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Original Article

Optimal hemoglobin level for anemia treatment in a cohort of hemodialysis patients

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Abstract

Background: Anemia is a major risk factor that contributes to mortality in patients with chronic kidney disease. There is controversy over the optimal hemoglobin (Hb) target in these patients. This study investigated the association between Hb level and mortality in a cohort of hemodialysis (HD) patients in Korea.

Methods: This study was a multicenter prospective observational study of maintenance HD patients that was performed for 5 years in western Seoul, Korea. Three hundred and sixty-two participants were enrolled. Laboratory values and mortality were accessed every 6 months. Repeated measures of laboratory values in each interval were averaged to obtain one semiannual mean value. The Hb values were divided into six groups: (1) Hb < 9 g/dL; (2) 9 g/dL ≤ Hb < 10 g/dL; (3) 10 g/dL ≤ Hb < 11 g/dL; (4) 11 g/dL ≤ Hb < 12 g/dL; (5) 12 g/dL ≤ Hb < 13 g/dL; and (6) Hb ≥ 13 g/dL. We analyzed the odds ratio for all-cause mortality, based on the Hb group, and adjusted for demographics and various laboratory values. Statistics were performed with SAS, version 9.1 software (SAS Institute Inc., Cary, NC, USA).

Results: Mortality odds ratios relative to the reference group (10–11 g/dL) in the fully adjusted model were 3.61 for < 9 g/dL; 3.17 for 9–10 g/dL*; 4.65 for 11–12 g/dL*; 5.50 for 12–13 g/dL*; and 2.05 for ≥ 13 g/dL (* indicates $P < 0.05$).

Conclusion: In this study, a Hb level of 10–11 g/dL was associated with the lowest mortality among the groups with Hb level < 13 g/dL. Larger interventional trials are warranted to determine the optimal Hb target for Korean HD patients.

Introduction

Anemia is a common complication in patients with chronic kidney disease (CKD), particularly in hemodialysis (HD) patients. Anemia contributes to symptoms such as fatigue, dyspnea, reduced exercise tolerance, depression, and cardiovascular consequences (e.g., left ventricular hypertrophy) [1]. Anemia is also associated with increased rates of hospitalization and mortality in patients with CKD [2,3]. Many studies have shown the beneficial effects of anemia treatment such as improved quality of life; protection against cardiovascular disease [4]; and reduced mortality, morbidity, and hospitalization rates [5] in patients with

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CKD. Until 2 decades ago, the mainstay of treatment was blood transfusion and the administration of androgenic anabolic steroids. Since the introduction of erythropoiesis-stimulating agents (ESAs) in the late 1980s, treatment modalities have undergone profound changes, which have made it possible to achieve desirable hemoglobin (Hb) levels in patients with CKD. As a result, the mean Hb and hematocrit (Hct) levels in patients with CKD, particularly patients on hemodialysis, increased steadily through 2007 in the United States [6] and through 2006 in Korea [7].

In recent decades, many observational studies and interventional trials have been performed to define the target level of Hb in patients with CKD. Several guidelines for anemia treatment from international groups and various countries have been revised for patients with CKD. However, controversy exists over the optimal level of anemia correction. In addition, there are no guidelines for the care of Korean patients with CKD—most Korean nephrologists use international guidelines, [e.g., the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines] [8] or Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [9]. The current recommended target Hb level may not optimize survival in Korean patients with CKD, particularly in patients with end-stage renal disease (ESRD).

In view of the current controversy over the target Hb level in patients with CKD and because of ethnic differences in anemia in various regions of the world, reporting results from Korean HD patients can serve as a complementary guide for clinical nephrologists and as a preliminary study for future work up. We conducted the present study, and adjusted for potential confounders and laboratory values over time, to investigate the association between Hb levels and mortality in a cohort of Korean HD patients from dialysis clinics in western Seoul.

Methods

Patients

This study was a multicenter prospective observational study of maintenance HD patients. It was performed using a cohort from 10 dialysis clinics in western Seoul between September 2006 and September 2011. We included patients who were older than 18 years and had been on HD for >3 months in September 2006. Patients with malignancies were excluded. All patients underwent conventional HD for 4 hours per session three times per week with synthetic membranes. We gathered data every 6 months for 5 years from September 2006 to September 2011. This study was approved by the Institutional Review Board of the Clinical Research Institute at Korea University Guro Hospital (Seoul, Korea). All patients provided informed consent.

