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Hyporesponsiveness to long-acting erythropoiesis-stimulating agent is related to the risk of cardiovascular disease and death in Japanese patients on chronic hemodialysis: observational cohort study

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Abstract

Background: Responsiveness to erythropoiesis-stimulating agents (ESAs) is thought to be related to prognosis in patients on hemodialysis. A multi-center, prospective cohort study was conducted to investigate the effects of hyporesponsiveness to long-acting ESAs on cardiovascular events and mortality in Japanese patients on chronic hemodialysis.

Methods: A total of 127 chronic hemodialysis patients treated with long-acting ESAs were followed-up prospectively. Responsiveness to ESA was evaluated using an erythropoietin resistance index (ERI) calculated by dividing the weekly body-weight-adjusted ESA dose by the hemoglobin concentration. The primary endpoint of this survey was defined as a combination of cardiovascular events and all-cause deaths. The association between hyporesponsiveness to ESAs evaluated by the highest quartile of the ERI and the primary endpoint was investigated.

Results: During the follow-up period (median 4.6 years), 32 patients reached the primary end point. Kaplan-Meier curve analysis showed that patients with ESA hyporesponsiveness belonging to the highest quartile of the ERI reached the primary end point more frequently than those without ($P = 0.031$). Cox regression analysis showed that an ERI in the highest quartile was an independent predictor of the primary end point, even after adjustment using a propensity score (hazard ratio 2.76, 95% confidence interval 1.19–6.40).

Conclusions: ESA hyporesponsiveness in hemodialysis patients treated with long-acting ESAs is related to cardiovascular events and death.

Keywords: Erythropoiesis-stimulating agents, Cardiovascular event, Dialysis, Hyporesponsiveness, Mortality

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Introduction

Anemia, a common complication in all stages of chronic kidney disease (CKD), is more pronounced in end-stage renal disease (ESRD) patients on chronic dialysis, and it is one of the independent risk factors for cardiovascular disease and death in these patients [1–3]. Since treatment of anemia with erythropoietin-stimulating agents (ESAs) reportedly reduced the need for blood transfusions and improved quality of life [4, 5], ESAs have been widely used as first-line drugs for renal anemia in ESRD patients in daily practice. However, evidence from randomized, controlled trials suggested that treatment with ESA to higher target hemoglobin levels increased the risk of mortality in subjects on chronic hemodialysis [6, 7], and higher doses of ESA and lower achieved hemoglobin levels have been found to be related to increased mortality [8, 9]. Relationships between poor prognosis and ESA hyporesponsiveness in patients on chronic dialysis have been reported in several studies [10–12], although there are no quantitative definitions of ESA hyporesponsiveness based on the evidence from studies examining the prognosis of patients in relation to ESA responsiveness. In addition, the definitions of ESA hyporesponsiveness were rather different among these studies. The average dose of ESA and hemoglobin levels are reportedly lower in Japan than in Western countries [13], but the relationship between ESA responsiveness and prognosis in Japanese patients on chronic dialysis has been evaluated in few studies [14, 15], and most of the ESAs used in these studies were epoetin alfa and beta. Recently, Sakaguchi et al. reported that the long-acting ESA use was associated with an increased risk of mortality compared with short-acting ESA use in Japanese patients on chronic hemodialysis [16]. As this association was reportedly relevant particularly among patients with high ERI, more careful attention should be needed on ESA hyporesponsiveness in the long-acting ESA user. However, the relationship of ESA hyporesponsiveness to poor prognosis in dialysis patients treated with long-acting ESAs, darbepoetin alfa and epoetin beta pegol, has not been sufficiently investigated. Therefore, the aim of the present study was to investigate whether ESA hyporesponsiveness is related to the risk of cardiovascular disease and death in Japanese patients on chronic hemodialysis with the long-acting ESAs, darbepoetin alfa and epoetin beta pegol.

