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Relationship between variations in time-dependent response to erythropoiesis-stimulating agents and mortality in hemodialysis patients: a single-center study

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Abstract

Background: Hemodialysis (HD) patients who are resistant to erythropoiesis-stimulating agents (ESAs) have a higher mortality rate. The aim of this study was to assess the relationship between the time-dependent variability of ESA response in HD patients and mortality.

Methods: A total of 375 HD patients were enrolled in this study. The ESA resistance index (ERI) was calculated by dividing the weekly weight-adjusted ESA dose by hemoglobin concentration, and the average ERI was calculated from the ERI values every 2 months during a 36-month follow-up period. We divided the patients into six groups based on the patterns of their ERI level fluctuations: low-low (Low group), intermediate-intermediate (Intermediate group), high-high (High group), Low-intermediate group, Intermediate-high group, and Low-high group.

Results: There were 94 (25.1 %) deaths, and they included 51 (13.6 %) deaths from cardiovascular disease (CVD). A multivariate analysis with adjustment for age, serum albumin and C-reactive protein levels, and history of CVD showed that the High group was independently and significantly related to all-cause mortality (odds ratio = 5.53, 95 % CI 2.29–13.99, $p = 0.0001$) and CVD-related mortality (odds ratio = 3.49, 95 % CI 1.40–8.47, $p = 0.0081$).

Conclusions: High ERI levels are an independent risk factor for all-cause and CVD mortality in HD patients.

Keywords: Anemia, Hemodialysis, Mortality, Erythropoiesis-stimulating agent, Resistance, Variability

Background

Renal anemia in end-stage renal disease (ESRD) patients is mainly attributable to decreased erythropoietin production by the kidney. Erythropoiesis-stimulating agent (ESA) therapy has resulted in substantial health benefits for ESRD patients, including improved quality of life, a reduced need for blood transfusion, and greater exercise capacity [1]. Unfortunately, a considerable proportion of ESRD patients exhibit a suboptimal hematologic response to ESAs, as evidenced by persistence of the anemia despite adequate dosing or by the need for high-dose ESA therapy to achieve the recommended hemoglobin target [2].

After making adjustments for other variables, previous studies have shown that the need for ESA therapy is an independent predictor of all-cause mortality in HD patients [3]. Lopez-Gomez et al. reported finding a relationship between ESA resistance in HD patients and 1-year mortality [4], and ESA resistance remained a significant predictor of mortality in HD patients [5, 6]. It appears that resistance to ESA therapy in HD patients could be clinically useful as an index of prognostic marker.

However, the time-dependent changes of ESA resistance index (ERI) has not examined, although consistently high ESA resistance was expected to be an adverse effect on mortality of HD patients. The aim of our study was to assess the presence of variability in the time

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course of ERI and the association between high ERI values and increased mortality of HD patients.

Methods

Subjects and protocol

This was a prospective, observational cohort study conducted at a single center in Japan. The subjects were recruited from among patients who had been routinely treated through an arteriovenous fistula in the dialysis unit of the Jyoban Hospital for at least 6 months. A total of 400 HD patients were registered in this study, and the 375 patients for whom sufficient data were available to calculate ERI were the subjects of the analysis in this study. The Institutional Review Board of the Jyoban Hospital approved all study protocols (No. 12), and the protocols were carried out in accordance with the Declaration of Helsinki guidelines regarding ethical principles for medical research involving human subjects. Written informed consent was obtained from every subject.

Baseline data at the time of patient entry into the study were collected on demographics, medical history, laboratory data, anemia therapy, medications, and history of cardiovascular disease (CVD). Data were collected at 2-month intervals on events, including all-cause deaths, and on CVD mortality. A CVD death was defined as a death that was attributed to acute myocardial infarction, ischemic heart disease, cardiac arrest, congestive heart failure, pulmonary edema due to exogenous fluid, cardiac arrhythmia, cerebrovascular accident, including intracranial hemorrhage or ischemic brain damage, and peripheral artery disease. The patients who were enrolled as subjects ($n = 375$) underwent stable regular HD with a bicarbonate dialysate. Their underlying diseases of ESRD were diabetic nephropathy ($n = 162$), chronic glomerulonephritis ($n = 123$), nephrosclerosis ($n = 78$), and chronic pyelonephritis ($n = 4$), or unknown origin ($n = 8$).

