [5, 12]. Nineteen patients (38 %) were on desired range of Hb at baseline. Seven patients had on oral iron supplementation at baseline, and we maintained oral iron therapy in these patients. We did not give iron supplementation to the patients who were not on oral iron therapy on enrollment. Dose adjustments of ESA therapy were made monthly. If Hb levels were in the desired range (11–12.5 g/dL), no change to ESA dose was made. ESA was held for 2 week if serum Hb was higher than 13 g/dL and the dose was reduced by 30–50 %. If serum Hb levels were 12.5–13 g/dL, ESA dose was decreased by 20–30 %. When Hb levels were 10–11 g/dL, ESA dose was increased by 20 %. The ESA dose was increased by 30–50 %, if the serum Hb was less than 10 g/dL. We also considered the patient's characteristics such as previous Hb levels, ESA doses and ESA dose-Hb response behaviors in adjusting ESA doses. Doses were individualized as to maintain an appropriate Hb level for each patient.

Demographic and laboratory parameters

Thirty-seven patients (67.3 %) were on continuous ambulatory peritoneal dialysis (CAPD), while 18 patients (32.7 %) were treated with continuous cycling peritoneal dialysis (CCPD). Dialysis adequacy was assessed by measuring Kt/V. The dialysis and residual components of Kt/V were calculated based on 24-h urine and dialysate collections performed prior to the study entry. Residual renal function (RRF) was expressed as the mean value of the sum of the residual urea and creatinine clearances. The peritoneal equilibration test was performed according to the method described by Twardowski. Anthropometric indexes were measured in the morning after the complete emptying of overnight dialysate. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2) and waist circumference (WC) was measured at the narrowest point between the 12th rib and the iliac crest.

Blood samples were drawn after an overnight fasting of at least 12 h. Biochemical parameters were measured using an autoanalyzer (Olympus AU 800; Olympus Diagnostica GmbH, Hamburg, Germany). PTH levels were determined by means of chemiluminescent immunoassay (Liaison N-tact; DiaSorin Inc, Stillwater, MN), and CRP values were measured using a nephelometer (Behring BN II; Dade Behring, Deerfield, IL).

Outcomes

Deaths from all causes such as cardiovascular events, sudden death, stroke and infection were recorded during follow-up while the patients were still on PD therapy.

Patients who received a kidney transplant or transferred to HD were no longer followed

Area under the ESA dose curve (AUC the ESA dose)

At baseline, mean ESA dose was 86.5 ± 50.3 IU/kg/week. We measured the area under the curve for the ESA dose as a better measurement of the monthly ESA requirements during 6 months of follow-up.

We used two different areas to measure AUC the ESA dose (IU/kg/week) as follows:

(1) Area A: Where *y*-axis is ESA dose and x-axis is time (month), the area under the coordinates and above the base line where y is zero ($y = 0$). AUC the ESA dose was calculated by the following formula: $AUC_{0–1\ month} = (ESA\ dose_{baseline} + ESA\ dose_{1st\ month})/2$; $AUC_{1–2\ month} = (ESA\ dose_{1th\ month} + ESA\ dose_{2nd\ month})/2$; …; $AUC_{5–6\ month} = (ESA\ dose_{5th} + ESA\ dose_{6th\ month})/2$.

(2) Area B: Where *y*-axis is ESA dose and *x*-axis is time (month), the area under the coordinates and a base line where y is the y value of the starting data point. AUC the ESA dose was calculated by the following formula: $AUC_{0–1\ month} = (ESA\ dose_{baseline} - ESA\ dose_{1st\ month})/2$; $AUC_{1–2\ month} = (ESA\ dose_{1th\ month} - ESA\ dose_{2nd\ month})/2$; …; $AUC_{5–6\ month} = (ESA\ dose_{5th} - ESA\ dose_{6th\ month})/2$.

Measurement of carotid intima-media thickness

Ultrasonography of the carotid arteries was performed by an experienced and independent ultrasonographer, who was masked to all clinical data, using a 10 MHz vascular ultrasound probe (Vingmed Ultrasound, System 5, Horten, Norway). Carotid intima-media thickness (CIMT) was defined as a low-level echo gray band that does not project into the arterial lumen and is the distance from the leading edge of the lumen–intima interface to the leading edge of the media–adventitia interface of the far edge. Three segments were measured bilaterally: the 1-cm section of the common carotid artery immediately proximal to the beginning of the dilatation of the bifurcation, the 1-cm section of the bifurcation immediately proximal to the tip of the flow divider and the 1-cm section of the internal carotid artery immediately distal to the tip of the flow divider. The mean of the six measurements was used as the carotid artery IMT. A plaque was defined as a focal thickening relative to the adjacent segment with a distinct area of hyperechogenicity or protrusion into the lumen of the vessel that was at least 50 % thicker than the surrounding area.

