

Responsiveness to Erythropoiesis-Stimulating Agents and Hemoglobin Variability in Japanese Patients With End-Stage Kidney Disease

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Abstract

Background

Serum hemoglobin variability is a risk factor for cardiovascular mortality in end-stage kidney disease (ESKD). However, the indicators that reflect hemoglobin variability remain insufficiently investigated. We examined the association between the erythropoietin resistance index (ERI), a marker of responsiveness to erythropoiesis-stimulating agents, and hemoglobin variability in ESKD.

Methods

In this retrospective observational study, we enrolled 38 outpatients receiving maintenance hemodialysis, including two undergoing combined peritoneal-hemodialysis therapy. ERI at baseline and residual standard deviation of hemoglobin (Hb-RSD) during follow-up were evaluated. Independent determinants of ERI were identified using multiple regression analysis after adjusting for potential confounders.

Results

Relative to the low-ERI group, the high-ERI group (≥ 75 th percentile) exhibited higher Hb-RSD. ERI was positively correlated with Hb-RSD ($r = 0.473$, $p = 0.003$). In multivariable regression analyses, ERI remained independently associated with Hb-RSD after adjusting for confounding variables ($\beta = 0.607$, $p = 0.003$). Furthermore, a receiver operating characteristic analysis for high Hb-RSD (≥ 75 th percentile) identified an ERI cutoff of 7.8 IU/kg·g/dL (AUC 0.729; sensitivity 70%; specificity 78%).

Conclusions

Among patients with ESKD, higher ERI values were associated with greater hemoglobin variability. ERI may serve as a useful surrogate marker for predicting hemoglobin fluctuations. Larger multicenter studies with longer follow-up are needed to confirm these findings.

Background

Anemia is recognized as an important comorbidity of chronic kidney disease (CKD) and a risk factor for both cardiovascular disease and mortality [1, 2]. Previous studies have shown that anemia, CKD, and congestive heart failure are interrelated conditions that exacerbate one another, forming a vicious cycle of disease progression referred to as cardio-renal anemia syndrome (CRAS) [3]. Anemia progresses exponentially as kidney function declines in patients with CKD, and its pathophysiology is largely attributable to insufficient erythropoiesis. Indeed, a nationwide cross-sectional study demonstrated that more than 60% of patients had developed anemia at the time of dialysis initiation [4].

Erythropoiesis-stimulating agent (ESA) therapy has been shown to exert beneficial effects on renal anemia, particularly in patients with end-stage kidney disease (ESKD). Correction of severe anemia with

ESA has also been reported to provide cardioprotective benefits, including reductions in left ventricular mass and improvements in cardiac function [5–9]. Furthermore, accumulating evidence indicates that not only hemoglobin levels but also hemoglobin variability influence clinical outcomes in patients receiving ESA therapy. Yang et al. reported that greater hemoglobin variability was independently associated with higher mortality in hemodialysis patients [10]. In a Japanese hemodialysis cohort, greater mean annual hemoglobin variability was also associated with thromboembolism, major adverse cardiovascular events (MACEs), and all-cause hospitalization [11].

However, concerns have been raised regarding the safety and benefits of ESA therapy. In particular, ESA hyporesponsiveness has emerged as an important issue and is thought to be associated with a poor prognosis in CKD. The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) in patients with diabetes reported significantly higher rates of stroke and cardiac revascularization procedures among ESA non-responders [12]. A secondary analysis of the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study also found that high-dose ESA use was associated with cardiovascular events [13].

To our knowledge, clinical indicators that reflect hemoglobin variability, which may influence clinical outcomes, have not been sufficiently investigated. We hypothesized that hemoglobin variability increases with ESA hyporesponsiveness and that a higher erythropoietin resistance index (ERI), a marker of ESA responsiveness, is associated with greater hemoglobin variability. A previous study supports this hypothesis by demonstrating that hemoglobin variability becomes greater with increasing ESA demand, indicating ESA hyporesponsiveness [14]. In the present study, we examined the association between ERI and hemoglobin variability in Japanese patients with ESKD.