Subjects' anemia was treated according to the guidelines published in 2008 by the Japanese Society of Dialysis Therapy [7]. The target Hb level was 10–11 g/dl, and epoetin beta was administered to achieve the target Hb level. Intravenous iron was administered whenever a subject's transferrin saturation was found to be <20 % or the serum ferritin level was found to be <100 ng/ml. The conversion ratio adopted in this study was 200 epoetin (EPO):1 darbepoetin-α (DA) [8]. ERI was calculated as the weekly weight-adjusted dose of ESA divided by hemoglobin (Hb) concentration used to evaluate the dose-response effect in ESA treatment as follows [5, 6]: ERI (U/kg/week/g per 100 ml) = weekly ESA dose / (weight × Hb). Ascending quartiles of ERI were assessed based on the ERI levels at enrollment, and the ERI quartile groups were as follows: first, <5.1; second, 5.1 to <8.5; third, 8.5 to <13.7; and fourth, ≥ 13.7 U/kg/week/g per 100 ml. The definition of variability in the time course of ERI is shown in Fig. 1. ERI levels were categorized as low (first quartile of ERI), intermediate (second and third quartiles of ERI), and high (fourth quartile of ERI). The average ERI was calculated from ERI levels every 2 months during the follow-up period for each patient. To assess the size of the ERI fluctuations during the follow-up periods according to ERI quartiles at baseline, we divided the patients into six groups on the basis of their overall fluctuation pattern with reference to a previous report on Hb fluctuations and mortality [9]: low-low (Low group), intermediate-intermediate (Intermediate group), high-high (High group), Low-intermediate group, Intermediate-high group, and Low-high group, and the last three groups were treated as amplitude fluctuation groups.

Statistical analyses

All data are reported as means ± SD unless otherwise specified. The differences between groups were tested for statistical significance by Student's t test or one-way

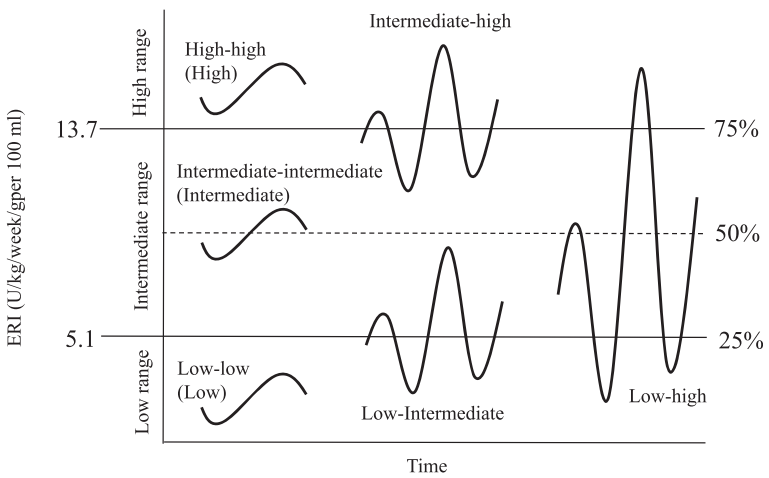

Fig. 1 Definition of variability in the time course of ERI

ANOVA for continuous variables, and by the χ^2 test for categorical variables. First, we evaluated the associations between the six ERI variation groups and cumulative all-cause and CVD-related mortality during the follow-up period by the Kaplan-Meier method. Next, we estimated the odds ratios (ORs) of all-cause and CVD-related mortality according to the ERI variability groups by the logistic regression. Logistic regression was also used to assess associations between patient characteristics and all-cause and CVD-related mortality. The candidates for explanatory variables were age, sex, dialysis vintage, body mass index (BMI), the presence of diabetes, mean serum albumin (≥3.5 vs. <3.5 g/dl), mean C-reactive protein (CRP ≥ 1.0 vs. <1.0 mg/dl), ferritin (≥100 vs. <100 ng/ml), phosphorus (≥6 vs. <6 mg/dl), and history of CVD (yes vs. no or missing). All significant variables in the univariate analysis ($p < 0.20$) and clinically established factors were entered into an intermediate multivariate logistic model of mortality, and all of the significant variables detected in the intermediate multivariate model and the established factors were entered into a final multivariate logistic mortality model. Statistical significance was defined as $p < 0.05$. All analyses were performed using the SAS version 9.1 (SAS Institute, Cary, NC, USA).

Results

The data of a total of 375 Japanese HD patients were analyzed, and their mean follow-up period was 31.3 ± 9.4 weeks. Patient characteristics at baseline are summarized in Table 1. The mean ESA doses during the follow-up period calculated in the form of EPO doses were 5444 ± 3538 IU/week in all patients, 5473 ± 3700 IU/week in males, and 5392 ± 3239 IU/week in females. One hundred sixty-three patients were treated with EPO, whereas 212 patients were treated with DA during the follow-up period. The ERI distribution pattern did not appear to differ between the sexes, but the average ERI was significantly higher in females than in males (12.1 ± 8.4 vs. 9.6 ± 7.3 U/kg/week/g per 100 ml, $p < 0.001$).