Patients and methods

Study design and population

This multi-center, prospective, observational cohort study included 127 stable patients receiving maintenance hemodialysis in the dialysis unit of 3 hospitals (Fujita General Hospital, Tani Hospital, and Hohrai East Clinic). Inclusion criteria were age ≥ 20 years and receiving

dialysis treatment for at least 3 months. Recruitment was performed between January and May 2015, and 203 patients were initially recruited. Of the originally enrolled patients, the following were excluded from this analysis: those who could not answer the questionnaire due to dementia or brain disease ($n = 59$), and those with acute/chronic inflammatory disease and active malignancy ($n = 9$). After additional exclusion of those not receiving ESA ($n = 6$), those receiving short-acting ESA ($n = 1$), and those who withdrew consent ($n = 1$), 127 participants were included in the study (Fig. 1).

Data collection

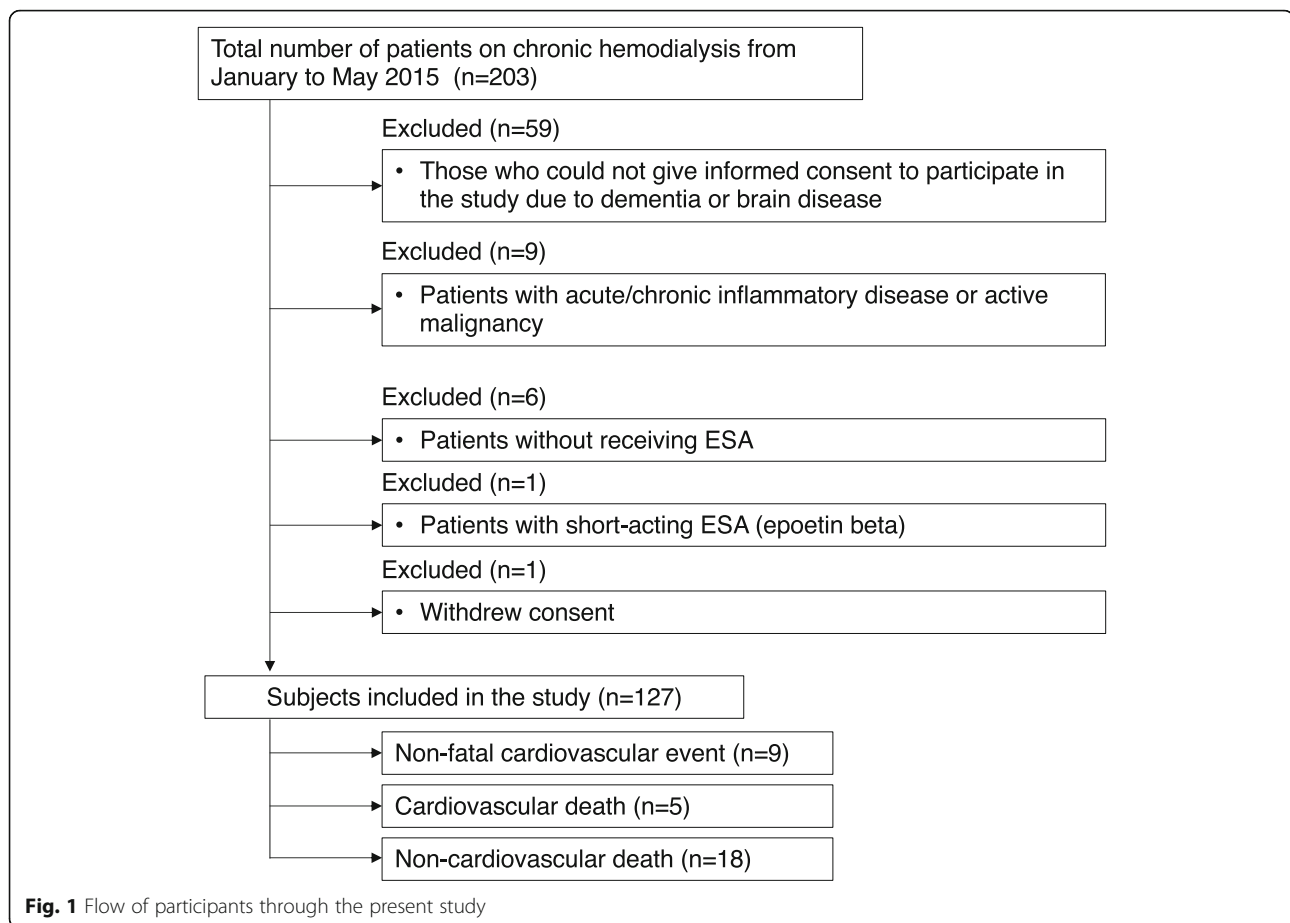
Blood samples were collected just before starting hemodialysis. Hemoglobin, serum albumin, calcium, phosphorus, intact parathyroid hormone (PTH), C-related protein (CRP), ferritin, and transferrin saturation (TSAT) were measured according to the automated standardized laboratory techniques in the clinical laboratory of each institution. Serum total calcium was adjusted for albumin using the formula proposed by Payne [17]. Dialysis dose were measured by single-pool Kt/V by the Daugirdas method [18]. Information on medications at baseline, as well as history of cardiovascular disease, was obtained from the patients' medical records. Cardiovascular disease included myocardial infarction, angina pectoris, congestive heart failure, arrhythmias, stroke, cerebrovascular disorder, chronic arteriosclerosis obliterans, and aortic dissection.