Materials and Methods

Study Design and Participants

This single-center, retrospective observational study consecutively enrolled 44 outpatients receiving maintenance hemodialysis at Nissan Tamagawa Hospital between September and December 2025, including those undergoing combined peritoneal and hemodialysis. One patient with baseline aplastic anemia requiring frequent transfusions and five patients not receiving ESA therapy were excluded, leaving 38 patients for the final analysis.

Physical and Laboratory Measurements

Clinical data were collected, including age, sex, duration of dialysis therapy, and use of concomitant peritoneal dialysis. The presence of diabetes, pre-existing cardiovascular disease (CVD), and medications used at the study initiation were also recorded. In the present study, CVD included heart failure, coronary artery disease, arrhythmia, valvular heart disease, ischemic stroke, hemorrhagic stroke, peripheral artery disease, history of cardiovascular surgery, and history of pacemaker implantation.

Blood pressure was recorded in the supine position, and a blood sample was collected immediately before the first hemodialysis session of the week. Hemoglobin (Hb) levels were measured using whole blood, whereas other biochemical assays were performed using serum samples. Transferrin saturation (TSAT), ferritin, albumin (Alb), blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), phosphate (P), intact parathyroid hormone (PTH), and C-reactive protein (CRP) levels were measured using routine laboratory methods at our hospital. Serum total Ca was adjusted for albumin using the formula recommended by the Japanese Society for Dialysis Therapy (Payne's formula) when hypoalbuminemia was present (serum albumin < 4.0 g/dL): corrected Ca (mg/dL) = total serum Ca (mg/dL) + (4 - serum Alb [mg/dL]) [15]. In addition, we collected cardiac function parameters, including ejection fraction (EF) and the ratio of early mitral inflow velocity to early diastolic mitral annular velocity (E/e'), from annual screening echocardiograms.

Assessment of responsiveness to erythropoiesis-stimulating agents and serum hemoglobin variability

ERI values were calculated as the body weight-adjusted epoetin dose divided by the hemoglobin concentration at the index date [16, 17]. Doses of darbepoetin alfa (DA) and epoetin beta pegol (continuous erythropoietin receptor activator, CERA) were converted to epoetin-equivalent doses according to previously described methods in patients with ESKD [18]. Hemoglobin variability was evaluated using the residual standard deviation of hemoglobin (Hb-RSD), calculated from all pre-dialysis hemoglobin measurements obtained at the start of each week during the observation period [19, 20].

Statistical Analysis

Data are expressed as numbers and percentages or medians with interquartile ranges. Comparisons of prevalence and values between groups were performed using Student's *t*-test and the χ^2 test. The correlation between ERI and clinical parameters was assessed using Spearman's rank correlation test. Independent determinants of ERI were identified using multiple regression analysis after adjusting for potential confounders. A receiver operating characteristic (ROC) analysis was performed to determine the cutoff value, area under the curve (AUC), sensitivity, and specificity. All statistical analyses were performed using SPSS for Windows (ver. 29.0.2.0, IBM, New York, NY, USA).

Results

Clinical characteristics of the subjects

The clinical characteristics of the study population are summarized in Table 1. A total of 38 patients (28 men and 10 women) with a median age of 73 years were included in this analysis. The median dialysis vintage was 6.7 years. Two patients underwent combined peritoneal and hemodialysis therapy. Thirty-seven patients were treated with DA, and one was treated with CERA. The median ESA dose,

standardized to epoetin, was 4,893 units per week, and the median ERI was 6.3 IU/kg·g/dL. The median observation period was 91 days, during which a median of seven hemoglobin measurements were obtained. At baseline, the median Hb level was 11.5 g/dL, and the median Hb-RSD over the observation period was 0.4 g/dL.