The patients were divided into the following six ERI variability groups based on their ERI quartiles levels: High group, $n = 31$ (8.3 %); Intermediate group, $n = 68$ (18.1 %); Low group, $n = 46$ (12.3 %); Intermediate-high group, $n = 30$ (8.0 %); Low-intermediate group, $n = 63$ (16.8 %); and Low-high group, $n = 137$ (36.5 %), and the characteristics of the six groups are shown in Table 2. Intravenous iron administration was not performed in the three patients of High group, seven of Intermediate group, six of Intermediate-high group, four of Low-intermediate group, and three of Low-high group. All of the other patients were administered with intravenous iron less than 50 mg/week.

Table 1 Baseline characteristics of the study subjects

	Total ($n = 375$)	Male ($n = 242$)	Female ($n = 133$)
Age, years	66.8 ± 13.6	64.6 ± 13.6	70.5 ± 12.2
BMI, kg/m^2	22.0 ± 3.5	22.3 ± 3.4	21.5 ± 3.7
HD vintage, months	65.3 ± 75.2	58.7 ± 69.1	77.6 ± 84.3
Single-pool Kt/V	1.4 ± 0.3	1.3 ± 0.2	1.6 ± 0.3
Hb, g/dl	10.8 ± 1.1	10.8 ± 1.1	10.7 ± 1.0
Ferritin, ng/ml	89.6 ± 86.7	84.7 ± 87.9	97.0 ± 82.7
Albumin, g/dl	3.6 ± 0.3	3.7 ± 0.4	3.6 ± 0.3
CRP, mg/dl	0.6 ± 1.5	0.6 ± 1.4	0.6 ± 1.8
Intact PTH, pg/ml	152.1 ± 164.7	146.9 ± 157.1	162.1 ± 178.8
Phosphorus, mg/dl	5.3 ± 1.3	5.3 ± 1.4	5.2 ± 1.2
Calcium, mg/dl	8.7 ± 0.7	8.6 ± 0.8	8.7 ± 0.6
ALP, U/l	245.4 ± 99.4	231.9 ± 84.7	268.3 ± 117.3
TSAT, %	21.9 ± 11.3	22.8 ± 11.9	20.1 ± 9.9
Systolic BP, mmHg	149.6 ± 22.5	150.5 ± 22.8	148.2 ± 22.0
Diastolic BP, mmHg	78.0 ± 13.9	79.5 ± 14.5	75.4 ± 12.5
History of CVD	11.2 %	12.4 %	8.3 %
ESA dosage, IU/week	5444 ± 3538	5473 ± 3700	5392 ± 3238.6
ERI, IU/kg/week/g/dl	10.5 ± 7.8	9.6 ± 7.3	12.1 ± 8.4

All data are presented as mean ± SD
BMI body mass index, *Hb* hemoglobin, *CRP* C-reactive protein, *PTH* parathyroid hormone, *ALP* alkaline phosphatase, *TSAT* transferrin saturation, *BP* blood pressure, *CVD* cardiovascular disease, *ERI* ESA resistance index

There were 94 deaths (25.1 %) during the follow-up period. The cause of death was CVD in 51 cases (13.6 %), infection in 23 cases (6.1 %), cancer in 5 cases (1.3 %), and gastrointestinal bleeding in 4 cases (1.1 %). Of the 51 deaths due to CVD, 29 were due to congestive heart failure, 8 were due to cerebrovascular accident including intracranial hemorrhage, and 5 were due to acute myocardial infarction; there were 4 cases of pulmonary edema due to exogenous fluid, 2 cases of death due to cardiac arrhythmia, and 3 cases of sudden death. We plotted the all-cause and CVD-related mortality curves of the six ERI variability groups by the Kaplan-Meier method (Fig. 2a, b), and the all-cause and CVD-related mortality rates were highest in the High ERI group. There was no significant difference in all-cause mortality between EPO group and DA group (Fig. 3, $p = 0.7680$). Moreover, there was no significant difference between each ERI groups and all-cause mortality in patients treated with EPO (Fig. 4a, $p = 0.3189$). However, High group had significantly higher mortality risk than those in the other ERI groups in patients treated with DA (Fig. 4b, $p < 0.0001$).