ESA responsiveness

To evaluate the dose-response effect of therapy with ESAs, an erythropoietin resistance index (ERI) was used, calculated as the weekly weight-adjusted ESA dose divided by the hemoglobin level: weekly ESA dose (U/week)/post-dialysis body weight (kg) \times hemoglobin (g/dL) [19]. The ERI was calculated only at the start of the study. All ESAs used in the present study were long-acting ESAs; darbepoetin alfa was used in 116 patients, and epoetin beta pegol was used in 11 patients. To compare with previous reports on the ERI with epoetin, darbepoetin alfa and epoetin beta pegol doses were converted in calculating the ERI based on the ratio of their equivalent peptide masses (200 units of epoetin to 1 μ g darbepoetin alfa and epoetin beta pegol, as previously described) [20]. On the basis of the ERI value, subjects were divided into four quartiles; subjects in the highest quartile were defined as those with ESA hyporesponsiveness in the present study.

Prospective follow-up

The patients were prospectively followed-up until November 2019 or until the study end point was reached. The primary endpoint of this survey was defined as a combination of cardiovascular events (fatal



and nonfatal myocardial infarction, angina pectoris, sudden death, congestive heart failure, arrhythmia, stroke, cerebrovascular disorder, chronic arteriosclerosis obliterans, subarachnoid hemorrhage, and aortic dissection) and all-cause death. Outcomes were surveyed every 12 months using the hospital medical records. All patients from the baseline cohort were assessed during follow-up.

Statistical analysis

The baseline characteristics of the study patients are expressed as percentages for categorical data and median and interquartile ranges for continuous variables with skewed distributions. The Kruskal-Wallis test was used to compare median values, and Tukey's test was used to evaluate differences in proportions. Patient survival was assessed using the Kaplan-Meier method with the log-rank test. The hazard ratios (HRs) and 95% confidence intervals (CIs) of the primary end point and all-cause death according to ERI levels were estimated by a Cox proportional hazards model analysis. Due to the limited number of patients, the results of multivariate Cox proportional hazard analysis were adjusted by the propensity score in the present study. A propensity score analysis was performed using a multivariate logistic

regression model, including confounding variables (age, sex, dialysis facility, diabetes, history of cardiovascular disease, dialysis duration, calcium, phosphorus, albumin, hemoglobin, CRP, intact PTH, TSAT, ferritin, use of renin-angiotensin-aldosterone system inhibitor, and Kt/V). The score was then incorporated into the multivariate analysis as a covariate. All data were analyzed using SPSS software (version 26; IBM Corporation, Chicago, IL, USA). Associations with $P < 0.05$ were considered significant.