Clinical assessment

We investigated baseline demographic and clinical data such as age, gender, presence of diabetes mellitus (DM), and body mass index (BMI) at the time of enrollment. Laboratory data such as Hb, iron metabolism indices (e.g., serum iron, total iron binding capacity, transferrin saturation, and serum ferritin), serum albumin, serum creatinine, serum calcium, serum phosphorus, intact parathyroid hormone (iPTH), and the single pool dialyzer clearance (Kt) per volume (V) of fluid (spKt/V) values were obtained at the commencement of the study, and then every 6 months during the follow-up period. For variables measured monthly, up to three consecutive repeated measures in each session (6-month intervals) were averaged to obtain one semiannual mean value and to mitigate the effect of short-term variations. For variables such as iPTH and spKt/V that were measured at 3-month intervals, all available repeated measures in each session were used. Each patient consequently may have had up to 10 repeated and semiannual varying values for each measure during the 5-year observation period. Observations with a missing value for any measure were excluded from the analysis. We identified patients who received kidney transplantation, changed to peritoneal dialysis, or were transferred permanently to other clinics. We included only available data from these patients.

The ESA doses were adjusted in accordance with the national reimbursement policy of health insurance in Korea, which only financially supports the use of ESAs to treat anemia in dialysis patients with a Hb level ≤ 11 g/dL [10]. All-cause mortality within a particular session was also assessed as an outcome variable.

We divided the Hb values into six groups: (1) Hb <9 g/dL; (2) 9 g/dL $\leq$ Hb <10 g/dL; (3) 10 g/dL $\leq$ Hb <11 g/dL; (4) 11 g/dL $\leq$ Hb <12 g/dL; (5) 12 g/dL $\leq$ Hb <13 g/dL; and (6) Hb ≥ 13 g/dL). A Hb level of 10–11 g/dL was the reference value.

Statistical analysis

We performed descriptive analysis to assess the baseline characteristics of the study population. All results, except for the iPTH values, are presented as the mean $\pm$ the standard deviation. Because the range of iPTH was so broad, it is presented as the median of the 25th and 75th percentile values.

The generalized estimating equation with exchangeable correlation structure was used to investigate its association between the variables and mortality because the laboratory values measured at different time points in the same person were correlated. To identify factors influencing mortality, univariate analysis was performed for each demographic and laboratory variable. Multivariate analysis was performed to calculate the odds ratio of mortality, based on the semiannual Hb level. Adjustment was performed for significant variables in univariate analysis, and performed for other variables that affect survival or the Hb level such as gender, BMI, and iron metabolism indices. Four models were examined, based on the level of multivariate adjustment: (1) the unadjusted base model (Model 1), which included Hb as the predicting variable and all-cause mortality as the outcome variable; (2) Model 2, which included adjustments for patient demographics (i.e., age, sex, presence of DM, BMI); (3) Model 3, which included adjustments for spKt/V, iron metabolism indices (i.e., ferritin, transferrin saturation), and the variables in Model 2; and (4) Model 4, which included adjustments for serum creatinine, serum albumin, serum phosphate, serum calcium-phosphorus products, and the variables in Model 3. All laboratory data were included as time-varying covariates with up to 10 semiannual averaged values per variable per patient.

All descriptive and multivariate statistics were performed with SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA). Statistical significance was defined as $P<0.05$.

Results

Study population

This study included 362 patients who were treated at 10 clinics in western Seoul in September 2004. The overall follow-up time

was 1,162 patient-years. There were 95 (26.2%) deaths, which is a death rate of 8.2 per 100 patient-years. The unadjusted analysis (i.e., Model 1) included 2,277 patient sessions, and the final analysis (i.e., Model 3) included 1,119 patient sessions.