Table 1
Baseline patient characteristics in relation to ERI levels

	All subjects	ERI (IU/kg $\times$ g/dL)		<i>p</i>
		Low-ERI < 10.1 (n = 28)	High-ERI ≥ 10.1 (n = 10)	
Age (years)	73 [68, 78]	71 [67, 78]	78 [74, 82]	0.098
Male, n (%)	28 (73)	22 (78)	6 (60)	0.404
Dialysis vintage (years)	6.7 [3.0, 10.0]	7.2 [3.7, 9.9]	6.5 [1.2, 9.3]	0.387
Combined peritoneal and hemodialysis, n (%)	2 (5)	2 (7)	0 (0)	1.000
Diabetes, n (%)	19 (50)	13 (46)	6 (60)	1.000
Pre-existing CVD, n (%)	24 (63)	18 (64)	6 (60)	1.000
SBP (mmHg)	140 [132, 150]	144 [136, 155]	138 [128, 144]	0.424
DBP (mmHg)	75 [67, 79]	75 [67, 80]	69 [67, 73]	0.563
Alb (mg/dL)	3.4 [3.2, 3.6]	3.4 [3.2, 3.6]	3.3 [3.2, 3.5]	0.104
CRP (mg/dL)	0.13 [0.05, 0.22]	0.10 [0.05, 0.20]	0.19 [0.09, 1.05]	0.008
BUN (mg/dL)	53 [47, 67]	53 [47, 68]	53 [46, 62]	0.624
Cr (mg/dL)	9.1 [7.8, 10.9]	10.2 [8.2, 11.7]	8.1 [6.7, 8.8]	0.005
Corrected Ca (mg/dL)	9.2 [8.8, 9.7]	9.2 [8.9, 9.7]	9.2 [8.5, 9.6]	0.280
P (mg/dL)	4.4 [4.1, 5.4]	4.4 [3.9, 5.2]	5.0 [4.4, 6.6]	0.054
Intact PTH (pmol/L)	121 [74, 173]	121 [72, 165]	126 [97, 176]	0.603

Note: Values for categorical variables are presented as numbers and percentages; values for continuous variables are presented as medians [interquartile range]. *P* values were determined using a *t*-test or χ^2 -test, as appropriate, for comparisons between the low and high ERI groups.

Abbreviations: ERI, erythropoietin resistance index; Low-ERI, ERI < 75th percentile; High-ERI, ERI $\geq$ 75th percentile; CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; Alb, albumin; CRP, C-reactive protein; BUN, blood urea nitrogen; Cr, creatinine; Ca, calcium; P, phosphate; PTH, parathyroid hormone; TSAT, transferrin saturation; pre-Hb, hemoglobin at baseline; post-Hb, hemoglobin at the end of the observation period; median-Hb, median hemoglobin during the observation period; Hb-RSD, residual standard deviation of hemoglobin; EF, ejection fraction; E/e', ratio of early mitral inflow velocity to early diastolic mitral annular velocity; DA, darbepoetin alfa; CERA, continuous erythropoietin receptor activator; ESA, erythropoiesis-stimulating agent; RAS, renin-angiotensin-aldosterone system.

	All subjects	ERI (IU/kg $\times$ g/dL)		<i>p</i>
		Low-ERI < 10.1 (n = 28)	High-ERI $\geq$ 10.1 (n = 10)	
TSAT (%)	27 [22, 39]	27 [22, 39]	26 [22, 37]	0.743
Ferritin (ng/dL)	218 [93, 314]	178 [81, 288]	273 [231, 474]	0.243
Pre-Hb (g/dL)	11.5 [11.2, 12.1]	11.7 [11.2, 12.1]	11.4 [9.9, 11.5]	0.056
Post-Hb (g/dL)	11.4 [10.7, 12.0]	11.3 [10.8, 12.0]	11.9 [9.5, 12.0]	0.688
Median-Hb (g/dL)	11.5 [11.2, 12.3]	11.5 [11.2, 12.0]	11.9 [10.8, 12.8]	0.958
Hb-RSD (g/dL)	0.4 [0.2, 0.5]	0.3 [0.2, 0.4]	0.6 [0.4, 1.0]	0.008
EF (%)	67 [61, 71]	69 [64, 71]	61 [42, 63]	0.027
E/e'	13 [10, 17]	13 [11, 18]	12 [10, 16]	0.606
DA, n (%)	37 (97)	28 (100)	9 (90)	0.263
CERA, n (%)	1 (2)	0 (0)	1 (10)	0.263
ESA dose (IU/week)	4,893 [3,262, 6,524]	3,262 [3,262, 4,893]	9,786 [6,524, 9,786]	< 0.001
ERI (IU/kg $\times$ g/dL)	6.3 [4.2, 10.1]	5.2 [3.9, 6.6]	12.6 [11.5, 14.3]	< 0.001
Iron supplementations, n (%)	11 (28)	6 (21)	5 (50)	0.116
RAS inhibitors, n (%)	19 (50)	13 (72)	6 (60)	0.714
Statins, n (%)	20 (52)	14 (50)	6 (60)	0.719