Assessment of Hb variability

Hb values and ESA dosing were recorded monthly during the first 6 months. Hb variability was measured as follows:

1. The velocity of Hb change was calculated by averaging the absolute slopes between sequential Hb values [1].:
$$\frac{\sum_{i=1}^{N} \frac{a_i}{b_i}}{N}.$$
2. SD Hb_{mean} was used for the residual deviation between the Hb values and the mean Hb target level of 11.7 g/dL [5].
$$\sqrt{\sum_{i=1}^{N} \frac{(X_i - 117.5)^2}{N-1}}.$$
3. SD Hb_{range} was used for the residual deviation between Hb values, and the higher (when Hb >12.5 g/dL) or lower (when Hb <11.0 g/dL) limits of the Hb target range the residual deviation between the same six Hb measures and the lower (if measured Hb <11.0 g/dL) or higher (if measured Hb >12.5 g/dL) limits of the Hb target range were determined. Any Hb values within the range (11.0–12.5 g/dL) were assigned a deviation value of 0.
$$\sqrt{\frac{(X_1 - 110)^2 + (X_2 - 110)^2 + 0 + 0 + (X_5 - 125)^2 + 0}{N-1}}.$$

All methods mentioned above were successfully used to determine the Hb variability in hemodialysis patients [12]. We also calculated Hb deflections as described by Lau et al. [12]. A Hb $deflect_{negative}$ represents that the previous Hb value was higher than any Hb value at a given time point (Hb decreases). The average of the negative deflections was computed. Similar calculations were done to determine the average of the Hb $deflect_{positive}$ when the Hb value was increased compared to the previous Hb measurement.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 13.0, software (SPSS Inc, Chicago, IL). We considered *p* values less than 0.05 as statistically significant. All variables that are distributed normally are presented as mean ± SD, those with non-normal distribution as median and range. The Student *t* test was used to compare means between groups, and the chi-square test was used to compare proportions between groups. For correlations between variables, the Pearson test was used

Table 1 Baseline demographic and laboratory data in PD patients ($n = 50$)

Parameter	
Age (years)	46.9 ± 13.7
Gender (female) *n* (%)	25 (50)
Body mass index (kg/m^2)	26.5 ± 4.56
Waist circumference (cm)	94.4 ± 11.6
Smoking status	
Nonsmoker (%)	26 (52)
Former/current (%)	24 (48)
The presence of diabetes *n* (%)	7 (14)
The presence of CVD *n* (%)	5 (10)
CKD etiology *n* (%)	
Diabetic nephropathy	7 (14)
Hypertension	7 (14)
Glomerulonephritis	2 (4)
Secondary amyloidosis	2 (4)
Obstructive nephropathy	1 (2)
Unknown	23 (46)
Dialysis duration (months)	169 ± 51.7
PD modality *n* (%)	
CAPD	37 (74)
APD	13 (26)
History of peritonitis *n* (%)	
Yes	16 (32)
No	34 (68)
Residual urine volume (mL/day)	397.5 (0–1,215.1)
Systolic blood pressure (mmHg)	127.3 ± 25.8
Diastolic blood pressure (mmHg)	79.8 ± 11.2
Elemental calcium intake (g/day)	2.1 ± 1.3
Kt/V	2.05 ± 0.6
Laboratory parameters	
C-reactive protein (mg/L)	7.8 (1–30)
Serum albumin (g/dL)	4.0 ± 0.5
Erythrocyte sedimentation rate (cm/h)	38.1 (4–72)
Calcium (mg/dL)	9.0 ± 0.9
Phosphate (mg/dL)	5.2 ± 1.1
Parathyroid hormone (pg/mL)	537.4 (6.6–2,500)
Uric acid (mg/dL)	6.8 ± 0.7
HbA1c (%)	5.6 ± 1.1
Ferritin (μg/L)	558 (168–1,350)
TSAT (%)	30.3 ± 9.1
Medication *n* (%)	
ACE inhibitor or ARB use	25 (50)
Statin use	26 (52)
Oral vitamin D	26 (52)
Phosphate binders	34 (68)
Carotid intima-media thickness (cm)	0.7 ± 0.2
Carotid plaque *n* (%)	
Yes	19 (38)
No	31 (62)
Pelvic calcification *n* (%)	
Yes	24 (48)
No	26 (52)