Table 1. Baseline characteristics of the study population

Variable	Total ($n=362$)
Age (y)	58.4 ± 12.8
Women	45.8
Diabetes mellitus	37.3
Body mass index (kg/m^2)	21.7 ± 3.3
Single pool Kt/V	1.50 ± 0.27
Initial laboratory values	
Blood hemoglobin (g/dL)	10.1 ± 1.1
Serum albumin (g/dL)	3.9 ± 0.3
Serum creatinine (mg/dL)	9.3 ± 2.7
Serum phosphorus (mg/dL)	5.1 ± 1.6
Serum calcium (mg/dL)	8.8 ± 0.8
Calcium-phosphorus products (mg^2/dL^2)	46.1 ± 14.6
iPTH (pg/mL) *	66.5 (34.0, 166.3)
Serum ferritin (ng/mL)	266.3 ± 237.2
Serum iron (ng/mL)	82.4 ± 35.8
TIBC (mg/dL)	208.2 ± 39.4
Transferrin saturation	40.2 ± 16.7

* The iPTH level is presented as the median (25th percentile, 75th percentile).
Data are presented as % or mean ± SD, unless otherwise indicated.
iPTH, intact parathyroid hormone; Kt/V, dialyzer clearance (Kt) per volume (V) of fluid; TIBC, total iron binding capacity; SD, standard deviation.

Table 1 shows the demographic characteristics and basal laboratory variables of the study population. The mean age was 58.4 ± 12.8 years, and the proportion of male patients (54.2%) was slightly larger than that of female patients (45.8%). The mean BMI was 21.7 ± 3.3 kg/m^2. One hundred and thirty-five (37.3%) patients were diagnosed as having DM.

Fig. 1 shows the frequency distribution of the average Hb per patient session. The most common hemoglobin level (42.2%) was 10–11 g/dL. The second most common Hb level (24.9%) was 9–10 g/dL. Nearly 67.1% of patient sessions were associated with a Hb level of 9–11 g/dL.

Analysis of factors affecting patient survival

After adjusting for Hb level, the risk analysis of relevant variables showed that age, presence of DM, serum creatinine, serum albumin, serum phosphorus, and calcium-phosphorus products had a statistically significant influence on the odds ratio of mortality (Table 2). However, gender, BMI, iron metabolism indices, serum calcium, and iPTH had no significant effect. A young age, absence of DM, higher serum creatinine, and high serum albumin were associated with lower mortality. Higher serum phosphorus and calcium-phosphorus products seemed to be associated with better survival. However, the association was no longer significant after additional adjustments for age, BMI, serum creatinine, and serum albumin (Table 3).

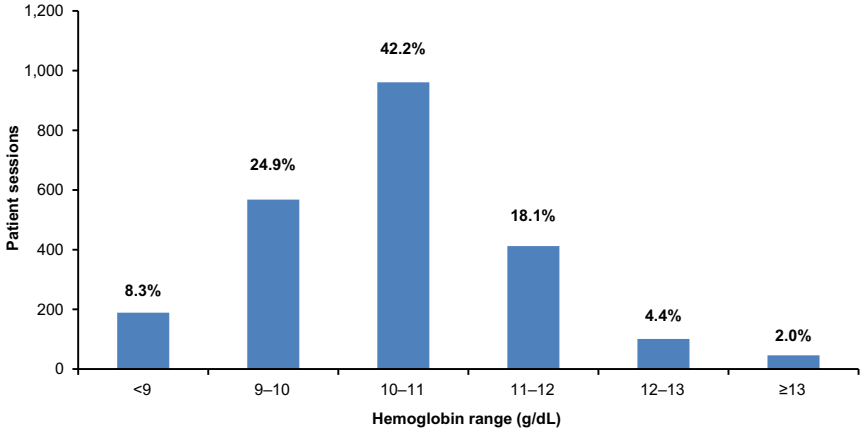

Figure 1. Distribution of semiannually hemoglobin values. The results are expressed as patient sessions.

Table 2. Risk of all-cause mortality associated with relevant variables

Variable	Odds ratio	95% CI	*P*
Age	1.04	1.02–1.06	<0.001*
Gender	1.13	0.74–1.72	0.569
Diabetes mellitus	1.37	1.06–1.92	0.035*
Body mass index (kg/m^2)	0.97	0.91–1.03	0.398
Serum albumin (g/dL)	0.35	0.16–0.74	0.005*
Serum creatinine (mg/dL)	0.83	0.76–0.89	<0.001*
Serum phosphorus (mg/dL)	0.78	0.67–0.92	0.003*
Serum calcium (mg/dL)	0.92	0.72–1.17	0.507
Calcium-phosphorus products (mg^2/dL^2)	0.97	0.96–0.99	0.002*
iPTH (pg/mL)	0.99	0.99–1.00	0.611
Serum ferritin (ng/mL)	1.00	1.00–1.01	0.102
Transferrin saturation (%)	1.00	0.98–1.02	0.936

* Indicates a significant value ($P<0.05$).
CI, confidence interval; iPTH, intact parathyroid hormone.