Results

Table 1 summarizes the baseline characteristics according to ERI quartile of the study population. The ERI was calculated for all patients, with a median (IQR) of 5.36 (2.73–11.31). Subjects belonging to quartile four (ERI level ≥ 11.31) were defined as the high ERI group with ESA hyporesponsiveness in the present study. The median (IQR) hemoglobin concentration was 10.6 (10.1–11.1), and the median (IQR) ESA dose was 15 (10–30) $\mu\text{g}/\text{week}$. The median values for body mass index, hemoglobin concentration, and serum albumin decreased with increasing ERI levels. Lower hemoglobin levels and higher ESA dose were seen in patients with higher ERI levels (Table 1). The ERI

Table 1 Baseline characteristics by ERI quartile

	All	ERI quartiles				P for trend
		Q1 (< 2.73)	Q2 (2.74–5.36)	Q3 (5.37–11.30)	Q4 (11.31 ≤)	
N	127	32	31	32	32	
Age (years)	67 (59–74)	66.5 (51.3–71.0)	62.0 (55.0–67.0)	71.5 (66.3–80.8)	69.5 (63.3–75.8)	< 0.001
Male gender (%)	55.1	65.6	61.3	43.8	50.0	0.271
Dialysis duration (y)	6.7 (2.8–12.3)	6.5 (3.7–12.0)	9.3 (3.7–13.3)	7.0 (3.0–12.8)	3.0 (1.8–10.3)	0.140
Smoking (history) (%)	44.1	43.8	54.8	37.5	40.6	0.537
History of cardiovascular disease (%)	19.7	15.6	12.9	31.3	18.8	0.266
Body mass index (kg/m ²)	21.4 (19.0–23.7)	23.1 (21.0–25.9)	21.2 (19.9–23.1)	20.8 (19.1–23.1)	20.3 (17.7–22.6)	0.006
Diabetes (%)	44.9	43.8	41.9	50.0	43.8	0.923
Pre-dialysis SBP (mmHg)	150 (136–165)	147 (137–158)	153 (139–168)	154 (133–163)	156 (134–173)	0.414
Pre-dialysis DBP (mmHg)	80 (71–86)	83 (76–88)	80 (71–96)	74 (66–81)	78 (72–88)	0.102
Hemoglobin (g/dL)	10.6 (10.1–11.1)	11.0 (10.4–11.4)	11.0 (10.3–11.3)	10.3 (9.8–11.0)	10.3 (9.7–10.8)	0.002
Albumin (g/dL)	3.5 (3.2–3.7)	3.7 (3.4–3.8)	3.5 (3.2–3.7)	3.4 (3.1–3.7)	3.4 (3.1–3.5)	0.027
Calcium (mg/dL)	9.2 (8.9–9.6)	9.0 (8.7–9.5)	9.2 (8.8–9.7)	9.5 (9.1–9.7)	9.3 (8.9–9.6)	0.133
Phosphorus (mg/dL)	5.0 (4.2–5.8)	4.8 (4.2–5.6)	4.9 (3.8–5.7)	5.0 (4.1–5.8)	5.3 (4.7–6.0)	0.404
Intact PTH (pg/mL)	128 (81–198)	151 (95–238)	129 (97–169)	163 (72–222)	100 (65–159)	0.125
C-related protein (mg/dL)	0.20 (0.18–0.22)	0.20 (0.08–0.20)	0.20 (0.08–0.20)	0.20 (0.20–0.23)	0.20 (0.20–0.29)	0.164
Ferritin (ng/dL)	34 (19–71)	41 (25–67)	24 (18–41)	31 (15–83)	50 (24–85)	0.161
TSAT (%)	24.2 (18.3–29.4)	21.4 (15.3–30.4)	25.6 (19.5–29.4)	26.8 (18.4–30.0)	21.7 (17.7–29.6)	0.551
Kt/V	1.47 (1.31–1.73)	1.45 (1.25–1.72)	1.64 (1.27–1.74)	1.51 (1.42–1.80)	1.40 (1.31–1.72)	0.345
ESA type (%)						
Darbepoetin alfa	91.3	100	100	96.8	68.8	< 0.001
Epoetin beta pegol	8.7	0	0	3.2	31.3	< 0.001
ESA dose (μg/week)						
Darbepoetin alfa	15 (10–20)	5 (5–5)	10 (10–15)	20 (15–20)	40 (38–60)	< 0.001
Epoetin beta pegol	75 (50–100)	NA	NA	25 (25–25)	75 (75–100)	< 0.001
ERI	5.36 (2.73–11.31)	1.61 (1.36–2.21)	4.32 (3.45–4.81)	7.37 (6.11–9.43)	20.42 (14.76–24.45)	< 0.001
ARB or ACEi (%)	62.2	59.4	64.5	62.5	62.5	0.980