Mean ± SD is reported if the variable is normally distributed; median (range) is reported otherwise. Categorical variables are reported using n (%). *CVD;* cardiovascular disease, *CKD;* chronic kidney disease, *CAPD;* continuous ambulatory peritoneal dialysis, *APD;* automated peritoneal dialysis, *TSAT;* transferrin saturation, *ACE;* angiotensin converting enzyme, *ARB;* angiotensin receptor blocker

for normally distributed data and the Spearman test for those with nonparametric distributions. To assess the influence of tested parameters on Hb-var assessed by different methods, multiple regression analysis was performed. Survival analyses were performed by Kaplan–Meier curves. Cox regression analysis was used to examine the association between Hb-var and mortality.

Results

This study included 50 prevalent PD patients (mean age 46.9 ± 13.7 years, 25 women) who were in the maintenance phase of ESA therapy. Baseline demographic and laboratory data are summarized on Table 1. Hb values, percentages of PD patients with Hb in the desired range (10–12.5 g/dL), AUC the ESA dose (Area A) and AUC the ESA dose (Area B) during 6 months of follow-up are shown on Fig. 1. Anemia management-associated changes are summarized on Table 2. SD Hb_{mean} was well correlated with SD Hb_{range} (0.887, $p = 0.0001$) and Hb change velocity (0.671, $p = 0.001$). Hb change velocity was also correlated with Hb_{range} (0.695, $p = 0.0001$).

Hb variability as measured by methods cited above was not different in diabetic patients ($n = 7$) compared to non-diabetics ($n = 43$). When age, BMI, WC, dialysis duration, elemental calcium intake, residual urine volume, average ESA dose changes, mean ESA dose, CIMT and all laboratory parameters (shown on Table 1) including CRP, ferritin, transferrin saturation were included correlation analysis, the mean velocity of Hb change was only related to age (Pearson correlation −0.303, $p = 0.039$). In patients who were younger than 40 years, the mean velocity of Hb change was higher than that of older patients (0.072 ± 0.002 vs. 0.074 ± 0.003 g/dL, respectively, $p = 0.015$). There was an association between frequency of ESA dose changes and the mean velocity of Hb change. In patients who had changes in ESA dosing more than two during 6 months, the mean velocity of Hb change was significantly higher (0.075 ± 0.004 vs 0.073 ± 0.002 g/dL, $p = 0.037$).