Note: Values for categorical variables are presented as numbers and percentages; values for continuous variables are presented as medians [interquartile range]. *P* values were determined using a *t*-test or χ^2 -test, as appropriate, for comparisons between the low and high ERI groups.

Abbreviations: ERI, erythropoietin resistance index; Low-ERI, ERI < 75th percentile; High-ERI, ERI $\geq$ 75th percentile; CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; Alb, albumin; CRP, C-reactive protein; BUN, blood urea nitrogen; Cr, creatinine; Ca, calcium; P, phosphate; PTH, parathyroid hormone; TSAT, transferrin saturation; pre-Hb, hemoglobin at baseline; post-Hb, hemoglobin at the end of the observation period; median-Hb, median hemoglobin during the observation period; Hb-RSD, residual standard deviation of hemoglobin; EF, ejection fraction; E/e', ratio of early mitral inflow velocity to early diastolic mitral annular velocity; DA, darbepoetin alfa; CERA, continuous erythropoietin receptor activator; ESA, erythropoiesis-stimulating agent; RAS, renin-angiotensin-aldosterone system.

	All subjects	ERI (IU/kg $\times$ g/dL)		<i>p</i>
		Low-ERI < 10.1 (n = 28)	High-ERI $\geq$ 10.1 (n = 10)	
Phosphate-lowering therapies, n (%)	30 (78)	24 (85)	6 (60)	0.170
Vitamin D receptor activators, n (%)	32 (84)	24 (85)	8 (80)	0.644
Calcimimetics, n (%)	22 (57)	16 (57)	6 (60)	1.000
Levocartine, n (%)	19 (50)	15 (53)	4 (40)	0.714
Note: Values for categorical variables are presented as numbers and percentages; values for continuous variables are presented as medians [interquartile range]. <i>P</i> values were determined using a <i>t</i> -test or χ^2 -test, as appropriate, for comparisons between the low and high ERI groups.				
Abbreviations: ERI, erythropoietin resistance index; Low-ERI, ERI < 75th percentile; High-ERI, ERI $\geq$ 75th percentile; CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; Alb, albumin; CRP, C-reactive protein; BUN, blood urea nitrogen; Cr, creatinine; Ca, calcium; P, phosphate; PTH, parathyroid hormone; TSAT, transferrin saturation; pre-Hb, hemoglobin at baseline; post-Hb, hemoglobin at the end of the observation period; median-Hb, median hemoglobin during the observation period; Hb-RSD, residual standard deviation of hemoglobin; EF, ejection fraction; E/e', ratio of early mitral inflow velocity to early diastolic mitral annular velocity; DA, darbepoetin alfa; CERA, continuous erythropoietin receptor activator; ESA, erythropoiesis-stimulating agent; RAS, renin-angiotensin-aldosterone system.				

We compared patient characteristics between the low and high-ERI groups, defined as < 75th and $\geq$ 75th percentiles, respectively. Patients in the high-ERI group, who required higher ESA doses, showed elevated CRP levels, lower Cr, and reduced EF. The high-ERI group also exhibited greater Hb-RSD, whereas the anemia control remained comparable during the observation period.