Table 3. Risk of all-cause mortality associated with serum phosphorus and calcium-phosphorus products, after adjusting for nutrition markers

Variable	Odds ratio	95% CI	*P*
Serum phosphorus (mg/dL)	0.90	0.73–1.12	0.388
Calcium-phosphorus products (mg^2/dL^2)	0.99	0.97–1.01	0.360

CI, confidence interval.

Association of Hb with patient survival

An association between the semiannual average Hb value and mortality within the same session was analyzed using the generalized estimating equation model (Table 4). A Hb level of 10–11 g/dL was selected as the reference group. The base model (i.e., Model 1) did not include adjustments for demographics or laboratory values. Additional models included adjustment for demographics and relevant variables. Model 4 was adjusted in the same manner as Model 3 and adjusted for variables that had a significant influence on the odds ratios of mortality, based on the Hb level (Table 2).

Using Models 1 and 2, a Hb level of 10–11 g/dL had a lower mortality odds ratio than a Hb level of 11–12 g/dL. In Model 3, the lowest mortality odds ratio—other than that of the group with a Hb level > 13 g/dL—was observed in the Hb 10–11 g/dL group. Model 4 showed similar results, except that comparing the Hb 10–11 g/dL group with the Hb < 9 g/dL group did not show a statistically significant difference.

Adjusting the demographic and laboratory values to those of the base model resulted in changes in the mortality odds ratio within Hb groups. However, the trend toward the Hb 10–11 g/dL group having lower mortality than groups with Hb level < 13 g/dL was maintained in all multivariate analyses (Fig. 2).

Discussion

In a cohort of 362 Korean HD patients, we prospectively collected repeated measures of laboratory values and assessed the 6-month mortality risk associated with the Hb level. We demonstrated that a Hb level of 10–11 g/dL (i.e., the reference range) was associated with the lowest mortality risk among the groups with Hb levels < 13 g/dL. In all models, a Hb level ≥ 13 g/dL was also associated with lower mortality than the other Hb groups, except for the reference range group; however, this result was not statistically significant.

Several variables such as age, presence of DM, and dialysis adequacy, which were considered to have an effect on survival, were adjusted for in Models 2 and 3. Iron metabolism indices associated with the Hb level were also adjusted for in Model 3. The repeated measures that had a significant influence on mortality were used for the cumulative adjustment in Model 4 (Table 2). These measures were indicators of malnutrition and inflammation and have been associated with important outcomes in dialysis patients in previous studies [11,12].

The confounding effects of these variables and their changes over time may be controlled for by adjustment. In our results, the association between the Hb level and mortality were not attenuated by adjusting for potential confounding factors.

Table 4. Risk of all-cause mortality, based on the hemoglobin model

Hb range (g/dL)	Model 1*			Model 2†			Model 3‡			Model 4§		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Hb < 9	2.03	0.95–4.33	0.065	2.05	0.96–4.38	0.062	5.56	0.79–9.76	0.001‖	3.61	0.97–14.23	0.065
9 ≤ Hb < 10	1.55	0.88–2.73	0.125	1.62	0.92–2.85	0.094	2.81	0.98–5.17	0.019‖	3.17	1.29–7.75	0.014‖
10 ≤ Hb < 11	1	Ref	Ref	1	Ref	Ref	1	Ref	Ref	1	Ref	Ref
11 ≤ Hb < 12	1.88	1.07–3.30	0.027‖	1.83	1.03–3.24	0.038‖	3.72	1.46–7.52	0.002*	4.65	1.97–11.70	< 0.001‖
12 ≤ Hb < 13	1.29	0.44–3.75	0.629	1.33	0.45–3.87	0.601	4.59	1.18–12.46	0.011‖	5.50	1.48–17.92	0.007‖
Hb ≥ 13	1.31	0.29–5.84	0.718	1.19	0.23–6.15	0.828	1.43	0.12–14.92	0.762	2.05	0.14–22.18	0.566