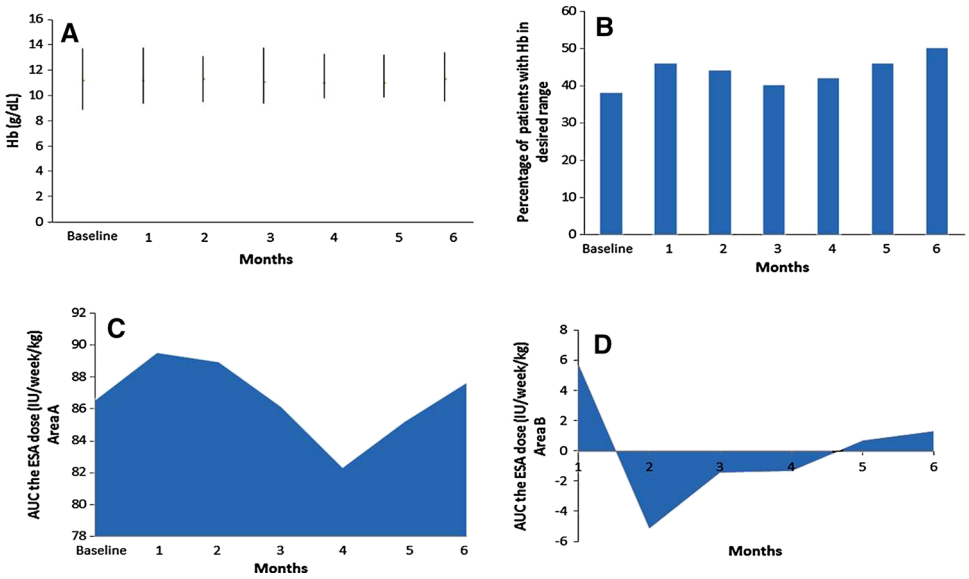

Fig. 1 Characteristics of anemia management in PD patients during 6 months of follow-up. **a** Hb levels. **b** Percentage of PD patients with Hb in the desired range (10–12.5 g/dL). **c** *AUC* area under the curve. *Area A* Where *y*-axis is ESA dose (IU/kg/week) and *x*-axis is time (month), the area under the coordinates and above the base line where *y* is zero ($y = 0$). AUC the ESA dose was calculated by the following formula: $AUC_{0-1\ month} = (ESA\ dose_{baseline} + ESA\ dose_{1st\ month})/2$; $AUC_{1-2\ month} = (ESA\ dose_{1th\ month} + ESA\ dose_{2nd\ month})/2$ …. **d** *AUC* area under the curve. *Area B* The area under the coordinates and a base line where *y* is the *y* value of the starting data point. AUC the ESA dose was calculated by the following formula: $AUC_{0-1\ month} = (ESA\ dose_{baseline} - ESA\ dose_{1st\ month})/2$ …

Table 2 Anemia management-associated changes in PD patients ($n = 50$)

Parameter	
Average ESA dose changes (IU/kg/week)	3.8 (0–7.1)
Frequency of ESA dose changes/6 months	
1	11
2	9
3	7
4	6
Mean ESA dose (IU/kg/week)	101.1 ± 64.4
Mean Hb (average of Hb values) (g/dL)	11.1 ± 1.1
SD Hb_{mean} (g/dL)	1.53 ± 0.9
Hb change velocity (g/dL)	0.07 ± 0.002
SD Hb_{range} (g/dL)	1 ± 0.8
Average Hb $deflect_{positive}$ (g/dL)	1.1 ± 0.9
Average Hb $deflect_{negative}$ (g/dL)	1.1 ± 0.9

Values are expressed as mean ± SD. *ESA* erythropoietin stimulating agents

When the parameters cited above were included in the univariate analysis, only CIMT was negatively correlated with SD Hb_{range} (-0.326, $p = 0.021$). More rapid rises in Hb (the extent of Hb $deflect_{positive}$) was also significantly higher in patients with higher albumin levels and residual renal function. In addition, Hb $deflect_{positive}$ was correlated with the extent of ESA dose changes (IU/kg/week) (0.483, $p = 0.001$). Hb $deflect_{positive}$ also was lower in patients with CIMT ≥0.7 cm compared to those with CIMT <0.7 cm (0.83 ± 0.49 vs. 1.08 ± 0.67 g/dL, $p = 0.036$) (Table 3). In regression analysis, the extent of ESA dose changes ($\beta = 0.352$, $p = 0.019$), albumin ($\beta = 0.360$, $p = 0.020$) and residual renal function ($\beta = 0.401$, $p = 0.39$) were related to Hb $deflect_{positive}$.

Average Hb $deflect_{negative}$ was also correlated with the extent of ESA dose changes (IU/kg/week) ($\rho = 0.381$, $p = 0.007$). More rapid decreases in Hb were lower in patients with CIMT ≥0.7 mm compared to those with CIMT <0.7 cm (0.82 ± 0.52 vs. 1.28 ± 0.71 cm,

Table 3 The factors associated with Hb $deflect_{positive}$

Parameter	Hb $deflect_{positive}$
Albumin level	
>3.5 g/dL	1.2 ± 0.8[a]
<3.5 g/dL	0.7 ± 0.5
Residual renal function	
Yes	1.3 ± 0.8[b]
No	0.8 ± 0.6
Carotid intima-media thickness	
≥0.7 cm	0.83 ± 0.52[c]
<0.7 cm	1.28 ± 0.71

[a] Versus <3.5 g/dL, $p = 0.025$

[b] Versus No, $p = 0.042$

[c] Versus <0.7 cm, $p = 0.021$

Table 4 The factors correlated with carotid intima-media thickness

Parameters	ρ	p value
Age (years)	0.647	0.001
Waist circumference (cm)	0.399	0.007
Serum albumin (g/dL)	−0.371	0.009
Uric acid (mg/dL)	−393	0.005
SD Hb_{range}	−0.326	0.021

$p = 0.033$). In regression analysis, only the extent of ESA dose changes was related to average Hb $deflect_{negative}$ ($\beta = 0.323$, $p = 0.025$).

Associations with CIMT

Older age, higher WC, lower albumin, higher uric acid, lower SD Hb_{mean} and SD Hb_{range} values were correlated with CIMT (Table 4). In multivariate analysis, only WC ($\beta = 0.296$, $p = 0.042$) and albumin ($\beta = -0.221$, $p = 0.032$) were associated with CIMT.