Association between ERI and Hb-RSD

We first examined the unadjusted correlations between clinical variables and Hb-RSD. ERI was positively correlated with Hb-RSD ($r = 0.473$, $p = 0.003$). In addition, log-transformed CRP was positively correlated with Hb-RSD, whereas Alb and Cr showed negative correlations (Table 2). We next performed multivariable regression analyses to assess the association between ERI and Hb-RSD after adjustment for covariates. ERI remained independently and positively associated with Hb-RSD ($\beta = 0.607$, $p = 0.003$), and this association was independent of uremic toxin, iron status, malnutrition and inflammation, bone mineral metabolism, and cardiac function (Table 3). Notably, a sensitivity analysis excluding the two patients receiving combined peritoneal and hemodialysis therapy yielded results that were essentially unchanged (data not shown).

Table 2
Correlation between clinical variables and Hb-RSD

Age	<i>r</i>	<i>p</i>
	-0.015	0.930
Dialysis vintage	-0.034	0.840
SBP	0.009	0.954
DBP	0.023	0.884
Alb	-0.370	0.022
Log [CRP]	0.352	0.030
BUN	-0.081	0.604
Cr	-0.304	0.047
Corrected Ca	-0.124	0.457
P	0.193	0.246
Log [intact PTH]	-0.139	0.406
TSAT	-0.055	0.743
Ferritin	0.255	0.123
Pre-Hb	0.032	0.849
EF	-0.243	0.142
E/e'	-0.089	0.606
ESA dose	0.393	0.015
ERI	0.473	0.003

Note: The correlation coefficient (*r*) was determined using simple linear regression analysis.

Abbreviations: Hb-RSD, residual standard deviation of hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; Alb, albumin; CRP, C-reactive protein; BUN, blood urea nitrogen; Cr, creatinine; Ca, calcium; P, phosphate; PTH, parathyroid hormone; TSAT, transferrin saturation; pre-Hb, hemoglobin at baseline; EF, ejection fraction; E/e', ratio of early mitral inflow velocity to early diastolic mitral annular velocity; ESA, erythropoiesis-stimulating agent; ERI, erythropoietin resistance index.

Table 3
Multiple regression analyses of determinants for Hb-RSD

ERI (per 1 IU/kg·g/dL)	β	p
Model 1	0.607	0.003
Model 2	0.589	0.013
Model 3	0.631	0.006
Model 4	0.563	0.011
Model 5	0.588	0.013
Model 6	0.596	0.006
Note: β standardized regression coefficient was derived from the multivariable regression analysis.		
Covariates:		
Model 1: Age, sex, diabetes, pre-existing CVD, dialysis vintage, peritoneal dialysis use, and pre-Hb		
Model 2: Model 1 + BUN, Cr		
Model 3: Model 1 + TSAT, ferritin		
Model 4: Model 1 + Alb, log [CRP]		
Model 5: Model 1 + corrected Ca, P, and log [intact PTH]		
Model 6: Model 1 + EF, E/e'		
Abbreviations: Hb-RSD, residual standard deviation of hemoglobin; ERI, erythropoietin resistance index; CVD, cardiovascular disease; pre-Hb, hemoglobin at baseline; BUN, blood urea nitrogen; Cr, creatinine; TSAT, transferrin saturation; Alb, albumin; CRP, C-reactive protein; Ca, calcium; P, phosphate, PTH, parathyroid hormone; EF, ejection fraction; E/e', ratio of early mitral inflow velocity to early diastolic mitral annular velocity.		

Receiver operating characteristic (ROC) analysis of ERI as a predictor of hemoglobin variability

An ROC analysis was performed to evaluate the ability of ERI to predict hemoglobin variability. An Hb-RSD value $\geq$ 75th percentile was used as the threshold for the binary outcome. The ERI demonstrated a cutoff value of 7.8 IU/kg·g/dL, with an AUC of 0.729, a sensitivity of 70%, and a specificity of 78% (Fig. 1).

Discussion

The present study demonstrated that higher ERI values were associated with greater hemoglobin variability in patients with ESKD. This association remained robust after adjustment for patient

characteristics related to anemia. These findings suggest that the ERI serves as an independent determinant of hemoglobin variability. To the best of our knowledge, this is the first report to identify this relationship in patients with ESKD.