Figure 5 shows the unadjusted ORs for all-cause and CVD-related mortality in each ERI variability group. The risk for all-cause mortality in the High group was significantly higher than those in the other groups (OR = 10.13, 95 % CI 3.56–32.07, $p = 0.001$). The High group

Table 2 Characteristics of the six groups for ERI variability

	High ($n = 31$)	Intermediate ($n = 68$)	Low ($n = 46$)	Intermediate-high ($n = 30$)	Low-high ($n = 137$)	Low-intermediate ($n = 63$)
Male	45.2 %	73.5 %	78.3 %	63.3 %	58.4 %	68.3 %
Female	54.8 %	26.5 %	21.7 %	36.7 %	41.6 %	31.8 %
Age, years	75.1 ± 9.9	67.8 ± 12.9	60.5 ± 11.8	70.1 ± 13.3	66.6 ± 14.7	65.3 ± 12.3
BMI	19.7 ± 3.1	22.6 ± 3.3	23.9 ± 2.8	21.4 ± 3.9	21.4 ± 3.3	22.7 ± 3.6
HD vintage, months	62.9 ± 87.4	62.1 ± 68.1	70.6 ± 62.4	58.6 ± 59.2	65.1 ± 80.3	69.8 ± 81.8
Phosphorus, mg/dl	5.2 ± 1.6	5.3 ± 1.3	5.5 ± 1.3	5.0 ± 1.4	5.2 ± 1.2	5.3 ± 1.3
Calcium, mg/dl	8.5 ± 0.8	8.7 ± 0.8	8.8 ± 0.6	8.5 ± 0.6	8.7 ± 0.6	8.6 ± 0.8
Intact PTH, pg/ml	116.8 ± 87.5	138.4 ± 92.6	187.4 ± 267.7	167.3 ± 128.2	156.7 ± 191.0	140.7 ± 90.7
ALP, U/l	249.8 ± 137.2	234.0 ± 69.5	243.0 ± 121.0	225.1 ± 66.4	259.3 ± 109.9	236.8 ± 73.7
Ferritin, ng/ml	134.8 ± 101.8	78.8 ± 76.9	75.5 ± 63.9	71.1 ± 61.7	86.9 ± 94.8	104.1 ± 88.3
Hb, g/dl	9.7 ± 1.0	10.9 ± 0.9	11.4 ± 1.0	10.4 ± 1.0	10.8 ± 1.2	11.0 ± 0.8
Albumin, mg/dl	3.5 ± 0.4	3.6 ± 0.3	3.8 ± 0.3	3.6 ± 0.3	3.6 ± 0.4	3.7 ± 0.3
CRP, mg/dl	1.2 ± 1.7	0.5 ± 1.2	0.4 ± 0.9	0.5 ± 0.7	0.6 ± 1.8	0.6 ± 1.7
TSAT, %	20.8 ± 11.4	21.7 ± 10.1	23.7 ± 12.6	18.1 ± 9.0	21.5 ± 11.3	23.6 ± 12.4
Kt/V	1.5 ± 0.3	1.4 ± 0.2	1.4 ± 0.2	1.4 ± 0.3	1.4 ± 0.3	1.4 ± 0.3
Systolic BP, mmHg	150.7 ± 22.3	145.6 ± 26.0	147.3 ± 22.2	155.7 ± 19.1	150.6 ± 21.1	150.1 ± 23.1
Diastolic BP, mmHg	76.5 ± 12.1	76.4 ± 15.3	81.3 ± 13.4	80.1 ± 12.3	77.4 ± 13.7	78.4 ± 14.9

was also significantly associated with CVD-related mortality (OR = 3.67, 95 % CI 1.22–12.03, $p = 0.003$).

The results of the multivariate logistic regression model adjusted for the age, sex, dialysis vintage, BMI, the presence of diabetes, ferritin, albumin, CRP, phosphorus, and history of CVD showed that the High group was at significantly higher risk for all-cause mortality (OR = 3.63, 95 % CI 2.03–6.28, $p < 0.0001$; Table 3). For CVD-related mortality, the High group had significantly higher risk adjusted for the above variables except for phosphorus (OR = 3.81, 95 % CI 1.68–8.04, $p = 0.0019$). Older age, male, diabetes, and serum albumin levels were independent predictors for all-cause mortality, whereas only older age was an independent predictor for CVD-related mortality.

Finally, we examined factors related to the High group. The High group was associated with older age and had a lower BMI, Hb and albumin, lower iron dosage, and a higher ferritin and CRP levels (Table 4).