CIMT measurements were equal or higher than 0.7 cm in 23 (46 %) of the patients. When we compared clinical and laboratory parameters in patients with CIMT ≥0.7 cm versus CIMT <0.7 cm, patients with CIMT ≥0.7 cm were older (53.7 ± 13.1 vs. 41.1 ± 13.1 years, $p = 0.048$) had higher WC (98.4 ± 11.9 vs. 91.2 ± 10.6 cm, $p = 0.041$), lower serum albumin (3.9 ± 0.5 vs. 4.2 ± 0.4 g/dL, $p = 0.042$) and lower SD Hb_{range} (0.76 ± 0.52 vs. 1.16 ± 0.72 g/dL, $p = 0.021$). In patients with CIMT ≥0.7 cm, ESA doses (total or kg/week), monthly Hb or mean Hb values, number of ESA dose changes, were not different from patients with CIMT >0.7 cm (data not shown). In multivariate regression analysis, age ($Exp(B) = 1.084$, $p = 0.014$) and SD Hb_{range} ($Exp(B) = 0.054$, $p = 0.043$) were associated with CIMT ≥0.7 cm.

Mortality

Fifty patients were followed for a mean of 34.1 ± 13.6 months. 10 patients underwent renal transplantation, and 8 patients were transferred to hemodialysis. Of the 6 deaths, 3 deaths were due to CVD-related cause. Of these, 1 death was due to heart failure, 1 was due to stroke, and 1 was due to myocardial infarction. The cause of death was sudden death in 1 patient and infections in 2 patients. Twenty-six patients (52 %) had Hb levels <10 g/dL for at least 1 month, and 24 patients had Hb levels consistently ≥10 g/dL during first 6 months. Cumulative survival was better in patients with Hb levels ≥10 g/dL compared to patients who had Hb <10 g/dL for at least 1 month ($\chi^2 = 29.824$, $p = 0.0001$) (Fig. 2). However,

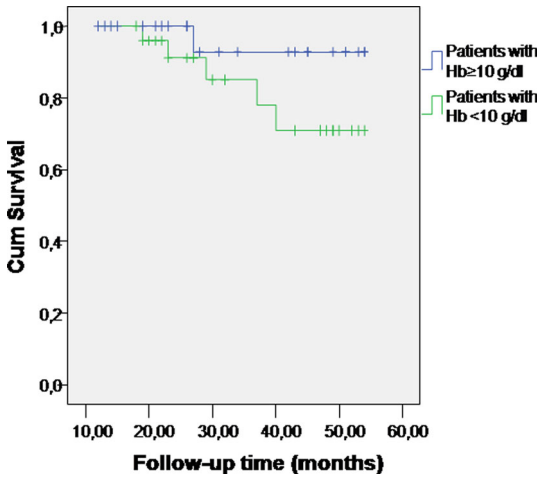

Fig. 2 Cumulative survival is better in patients with Hb levels ≥10 g/dL compared to patients who had Hb <10 g/dL at least 1 month ($\chi^2 = 29.824$, log-rank: $p = 0.0001$)

Hb-var was not related to morbidity and mortality in our Cox regression analysis.

Discussion

Most of the knowledge about Hb-var comes from studies involving HD patients. The major causes of Hb variability are iron deficiency or iron supplementation, angiotensin converting enzyme inhibitor or angiotensin receptor blocker therapy [13], infection and inflammation [14], blood loss and transfusion [15], dialysis adequacy [16], acute and chronic comorbid illness [5] and hyperparathyroidism [17]. Different pharmacokinetics (long vs short acting) and routes (subcutaneous vs intravenously) among ESAs can also effect Hb-var [7, 18].

There are a limited number of studies investigating Hb-var in PD patients (8–10). In the present study, we included only stable chronic PD patients without IV iron therapy or blood transfusion, intercurrent disease or hospitalizations during 6 months of follow-up. Our PD patients also were solely on short-acting ESAs via the subcutaneous route. In this way, we extensively eliminated the effects of these main factors on Hb-var except ESA dosing and frequency changes. We observed that more rapid changes in Hb levels or higher Hb-var due to ESA therapy occurred in younger patients as well as patients with higher residual renal function and CIMT less than 0.7 cm. In addition, higher albumin levels were associated with more rapid rises in Hb levels.