Clinical association between ESA responsiveness and hemoglobin variability

We found that ERI values, a marker of ESA hyporesponsiveness, were independently and positively associated with Hb-RSD, a quantitative measure of hemoglobin variability at the individual level. In our study, the median ERI and Hb-RSD values were 6.3 IU/kg·g/dL and 0.4 g/dL, respectively. Relative to previous reports in Japanese cohorts receiving maintenance hemodialysis, the ERI value was slightly lower, whereas the Hb-RSD value was slightly higher [21, 22]. Patients with elevated ERI values may therefore be at increased risk for greater hemoglobin variability, underscoring the importance of careful anemia management, including interventions for ESA hyporesponsiveness and appropriate ESA dose adjustment, with consideration of potential implications for clinical outcomes.

In many clinical settings, anemia in patients with CKD is managed according to the standardized guidelines. After assessing iron status and other key parameters, hemoglobin levels guide ESA dosing: higher hemoglobin levels prompt dose reductions, whereas increased ESA dosing leads to subsequent increases in hemoglobin levels. ESA doses are adjusted using threshold criteria based on hemoglobin values measured before the first weekly hemodialysis session. A previous study reported a positive correlation between ESA dose and the amplitude of hemoglobin excursions in patients undergoing peritoneal dialysis [14], suggesting that reduced ESA responsiveness requiring higher ESA doses may contribute to increased hemoglobin variability. In addition, Jörg et al. found that the Hb standard deviation rises sharply once a critical threshold of ESA responsiveness is exceeded in patients undergoing hemodialysis [23]. They also showed that the negative correlation between Hb levels and ESA doses became stronger as ESA responsiveness increased, indicating that patients with higher ESA responsiveness are more likely to maintain stable anemia control with lower ESA requirements. Taken together, the available evidence suggests that declining ESA responsiveness is accompanied by higher ESA requirements and greater hemoglobin variability.

Although we examined the relationship between ESA requirements and Hb-RSD, the association was attenuated after adjustment for clinical covariates in our cohort (data not shown). We speculated that ESA dose alone may be insufficient as a marker of ESA responsiveness because it does not account for patient body size and body composition, which influence erythropoietin requirements. El-Kannishy et al. reported a significant negative correlation between ESA dose and BMI, with ESA requirements continuing to decline as the BMI increased up to a certain threshold [24]. Chiang et al. also demonstrated that the lean tissue index, an indicator of muscle mass, was inversely associated with ESA requirements [25]. Because body weight reflects patient morphometry and may help explain interindividual differences in erythropoietin requirements, the ERI, which integrates anemia status with body weight, is considered a more appropriate and clinically practical index of ESA responsiveness and may also serve as a useful

predictor of hemoglobin variability in patients undergoing hemodialysis. In the additional ROC analysis, the predictive ability of the ESA dose for high Hb-RSD was indeed weaker than that of ERI in our cohort (data not shown).

Potential contributors to ESA hyporesponsiveness affecting hemoglobin variability

ESA responsiveness is influenced by multiple internal and external factors [26, 27], several of which were included as confounders in our multivariable regression models. Many of these factors can also contribute to concurrent fluctuations in hemoglobin levels [20], and therefore are considered to represent shared determinants of both ESA responsiveness and hemoglobin variability. These contributors are generally thought to fall into several major categories, including: 1) drug-related factors (e.g., ESA pharmacokinetics, dosing frequency and administration route, and concomitant medications that interfere with erythropoiesis, including renin-angiotensin system inhibitors and chemotherapeutic agents); 2) patient-related factors (e.g., age, sex, race, muscle mass, nutritional status, fluid status, pre-existing comorbidities including diabetes, cardiovascular disease, and hematologic disorders, and patient adherence); 3) origin of CKD (e.g., diabetes-related kidney disease, vasculitis-associated kidney injury, tubulointerstitial nephritis, and cardiorenal syndrome); 4) CKD-related comorbidities (e.g., reduced endogenous erythropoietin production, shortened red blood cell lifespan, inadequate dialysis, and hyperparathyroidism); 5) absolute or functional iron deficiency (e.g., gastrointestinal bleeding, hemodialysis-related iron loss, frequent blood sampling, ESA-induced increases in erythropoiesis, and chronic inflammation characteristic of the malnutrition-inflammation-atherosclerosis [MIA] syndrome [28]); 6) inflammatory conditions (e.g., exposure to bioincompatible dialysis membranes, infections including those related to vascular access, MIA syndrome, and malignancy); and 7) regional differences in clinical guidelines, institutional policies, and physicians' practice patterns.