Discussion

The results of this study showed that the High group, which had consistently high ERI values, was the highest risk group for all-cause and CVD-related mortality in Japanese HD patients compared with three amplitude fluctuation groups. These findings were consistent with the results of a previous study by Fujikawa et al. [10] who showed that factoring out fluctuating ERI increases the ability of consistently high ERI levels as an independent risk factor for all-cause and CVD mortality of 2104 HD patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Therefore, consistently high ERI values in HD patients are a strong independent risk factor for all-cause and CVD-related mortality.

The High group in our study was found to be associated with older age, female gender, low BMI, and low serum albumin levels, and these findings are consistent with the results of previous studies [3, 4, 11, 12]. However, CRP was not found to be associated with the High group, although inflammatory conditions can elevate the ERI by inducing the production of cytokines that suppress erythropoiesis [13–15]. This was probably because the Low group, which had consistently low ERI values, had an unexpectedly high CRP levels. Examination of high CRP in the Low and High groups will provide an information as to how factors affecting inflammation elevate ERI. Schneider et al. [16] recently reported finding that time-varying ESA resistance was associated with higher rates of sudden death, infectious complications, and all-cause mortality in the German Diabetes and Dialysis study (4D study). The factors predicting ESA resistance may be different from the study cohort.

The ERI values in the present study were lower than in a previous study [4]. This is in part due to the fact that ESA doses in Japan are lower than elsewhere [17], and the low ERI values may predict a favorable outcome in Japanese HD patients [18]. If higher ESA doses were available in the Japanese healthcare system, HD patient conditions causing high resistance to ESA might have higher ERI values. ERI of a less limited range may be

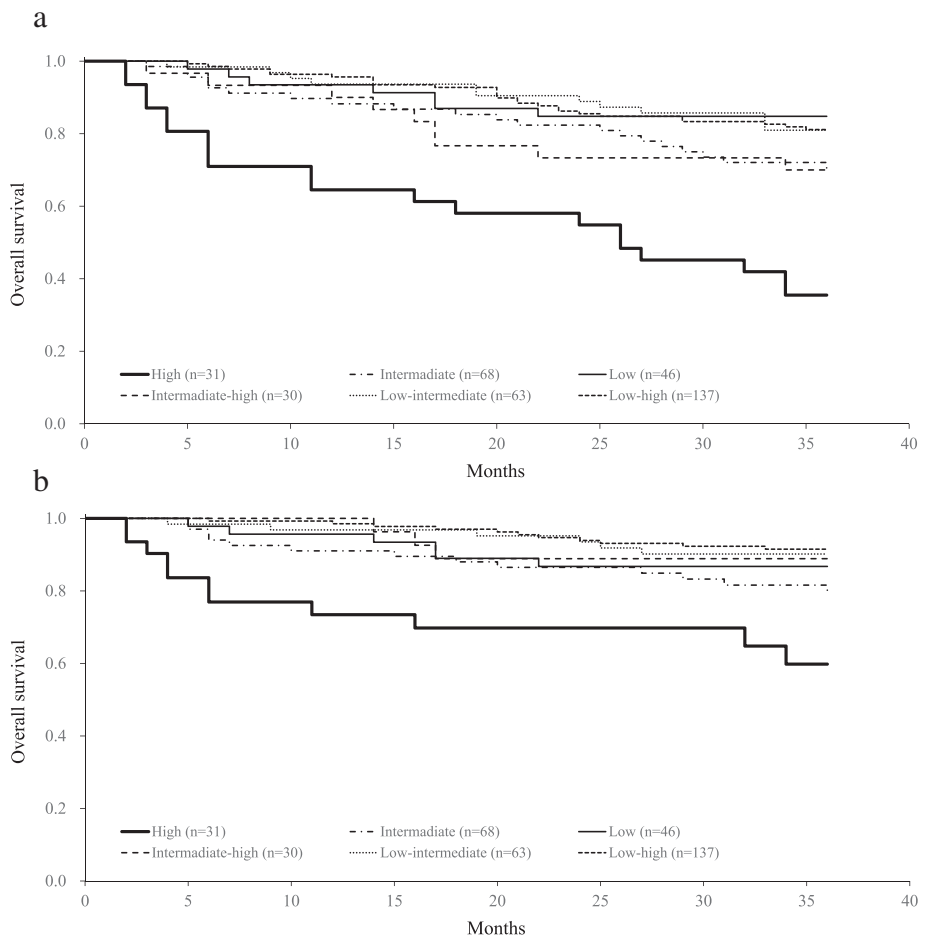

Fig. 2 Kaplan-Meier survival curves of the six ERI variability groups. **a** All-cause. **b** CVD-associated