* Model 1 is the unadjusted base model.
† Model 2 is adjusted for patient demographics (i.e., age, sex, presence of DM, BMI).
‡ Model 3 is adjusted for patient demographics (i.e., age, sex, presence of DM, BMI), dialyzer clearance per volume of fluid (spKt/V), and iron metabolism indices (ferritin, transferrin saturation).
§ Model 4 is adjusted for serum creatinine, serum albumin, serum phosphate, and serum calcium-phosphorus products, in addition to the variables in Model 3.
‖ Indicates a significant value ($P < 0.05$).
BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; Hb, hemoglobin; OR, odds ratio; Ref, reference.

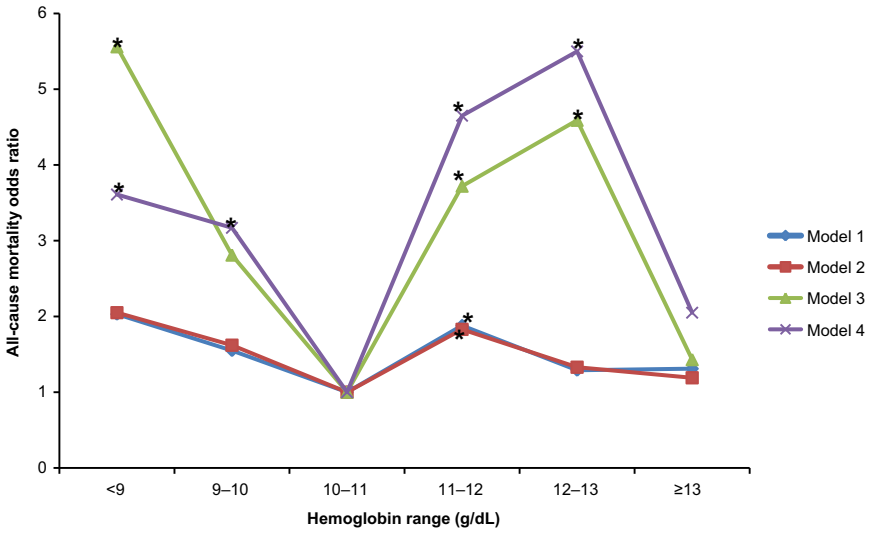

Figure 2. Association between hemoglobin level and risk of all-cause mortality in the study population.
* Indicates a significant value ($P < 0.05$).

Early observational studies from 1993 to 1999 showed an association between a low Hct level and increased mortality in long-term dialysis patients, but showed no association between increased mortality and a Hct value greater than the reference group (i.e., Hct 33–36% or Hct 36–39%) [2,13]. At that time, very few patients achieved a Hb level > 12 g/dL, and erythropoietin use was much less frequent than its use in the 2000s.

In the early 21st century, two observational longitudinal studies by Regidor et al [14] and by Messana et al [15] investigated the association between Hb/Hct level and mortality in long-term HD patients by repeated measures. These studies showed that a Hb level of 12–13 g/dL and a Hct level of 36–39% were associated with the greatest survival, after adjusting for demographics, comorbidities, and time-varying laboratory measures or medications. In these studies, Hb and Hct levels less than or greater than the greatest survival range (i.e., Hb < 12–13 g/dL and Hct > 36–39%) were associated with an increased mortality risk. In the study by Regidor et al [14], most (93%) patients received ESAs, and patients who received ESAs had Hb levels similar to patients who did not receive ESAs (mean Hb, 12.0 ± 1.3 g/dL versus 12.3 ± 1.5 g/dL, respectively) [14]. The study by Messana et al [15] showed that ESAs were administered in more than 99% of patient sessions in which patients had a Hb level > 13 g/dL [15]. These two studies indicate that Hb levels > 13 g/dL may be achieved through ESA therapy.

Several studies have suggested that a greater ESA dose at higher Hb/Hct levels was associated with an elevated mortality risk [16,17]. However, an independent association between the dose of ESAs or ESA hyporesponsiveness and survival remain to be determined [18].

In our study, Hb levels of 11–13 g/dL were associated with a higher mortality risk, compared to the reference group. However, Hb levels > 13 g/dL did not show a statistically significant result. Hemoglobin levels ≥ 13 g/dL were found in only 46 measures, which is approximately 2% of the total patient sessions. This count may have been too small to show a statistical significance.