In the current study, patients in the high-ERI group exhibited higher CRP values, and our regression analysis showed that higher CRP and lower Alb values were associated with greater hemoglobin variability. Although ferritin values tended to be higher in the high-ERI group, iron status appeared to be preserved in both groups, indicating that overt iron deficiency was unlikely. Patients in the high-ERI group also tended to be older and had lower Cr values, which may indicate reduced muscle mass. BUN values did not differ between ERI groups, and Kt/V showed a similar pattern among patients receiving hemodialysis alone (data not shown), suggesting comparable dialysis adequacy. In the regression analysis, lower Cr values were also associated with greater hemoglobin variability. Taken together, sarcopenia, driven by the inflammation-malnutrition complex and reduced muscle mass, may be a key contributor to ESA hyporesponsiveness and hemoglobin variability. Furthermore, although the prevalence of prior cardiovascular disease was similar between the two groups, patients in the high-ERI group had lower EF than those in the low-ERI group, a difference that may also be consistent with underlying sarcopenia and could contribute to ESA hyporesponsiveness and hemoglobin variability.

Limitations

This study has several limitations. First, because the study was hospital-based, we recruited an ethnically and socially homogeneous population; therefore, the generalizability of our findings may be limited. Second, because this was a retrospective observational study, the causal relationship between ESA responsiveness and hemoglobin variability needs to be confirmed in longitudinal and/or interventional studies. Third, time-dependent changes in ERI values and confounders related to hemoglobin fluctuations during the follow-up period were not evaluated. Fourth, the follow-up period in this study was relatively short. Therefore, we could not evaluate whether long-term hemoglobin variability affects patient prognosis, such as cardiovascular mortality. Fifth, not all potential contributors to ESA hyporesponsiveness or causes of anemia were systematically captured, and we were unable to ascertain whether any hematologic disorders were newly diagnosed after study initiation. Sixth, because ESA prescriptions were not consistently managed by a single physician, variation in physicians' practice patterns may have contributed, at least in part, to the observed differences in hemoglobin fluctuations.

Conclusions

This single-center retrospective cohort study demonstrated that ERI, a marker of ESA responsiveness, was associated with greater hemoglobin variability and may serve as a surrogate marker for hemoglobin fluctuations in Japanese patients with ESKD. These findings should be confirmed in studies with larger multicenter designs with longer observation periods in the future. Further investigations are needed to establish a standardized method for evaluating ESA responsiveness and to identify strategies to prevent hemoglobin variability, given its potential implications for clinical outcomes.

Declarations

Ethics approval and consent to participate:

This study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Japanese Ministry of Health, Labour and Welfare, 2021). The Ethics Committee for Clinical Research at Nissan Tamagawa Hospital approved the study protocol (permission no. tama2026-004), and informed consent was obtained using an opt-out approach via the department's website (<https://www.tamagawa-hosp.jp/>).

Consent for publication:

Not applicable.

Availability of data and materials:

All data generated or analyzed during this study are included in this published article.

Competing interests:

The authors declare no conflicts of interest in association with the present study.

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Authors' contributions:

T.H. and T.N. contributed to the discussion, research data, and writing of the manuscript. Y.I. contributed to the discussion and reviewed and edited the manuscript. M. H. and Y. T. researched the data. As the corresponding author and guarantor of this manuscript, T.H. takes full responsibility for the work as a whole, including the study design, access to data, and decision to submit and publish the manuscript.