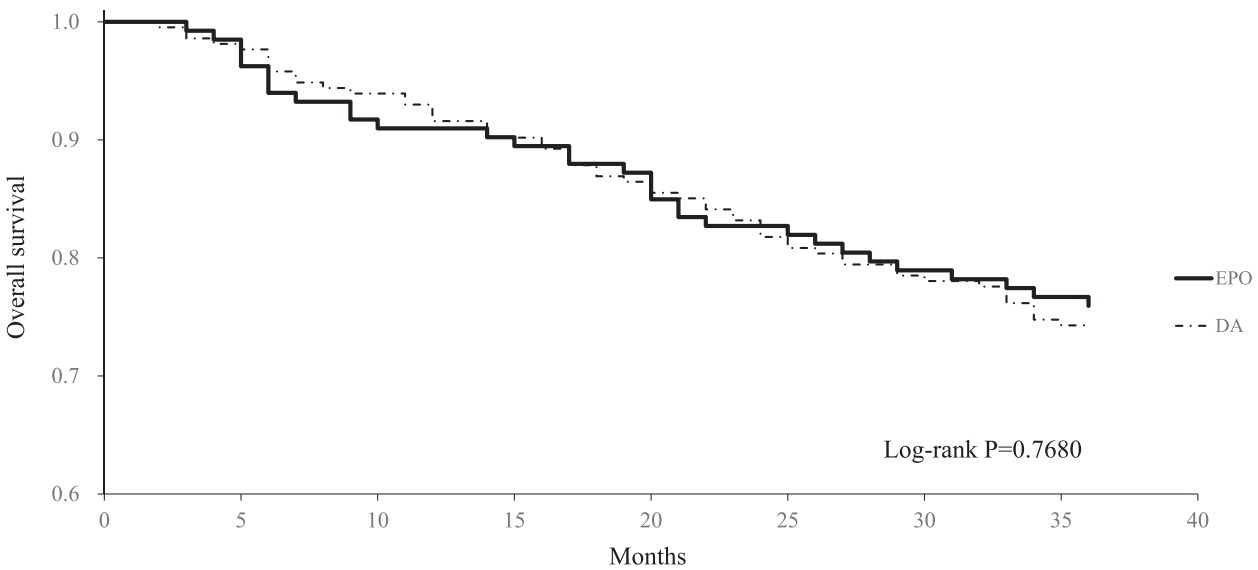

Fig. 3 Comparison of mortality risk in patients treated with epoetin (EPO) and darbepoetin (DA)