In all models, the group with a Hb level ≥ 13 g/dL was also associated with lower mortality, compared to the other Hb groups, except for the reference range group. However, this result was not statistically significant. Thirty-seven (80.43%) measures among Hb levels ≥ 13 g/dL had a previous measure of Hb > 11 g/dL. Nearly all of these Hb levels may be achieved naturally without ESA therapy, with regard to the national reimbursement policy of health insurance in Korea [10]. In recent studies, a normal Hb level (> 13 g/dL or > 12 g/dL) that was not achieved by ESA was not a risk factor for mortality in patients with CKD [18,19].

In contrast to the results of early observational studies, the results of several randomized controlled trials (RCTs) using ESAs for different target Hb levels have repeatedly demonstrated an increased risk of mortality or no benefit on mortality or cardiovascular events in patients treated to achieve higher Hb level [20–23]. These RCTs compared similar Hb groups with a high Hb target of 13.0–15.0 g/dL and a low Hb target of 9.0–11.5 g/dL.

Based on these results, the United States Food and Drug Administration (FDA) in 2011 modified recommendations for the dosing of ESAs in patients with CKD [24]. The new ESA label recommends starting ESA when a Hb level is < 10 g/dL and using the lowest possible ESA dose required to reduce the need for transfusions.

Several guidelines from international groups and various countries are currently being updated. The guidelines propose a Hb level of 10–12 g/dL as the target range. The optimal Hb target in patients with CKD remains unclear; however the Hb target range is lower than the range used in the past (Table 5).

This study was a longitudinal observational study that calculated semiannual averaged Hb values and mortality in the same session. The Hb range with the lowest mortality (10–11 g/dL) was lower than the Hb target in the KDOQI guidelines [8], but was in correspondence with the recent trend toward a lower Hb target.

This study has several limitations. First, because we conducted an observational study, the findings presented in this report do not reflect a cause-and-effect relationship, but only reflect associations. Therefore, we cannot rule out the possibility that such associations were influenced by unmeasured factors that contribute to anemia and survival such as underlying comorbidities or inflammation.

Table 5. Summary of recommendations for anemia in chronic kidney disease

		Hb target	ESA use
International guidelines			
KDOQI	2007 *	Hb level, 11.0–12.0 g/dL. The Hb target should not be ≥ 13.0 g/dL	–
KDIGO	2012	–	Start ESAs when the Hb level is 9.0–10.0 g/dL to avoid Hb levels < 9.0 g/dL. ESAs should not be used for Hb levels > 11.5 g/dL. ESAs are not recommended for Hb levels > 13 g/dL
ERBP	2004 †	Hb level, > 11 g/dL. In HD patients, a Hb level > 14 g/dL is not desirable	–
	2009 ‡	Hb level, 11–12 g/dL. The Hb level should not intentionally be > 13 g/dL	–
	2013 ‡	Hb level, 10–12 g/dL. The Hb level should not be > 13 g/dL	Start ESAs when the Hb level is 9.0–10.0 g/dL to avoid a Hb level < 9.0 g/dL. ESAs should not be used for Hb levels > 11.5 g/dL. ESAs are not recommended for Hb levels > 13 g/dL
National guidelines			
KSN	2005	Hb level, 11.0–12.0 g/dL	–
CSN	1999	Hb level, 11.0–12.0 g/dL	–
	2008	In HD and ND patients, a Hb level of 11.0 g/dL. In PD patients, a Hb level of 10.0–12.0 g/dL	Initiate ESAs when Hb level is < 10.0 g/dL; Prescribe ESAs to achieve the target Hb level
CARI	2008	Target Hb level, 11.0 g/dL. A target Hb > 13.0 g/dL is inadvisable	–
	2011	Hb level, 10.0–11.5 g/dL. A Hb level > 13.0 g/dL is not recommended	In dialysis patients, ESAs can be used to prevent Hb levels < 9.5 g/dL
UK Renal Association	2006	Hb level, 10.5–12.5 g/dL	Adjust ESAs when the Hb levels < 11 or > 12 g/dL to maximize the proportion of patients in the range of 10.5–12.5 g/dL
	2010	Hb level, 10–12 g/dL	Adjust ESAs when Hb levels are < 10.5 g/dL or > 11.5 g/dL to achieve a population distribution centered on a mean of 11 g/dL in the range of 10–12 g/dL
JSDT	2004	Hb level, 10–11 g/dL	ESAs should be initiated when Hb levels are < 10 g/dL
	2008	In HD patients, Hb level of 10–11 g/dL. In PD and ND patients, Hb level of ≥ 11 g/dL	In HD patients, ESAs should be adjusted when the Hb level is > 12 g/dL. In PD and ND patients, adjustments to ESAs should be considered when the Hb level is > 13 g/dL