Data are expressed as median (interquartile range). P values were obtained by comparison across all four groups using the Kruskal-Wallis test and χ^2 test, as appropriate. ERI erythropoietin resistance index, SBP systolic blood pressure, DBP diastolic blood pressure, PTH parathyroid hormone, TSAT transferrin saturation, ESA erythropoietin-stimulating agent, ARB angiotensin receptor blocker, ACEi angiotensin-converting enzyme inhibitor

correlated with age ($r = 0.25$, $P = 0.004$), body mass index ($r = -0.30$, $P = 0.001$), hemoglobin ($r = -0.33$, $P < 0.001$), serum albumin ($r = -0.26$, $P = 0.003$), and CRP ($r = 0.19$, $P = 0.035$).

The median follow-up time was 4.6 years (IQR 4.4–4.8 years). During the follow-up period, 32 of 127 (25%) patients reached the primary end point (9 cardiovascular events and 23 all-cause deaths occurred, with only 4 cardiovascular deaths). The causes of death were sepsis (6 cases); uremia (5 cases); malignancy (4 cases); respiratory failure (2 cases); myocardial infarction (1 case); stroke (1 case); cerebrovascular disorder (1 case); subarachnoid hemorrhage (1 case); and unknown (2 cases).

In order to generate a propensity score, multivariate logistic regression analysis was performed using high ERI (≥ 11.31) as an independent variable (Supplemental table).

Intact PTH had an inverse relationship to high ERI. Kaplan-Meier curve analysis showed that patients with ESA hypo-responsiveness belonging to quartile four (ERI ≥ 11.31) reached the primary end point more frequently than those without (Fig. 2). The incidence of all-cause death was also higher in the ESA hypo-responsiveness group with a higher ERI (Fig. 3). The results of univariate Cox regression analysis showed that a high ERI (≥ 11.31) was a predictor of both the primary end point and all-cause death (Table 2). A high ERI remained an independent predictor for both the primary end point and all-cause death after adjusting by the propensity score.

Discussion

The results of this prospective survey in a cohort of Japanese patients on chronic hemodialysis showed that ESA