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Figures

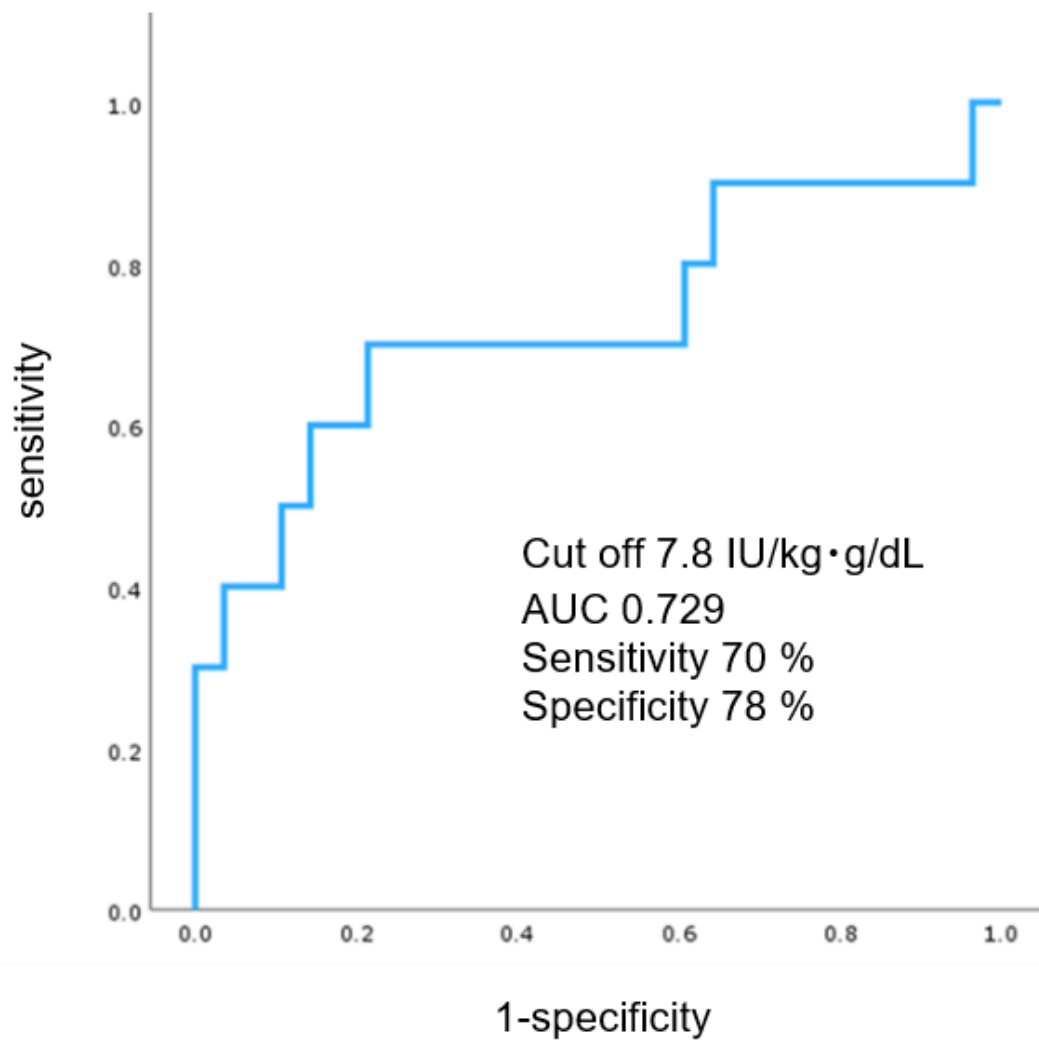


Figure 1

Receiver operating characteristic curve for the model predicting hemoglobin variability

Note: The receiver operating characteristic analysis of the ERI was performed using an Hb-RSD value $\geq$ 75th percentile as the binary outcome.

Abbreviations: ERI, erythropoietin resistance index; Hb-RSD, residual standard deviation of hemoglobin; AUC, area under the curve.