Previous studies reported that lower age is associated with greater Hb variability in HD patients [2, 19]. The underlying mechanism of that association is not entirely

clear [2]. Although, there were no differences in the extent or frequency of ESA dose changes, the PD patients who were younger than 40 years had also higher Hb-var assessed by the mean velocity of Hb change in our study. It was previously reported that elderly patients with normocytic anemia had a lower endogenous erythropoietin response compared to younger counterparts [20]. These results suggest that bone marrow may be more sensitive to ESA therapy in young patients.

In the present study, there was positive correlation between albumin levels and more rapid rises in Hb levels in PD patients treated with ESAs. However, previous studies showed an inversely association between higher serum albumin and Hb-var [2, 19]. Low serum albumin is associated with severe co-morbidity and inflammation in dialysis patients which were not extensively present in our patients. On the other hand, magnitude of Hb increase response to similar ESA dosage could be more pronounced in patients with higher albumin which in turn results in higher Hb-var.

In the literature, the effect of residual renal function (RRF) on Hb-var in dialysis patients is reported only in a single study [19]. Selby et al. found that weekly RRF was significantly higher in patients who did not experience Hb cycling. In this study, the authors used a different definition to describe Hb-var as Hb cycling. One complete Hb cycle was defined as 2 sequential excursions in opposite directions. Contrary to this study, extent of daily RRF was positively correlated with Hb $\text{deflect}_{\text{positive}}$ in our study. It is well known that patients with RRF have better metabolic status and nutrition and lower ESA resistance and anemia [21]. Consequently, more rapid rises in Hb levels secondary to ESA therapy could be expected in patients with RRF as with higher albumin.

Intima-media thickness of common carotid arteries measured by ultrasound is used as indicator of atherosclerosis. Increased CIMT is an independent predictor of cardiovascular deaths in HD patients [22, 23]. There are no data regarding the associations between Hb-var or ESA resistance and CIMT in the literature. This is the first study observing more rapid rises in Hb levels and Hb-var assessed by SD Hb_{range} which was increased in patients with CIMT <0.7 cm. A lesser degree of atherosclerosis might be responsible for the increased response to ESA therapy in these patients.

The relationship between Hb-var and mortality is controversial in maintenance dialysis patients. In a large-scale cohort, Hb-var was associated with mortality in HD patients [1]. On the contrary, increased risk of mortality was detected only in patients with continently low-Hb category or the number and timing of Hb levels <11 g/dL in other studies [2, 3]. Lau JH reported that more rapid rises in Hb and ESA dose increases were associated with mortality in HD patients [12]. In our study, patients who had Hb levels <10 g/dL for at least 1 month during 6 months of follow-up had worse survival. We could not observe any relationships between rapid Hb rises or ESA dose increases and mortality (data not shown).

In an observational study, the usual doses of ESA used in every day clinical practice were associated with higher mortality in HD patients but not PD patients. Mortality risk only increased when ESA doses exceeded to 15,000 IU/week in PD patients [24]. We had never used ESA doses more than 15,000 IU/week in our PD patients, because Government Health Insurance does not cover the cost of ESA doses more than 15,000 IU/week in Turkey.

In a large cohort study from Brazil, anemia but not Hb-var was associated with mortality in 2,156 incident PD patients [25]. While the small number of the patients ($N = 50$) and deaths ($n = 6$) reported in our study may not be adequate to detect the predictors of survival, neither Hb-var nor ESA doses were associated with mortality in our prevalent PD patients.

The small number of patients included is the major limitation of the present study. But, this is a single-center study and we included only chronic PD patients without IV iron therapy or blood transfusion, intercurrent disease and hospitalization during a 6-month period of evaluation. Accordingly, the effects of these main confounding factors on Hb-var except ESA dose and frequency changes were eliminated. Observational nature of the present study makes it difficult to determine a cause-and-effect relationship.

In conclusion, conflicting reports in relationships between Hb-var and underlining factors or mortality may be due to complex mechanisms. Different methodology to define Hb-var can be a considerable factor. On the other hand, inflammation or infection induces Hb-var as well as hypoalbuminemia which are also found to be independent risk factor for Hb-var. We showed that patients with higher albumin or RRF and lower age or CIMT showed higher Hb oscillations. In these patients, faster and greater extent Hb increases in response to ESAs resulted in Hb-var. In clinical practice, we prescribe ESAs mostly according to the patient's body weight and manage additional dosing secondary to Hb changes. This approach can cause undesirable Hb changes in some patients. It may be possible to minimize Hb oscillations in response to ESA dosing if we also consider other factors such as albumin, RRF and age in stable PD patients.

Conflict of interest None.

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