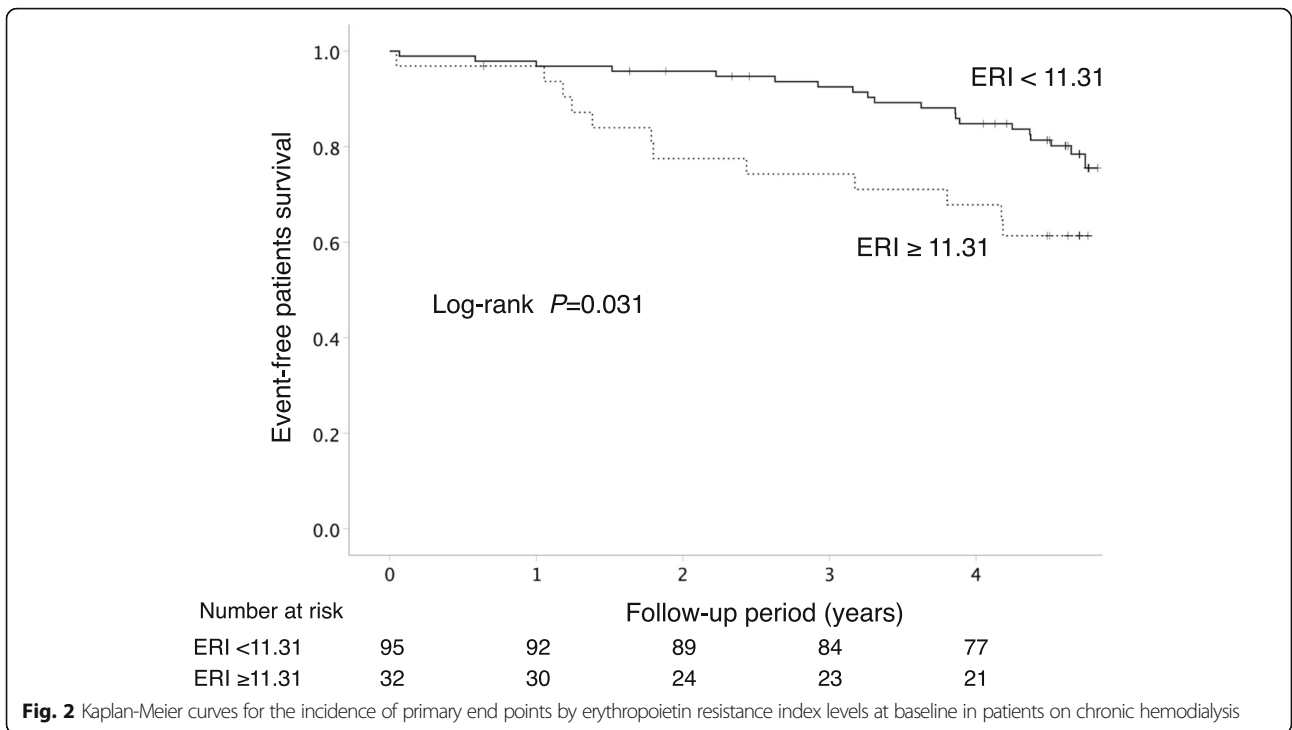


Fig. 2 Kaplan-Meier curves for the incidence of primary end points by erythropoietin resistance index levels at baseline in patients on chronic hemodialysis

hyporesponsiveness evaluated by the ERI is an independent predictor of adverse outcomes such as cardiovascular events and deaths. Since the relationship between the ERI and poor prognosis in dialysis patients has already been reported [12, 14, 15], the present study is confirmatory. However, most studies of the ERI have been

performed in patients treated with a short-acting ESA, epoetin, reporting that the ERI is related to the risk of cardiovascular events and all-cause mortality. The relationship between the ERI and poor prognosis has not been sufficiently investigated in dialysis patients treated with long-acting ESAs. The present study showed the