* Contents of the 2007 update of KDOQI anemia guidelines.
† Contents of European Best Practice Guidelines.
‡ Contents of the ERBP position statement.
CARI, Caring for Australasians with Renal Impairment; CKD, chronic kidney disease; CSN, Canadian Society of Nephrology; ERBP, European Renal Best Practice; ESAs, erythropoiesis-stimulating agents; Hb, hemoglobin; HD, hemodialysis; JSDT, Japanese Society for Dialysis Therapy; KDIGO, Kidney Disease: Improving Global Outcomes; KDOQI, National Kidney Foundation's Kidney Disease Outcomes Quality Initiative; KSN, Korean Society of Nephrology; ND, nondialysis; PD, peritoneal dialysis.

Second, our study enrolled a small number of patients, compared to other studies. Previous observational studies mentioned in this paper included at least 40,000 patients, compared to our 362 patients [2,13–15].

Because of the discrepancy of the KDOQI guidelines [8] and the reimbursement policy of Korea, ESAs were discontinued and reinstituted frequently [25]. A third limitation therefore is that it was difficult to identify exact ESA doses and thus they were not reported in this study.

Fourth, with the exception of DM, underlying diseases were not included in the analysis.

Fifth, among variables that had a significant influence on mortality (Table 2), the results of serum phosphorus and calcium-phosphorus products were inconsistent with previous findings [11,26]. The results were also not statistically significant after additional adjustments for nutritional parameters (Table 3). Therefore, it is possible that the influence of serum phosphorus and calcium-phosphorus products on mortality were caused by nutrition.

The strengths of our study are the following: (1) to the best of our knowledge, this is the first study in the 21st century to investigate the association between the Hb level and mortality in a contemporary cohort of Korean HD patients and (2) several laboratory variables associated with patient outcome were studied in the form of repeated measures of longitudinal data. The Hb levels may change drastically over time, and the management of patients with CKD is based on periodic measurements of blood. Therefore, longitudinal measurement of Hb and laboratory values, rather than measurements at only one point in time, may provide additional insights.

In conclusion, we found that Hb levels of 10–11 g/dL were associated with the lowest mortality among groups with Hb levels $<$ 13 g/dL in Korean patients on maintenance HD. We could not define the optimal Hb level because of the observational nature and small sample size of our study; therefore, larger interventional trials are warranted to determine the optimal Hb target for Korean HD patients.

Conflict of interest

The authors have no potential conflict of interest to report relevant to this article.

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References

[1] Levin A, Thompson CR, Ethier J, Carlisle EJ, Tobe S, Mendelssohn D, Burgess E, Jindal K, Barrett B, Singer J, Djurdjev O: Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis* 34:125–134, 1999

[2] Ma JZ, Ebben J, Xia H, Collins AJ: Hematocrit level and associated mortality in hemodialysis patients. *J Am Soc Nephrol* 10:610–619, 1999

[3] Ofsthun N, Labrecque J, Lacson E, Keen M, Lazarus JM: The effects of higher hemoglobin levels on mortality and hospitalization in hemodialysis patients. *Kidney Int* 63:1908–1914, 2003

[4] Parfrey PS, Foley RN, Wittreich BH, Sullivan DJ, Zagari MJ, Frei D: Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. *J Am Soc Nephrol* 16:2180–2189, 2005

[5] Locatelli F, Pisoni RL, Akizawa T, Cruz JM, DeOreo PB, Lameire NH, Held PJ: Anemia management for hemodialysis patients: Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines and Dialysis Outcomes and Practice Patterns Study (DOPPS) findings. *Am J Kidney Dis* 44:27–33, 2004