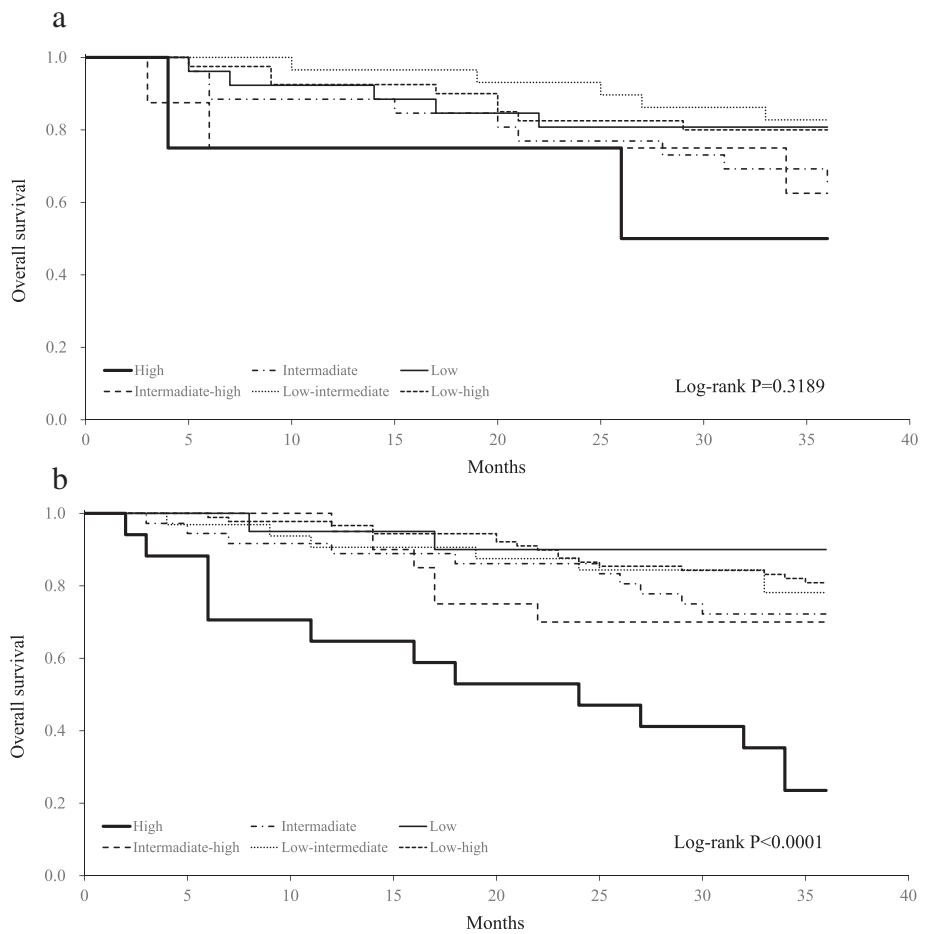

Fig. 4 Relationship between each ERI groups and all-cause mortality in patients treated with epoetin (EPO, **a**) and darbepoetin (DA, **b**)

expected to predict poor prognosis. Further study of ERI variability should be performed to determine the impact of the dose range. For a clinical understanding of ERI, it would be beneficial to examine how low ERI is affected by a limited range of ESA dosing.

According to the literature, 90 % of renal anemia patients respond to EPO in a dose-dependent manner, whereas the remaining 5–10 % of patients have either a blunted or absent response to ESAs, despite high-dose administration [19]. High ERI variability may be associated with hyporesponsiveness to ESA. Of the various

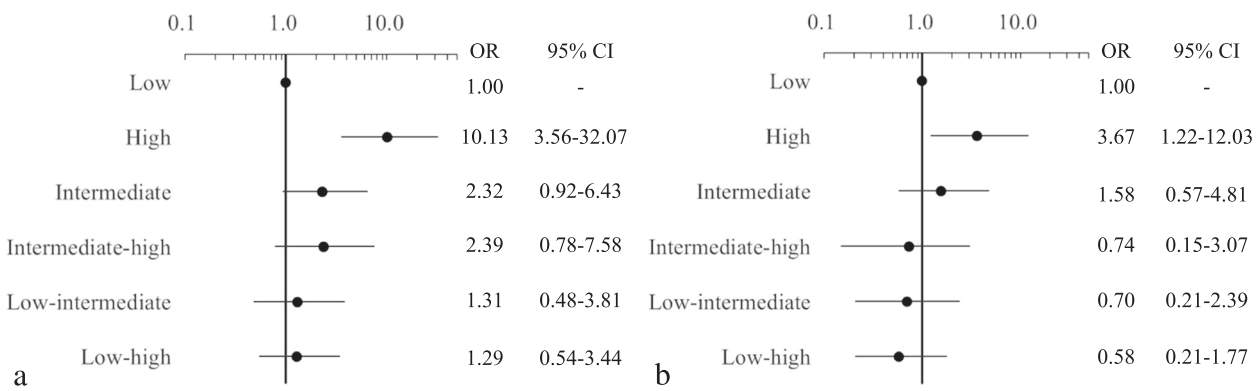

Fig. 5 Odds ratio for all-cause and CVD-associated mortality of the six ERI variability groups. **a** All-cause. **b** CVD-associated

Table 3 Independent factors associated with all-cause and CVD-related mortality in multivariate logistic regression analysis

	All-cause mortality			CVD-related mortality		
	HR	95 % CI	*p*	HR	95 % CI	*p*
ERI variability groups (high vs. non-high)	3.64	2.03–6.28	<0.0001	3.81	1.68–8.04	0.0019
Age (years)	1.06	1.03–1.08	<0.0001	1.04	1.01–1.07	0.0090
Sex (female vs. male)	0.51	0.31–0.81	0.0042	0.57	0.29–1.07	0.0821
Dialysis vintage (month)	1.00	1.00–1.01	0.1158	1.00	0.99–1.00	0.3642
BMI >22 kg/m^2 (yes vs. no)	1.15	0.73–1.80	0.5390	1.08	0.59–1.98	0.7986
Diabetes mellitus (yes vs. no)	1.60	1.03–2.47	0.0358	1.34	0.74–2.45	0.3333
History of CVD (yes vs. no)	1.21	0.57–2.29	0.5972	1.30	0.48–2.96	0.5763
Ferritin ≥100 ng/ml (yes vs. no)	1.43	0.93–2.18	0.1038	1.28	0.71–2.30	0.4052
Albumin ≥3.5 g/dl (yes vs. no)	0.47	0.29–0.76	0.0023	0.62	0.32–1.21	0.1567
CRP ≥1.0 mg/dl (yes vs. no)	0.68	0.37–1.20	0.1877	0.74	0.31–1.63	0.4686
Phosphorus ≥6 mg/dl (yes vs. no)	1.18	0.68–1.97	0.5407	1.14	0.54–2.23	0.7177