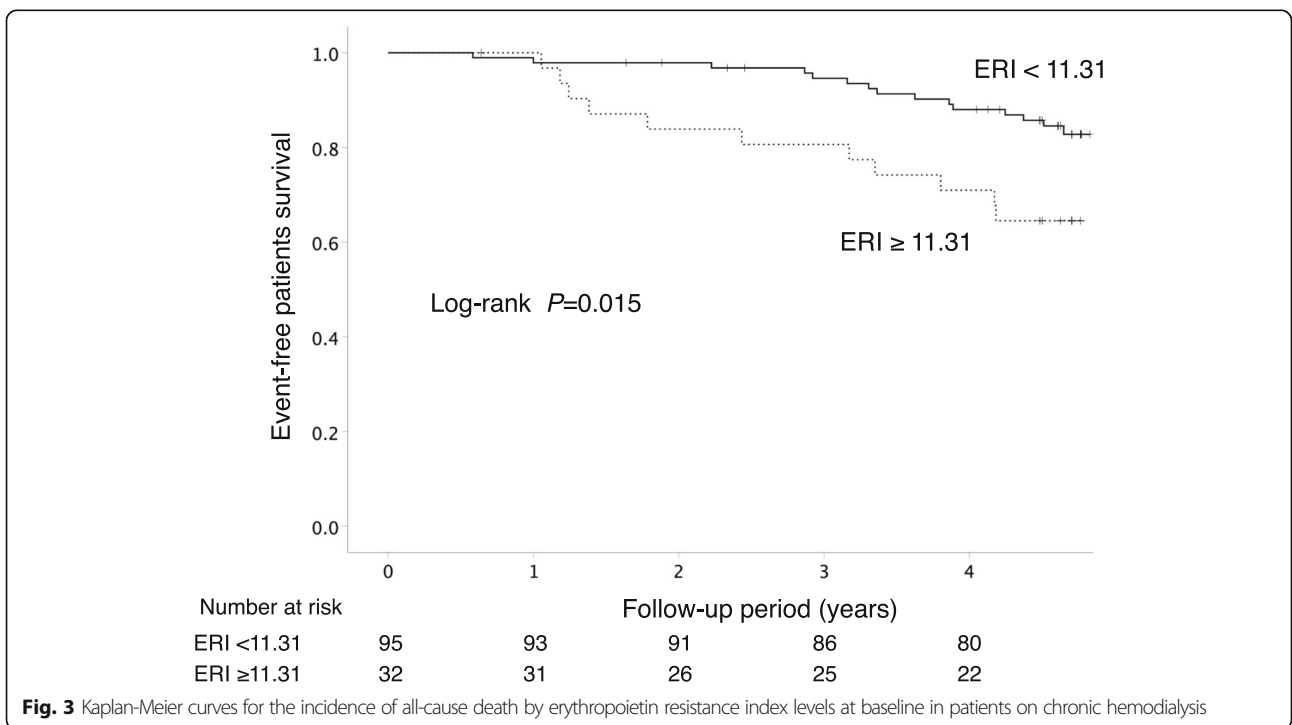


Fig. 3 Kaplan-Meier curves for the incidence of all-cause death by erythropoietin resistance index levels at baseline in patients on chronic hemodialysis

Table 2 Associations between the high erythropoietin resistance index and risks of the primary endpoint and of all-cause death

	Primary endpoint		All-cause death	
	HR (95% CI)	P	HR (95% CI)	P
High ERI (≥ 11.31 , Q4) vs. (< 11.31 , Q1, Q2, and Q3)				
Unadjusted	2.16 (1.05–4.42)	0.035	2.54 (1.16–5.52)	0.019
Age- and sex-adjusted	2.77 (1.33–5.78)	0.006	3.10 (1.41–6.86)	0.005
Propensity score adjusted	2.76 (1.19–6.40)	0.018	2.57 (1.05–6.27)	0.038

ERI erythropoietin resistance index, HR hazard ratio, CI confidential interval

Propensity score analysis was performed using a multivariate logistic regression model, including confounding variables (age, sex, dialysis facility, diabetes, history of cardiovascular disease, dialysis duration, calcium, phosphorus, albumin, hemoglobin, C-reactive protein, intact parathyroid hormone, transferrin saturation, ferritin, use of angiotensin receptor blocker or angiotensin-converting enzyme inhibitor, and Kt/V)

relationship of the ERI to cardiovascular events and all-cause mortality in dialysis patients treated with long-acting ESAs, darbepoetin alfa and epoetin beta pegol, in a prospective observational study.

To compare with previous reports on the ERI with epoetin, darbepoetin alfa and epoetin beta pegol doses were converted by multiplying by 200 in calculating the ERI in the present study. Several observational studies have examined the relationship between ESA hyporesponsiveness calculated by the same equation as in this study and poor prognosis in dialysis patients [12, 14, 15]. The findings of these studies were in accord with the results of the present study, and higher ERI levels were related to the risk of mortality and cardiovascular events in patients on chronic hemodialysis. A poor prognosis was reportedly associated with ERI levels ≥ 10.0 and ≥ 9.44 , respectively, in Japanese patients on dialysis [14, 15]; thus, the present result that an ERI level > 11.3 was related to the risk of cardiovascular disease and death was similar to these results, although both ESA doses and ERI levels reported in European patients on dialysis were much higher than in the present study [12].

In the present study, the ERI had a significant positive correlation with CRP and negative correlations with body mass index and serum albumin, which reflect inflammation and malnutrition in dialysis patients. Both the nutritional state and the presence of inflammation are recognized factors related to a poor prognosis in dialysis patients, so-called malnutrition-inflammation-atherosclerosis syndrome, and they were reportedly also related to ESA hyporesponsiveness [21–25]. Since low hemoglobin levels increase the risk of cardiovascular disease and death, ESA therapy is crucial in dialysis patients, but treatment of anemia with high-dose ESAs could have a negative effect on the prognosis of these patients. Mortality rate was reportedly higher in long-acting ESA user than in short-acting ESA user, and the increased rate of mortality was more prominent in patients with high dose ESA and high ERI [16]. Thus, management of nutritional status and chronic inflammation is needed to improve ESA hyporesponsiveness, as well as the poor prognosis, in patients who need high-dose

ESAs to increase their serum hemoglobin concentrations to target levels, in particular in long-acting ESA user, before increasing the dose of ESAs.