[6] Freburger JK, Ng LJ, Bradbury BD, Kshirsagar AV, Brookhart MA: Changing patterns of anemia management in US hemodialysis patients. *Am J Med* 125:906–914.e9, 2012

[7] Jin DC: Current status of dialysis therapy in Korea. *Korean J Intern Med* 26:123–131, 2011

[8] Kidney Disease Outcomes Quality Initiative (KDOQI): KDOQI Clinical practice guideline and clinical practice recommendations for anemia in chronic kidney disease. 2007 update of hemoglobin target. *Am J Kidney Dis* 50:471–530, 2007

[9] Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl* 2:279–335, 2012

[10] National reimbursement policy for medications 2013. Available at: http://www.nhis.or.kr/portal/site/main/MENU_WBDDC04 [Date accessed: 21 Nov 2013].

[11] Palmer SC, Hayen A, Macaskill P, Pellegrini F, Craig JC, Elder GJ, Strippoli GF: Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. *JAMA* 305:1119–1127, 2011

[12] Terrier N, Jaussent I, Dupuy AM, Morena M, Delcourt C, Chalabi L, Rouanet C, Canaud B, Cristol JP: Creatinine index and transthyretin as additive predictors of mortality in haemodialysis patients. *Nephrol Dial Transplant* 23:345–353, 2008

[13] Collins AJ, Li S, St. Peter W, Ebben J, Roberts T, Ma JZ, Manning W: Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. *J Am Soc Nephrol* 12:2465–2473, 2001

[14] Regidor DL, Kopple JD, Kovesdy CP, Kilpatrick RD, McAllister CJ, Aronovitz J, Greenland S, Kalantar-Zadeh K: Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. *J Am Soc Nephrol* 17:1181–1191, 2006

[15] Messana JM, Chuang CC, Turenne M, Wheeler J, Turner J, Sleeman K, Tedeschi P, Hirth R: Association of quarterly average achieved hematocrit with mortality in dialysis patients: a time-dependent comorbidity-adjusted model. *Am J Kidney Dis* 53:503–512, 2009

[16] Santos PR, Melo AD, Lima MM, Negreiros IM, Miranda JS, Pontes LS, Rabelo GM, Viana AC, Alexandrino MT, Barros FA, Neto BR, Brito AA, Da Silva Costa A: Mortality risk in hemodialysis patients according to anemia control and erythropoietin dosing. *Hemodial Int* 15: 493–500, 2011

[17] Brookhart MA, Schneeweiss S, Avorn J, Bradbury BD, Liu J, Winkelmayer WC: Comparative mortality risk of anemia management practices in incident hemodialysis patients. *JAMA* 303: 857–864, 2010

[18] Horl WH: Anaemia management and mortality risk in chronic kidney disease. *Nat Rev Nephrol* 9:291–301, 2013

[19] Goodkin DA, Fuller DS, Robinson BM, Combe C, Fluck R, Mendelssohn D, Akizawa T, Pisoni RL, Port FK: Naturally occurring higher hemoglobin concentration does not increase mortality among hemodialysis patients. *J Am Soc Nephrol* 22:358–365, 2011

[20] Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D: Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 355:2085–2098, 2006

[21] Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, Schwab SJ, Goodkin DA: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 339:584–590, 1998

[22] Drueke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, Burger HU, Scherhag A: Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 355:2071–2084, 2006

[23] Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, Feyzi JM, Ivanovich P, Kewalramani R, Levey AS, Lewis EF, McGill JB, McMurray JJ, Parfrey P, Parving HH, Remuzzi G, Singh AK, Solomon SD, Toto R: A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 361: 2019–2032, 2009

[24] Food and Drug Administration (FDA): FDA drug safety communication: modified dosing recommendations to improve the safe use of erythropoiesis-stimulating agents in chronic kidney disease 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm259639.htm [Date accessed: 15 January 2015].

[25] Park SK, Hwang KS, Park JS, Lee CH, Kang CM, Kim GH: Hemoglobin variability associated with different erythropoiesis stimulating agents in hemodialysis patients. *Korean J Nephrol* 30:41–47, 2011

[26] Tentori F, Blayney MJ, Albert JM, Gillespie BW, Kerr PG, Bommer J, Young EW, Akizawa T, Akiba T, Pisoni RL, Robinson BM, Port FK: Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 52:519–530, 2008