factors that affect patient responsiveness to an ESA, iron deficiency is thought to be the most prevalent cause of ESA hyporesponsiveness [20]. Intravenous iron administration has been shown to improve ESA responsiveness, leading to an increased Hb concentration and permitting the use of a decreased ESA dose [21]. Kuragano et al. have recently shown that iron administration was associated with an increased incidence for adverse events, including CVD, infection, and hospitalization, among HD patients who were treated with high doses of intravenous iron compared with HD patients who were not treated with iron [22]. In the present study, intravenous iron was frequently administered to the high ERI group who had the highest ferritin levels, suggesting the presence of ESA hyporesponsiveness that is associated with an increased mortality risk in high ERI group.

Table 4 Factors associated with high ERI variability

	High (*n* = 31)	Non-high (*n* = 345)	*p*
Sex			
Male	45.2	66.3	
Female	54.8	33.7	
Age, years	75.1 ± 9.9	66.1 ± 13.6	0.0003
BMI, kg/m^2	19.7 ± 3.1	22.2 ± 3.5	0.0001
HD vintage, months	62.9 ± 87.4	65.6 ± 74.1	0.8531
Kt/V	1.5 ± 0.3	1.4 ± 0.3	0.1084
History of CVD	9.7	11.3	0.783
Systolic BP, mmHg	150.7 ± 22.3	149.5 ± 22.5	0.7784
Diastolic BP, mmHg	76.5 ± 12.1	78.2 ± 14.1	0.5215
Iron dosage, mg	585.8 ± 590.8	884.4 ± 689.0	0.0200
Laboratory data			
Hb, g/dl	9.7 ± 1.0	10.9 ± 1.1	<0.0001
Ferritin, ng/ml	134.8 ± 101.8	85.6 ± 84.2	0.0023
Albumin, g/dl	3.5 ± 0.4	3.7 ± 0.3	0.0083
CRP, mg/dl	1.2 ± 1.7	0.6 ± 1.5	0.0281
Intact PTH, pg/ml	116.8 ± 87.5	155.2 ± 169.5	0.2213
Phosphorus, mg/dl	5.2 ± 1.6	5.3 ± 1.3	0.8339
Calcium, mg/dl	8.5 ± 0.8	8.7 ± 0.7	0.3027
ALP, U/l	249.8 ± 137.2	245.1 ± 95.7	0.8038
TSAT, %	20.8 ± 11.4	22.0 ± 11.3	0.5858

The present study had several limitations that were mainly due to the observational nature of the study. First, since this was a single-center cohort study, the data and results may not be representative of HD patients in other countries, particularly because ESA doses and Hb concentrations are generally lower in Japan than in other countries. However, the mortality rate and other baseline characteristics of our cohort were similar to those of Japanese dialysis patients in general [23]. Second, the longitudinal ERI assessments were based on data collected at 2-month intervals. Since using different measurement frequencies might make it possible to increase the prognostic potential of ERI variability, the most appropriate measurement frequencies and duration should be identified in subsequent investigations. Third, the average dose of EPO in Japan is lower than in other countries because of the healthcare expense reimbursement policy of the national health insurance system in Japan. Until April 2006, the maximum dose of EPO was limited to 9000 U/week of EPO alfa or EPO beta. Fourth, it is unknown why the patients treated with DA in High group had higher mortality risk. ESA selection bias by nephrologists may be associated with the results. Moreover, DA might be administered when response to EPO was insufficient for anemia treatment.

Conclusions

The results of this study demonstrated that consistently high ERI values in HD patients are an independent risk factor for all-cause and CVD mortality. Further study

will be necessary to obtain a more detailed understanding of the mechanisms that underlie the causal relationship between ERI and mortality.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
SS planned the study, searched the literature, assessed studies, extracted data, analyzed data, and prepared article. MK, MO, and TN assessed studies and assisted in the data analysis. HKat and KT searched the literature, assessed studies and assisted in article preparation. HKaw searched the literature and assisted in article preparation. KN planned the study, analyzed the data and assisted in article preparation. All authors read and approved the final manuscript.

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