Iron deficiency is considered one of the factors associated with both ESA responsiveness and prognosis in patients on dialysis. The Japanese nationwide registry data, including 142,339 Japanese patients on chronic dialysis, has shown a U-shaped relationship between the ERI and TSAT, with the bottom of the ERI curve around a TSAT of 30–40% [26]. However, there were no differences in ferritin and TSAT levels among the ERI levels in the present study. Significant differences were not observed in the iron states between patients who reached the primary end point and those who did not. These results might have been affected by the much lower levels of ferritin (median 34 ng/dL) in the present study with a limited number of subjects. Therefore, relationships among the iron states, responsiveness to ESAs, and prognosis in dialysis patients should be investigated across various ranges of ferritin levels in a longitudinal study with sufficient numbers of patients or in a randomized, controlled trial.

The present study has several limitations. First, single measurements of the ERI and covariates at baseline might have led to some misclassification of ESA responsiveness, and it was not possible to examine the effects of changes from the baseline category during follow-up. Also, some patients treated with long-acting ESAs at baseline might have been converted to short-acting ESAs during follow-up. Second, the sample size was small. Since the number of patients reaching the primary end point was relatively small, multivariate adjustment for covariates at baseline might be insufficient for evaluating the association between ERI levels and poor outcomes. Therefore, the results of multivariate Cox regression analysis were adjusted by the propensity score calculated from sufficient confounding variables at baseline in order to avoid this statistical inadequacy. Third, since this study was an observational study, it remains unclear whether a poor prognosis in dialysis patients is associated with a high dose of ESAs itself or factors causing ESA hyporesponsiveness, such as malnutrition, chronic

inflammation, and iron states. These limitations of the present study need to be addressed in future studies.

Conclusions

The present study showed that ESA hypo-responsiveness evaluated by the ERI was associated with increased risks of cardiovascular events and all-cause death in Japanese patients on chronic hemodialysis treated with long-acting ESAs. ERIs were related to malnutrition and chronic inflammation, and they had significant and independent effects on poor prognosis in these patients. Although there are no quantitative definitions of ESA hypo-responsiveness based on the evidence from studies examining the prognosis of dialysis patients, the ERI, easily calculated in daily practice, could be a useful tool for predicting the risk of cardiovascular events and deaths in patients treated with ESAs, including both short- and long-acting. Further investigations are still necessary to confirm these findings in an observational survey of sufficient size and with better statistical methods, and to determine whether interventions for improving hypo-responsiveness to ESAs reduce the risk of cardiovascular events and deaths in patients with ESA hypo-responsiveness in a clinical trial.

Abbreviations

ESA: Erythropoiesis-stimulating agent; ERI: Erythropoietin resistance index; CKD: Chronic kidney disease; ESRD: End-stage renal disease; PTH: Parathyroid hormone; CRP: C-reactive protein; TSAT: Transferrin saturation; HR: Hazard ratio; CI: Confidence interval

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s41100-021-00332-0>.

Additional file 1: Supplemental Table. Factors related to high ERI (≥ 11.31) in CKD patients on multivariate logistic regression analysis for generating propensity score.

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Authors' contributions

KT wrote the paper with input from all authors. All authors have approved the manuscript. Research idea and study design: KT; data acquisition: MF, HS, TI, AO, SW, MK, HK, HK, YT, JA, HS; data analysis/interpretation: KT, HS, KS; statistical analysis: KT; supervision or mentorship: JK.

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Availability of data and materials

The dataset generated and/or analyzed during the current study are available from corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study protocol complied with the Declaration of Helsinki and was approved by the ethics committee at Fukushima Medical University (acceptance no. 2069). All patients received an explanation of the procedures

and possible risks of this study and gave their written, informed consent to participate in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

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