Thresholds of iron markers for iron deficiency erythropoiesis—finding of the Japanese nationwide dialysis registry

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Reportedly, serum ferritin levels are much lower in Japanese hemodialysis (HD) patients than their Western counterparts. Therefore, the cutoff values of ferritin and transferrin saturation (TSAT) for iron deficiency might differ from other countries. We conducted a cross-sectional observational study using the Japanese nationwide registry data. We enrolled 142,339 maintenance HD patients and assessed the association between these markers, hemoglobin (Hb), and erythropoiesis-stimulating agent (ESA) resistance index (ERI) utilizing restricted cubic spline analyses. Median ferritin and TSAT levels were 73 (IQR: 31–158) ng/ml and 23.7 (16.8–32.0)%, respectively. These lower ferritin ranges may possibly stem from a lower inflammatory state in Japanese patients, as shown in median CRP of 1.0 mg/l. An adjusted nonlinear association between Hb and TSAT showed that Hb levels drop with the decrease in TSAT below 20%, regardless of serum ferritin levels, suggesting the absolute iron deficiency cutoff as 20% for TSAT. In patients with TSAT $>20\%$, the association between Hb and ferritin levels is nearly flat, whereas in patients with TSAT $<20\%$, ferritin <50 ng/ml was associated with low Hb. In long-acting ESAs-users with TSAT $>20\%$, U-shaped relationship was observed between ERI and ferritin with the bottom of ERI around 100 ng/ml of ferritin, possibly because high ferritin levels reflected an inflamed state leading to hyporesponsiveness to ESA. The patient subgroup with TSAT $<20\%$ and ferritin >100 ng/ml had significantly higher ERIs compared with the subgroup with TSAT $>20\%$ and ferritin <100 ng/ml, implying that TSAT, rather than ferritin, should be a primary iron marker predicting ESA response.

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INTRODUCTION

Anemia guidelines in chronic kidney disease all over the world vary, especially with regard to the cutoff values of iron parameters, namely ferritin and transferrin saturation (TSAT), below which iron administration is recommended. In the original Kidney Disease Outcomes Quality Initiative guidelines published in 2001,[1] the targets of ferritin and TSAT were greater than 100 ng/ml and 20%, respectively. In European Best Practice Guidelines in 2004,[2] the targets of these markers were 200–500 ng/ml and 30–50%, respectively. The similar target ranges were also advocated by the Caring for Australasians with Renal Impairment guidelines.[3] The revised K/DOQI guidelines in 2006 recommended a slightly higher target ranges compared with the prior ones; >200 ng/ml for ferritin and $>20\%$ for TSAT.[4] In the Kidney Disease Improving Global Outcomes guidelines recently published,[5] an iron trial was recommended in patients with ferritin $\leqslant 500$ ng/ml and TSAT $\leqslant 30\%$ if an increase in hemoglobin (Hb) concentration or a decrease in erythropoiesis-stimulating agents (ESAs) is desired. In brief, renal anemia guidelines in Western countries are becoming liberal in prescribing iron preparations while limiting ESA doses. This might be reasonable, considering the fact that many studies that tried to drive Hb levels up by excessive dosing of ESAs have resulted in worse outcomes[6–8], and it also might be plausible, considering recent clinical trials showing that iron administration was beneficial in terms of objective symptoms[9] and renal function[10] in patients with congestive heart failure, even in the state of functional iron deficiency that often complicates congestive heart failure.

However, Japanese guidelines are still conservative in the prescription of iron, having lower target ranges of iron parameters than Western countries, despite much lower ESA doses currently used.[11] Only when there is TSAT $<20\%$ and (not or) ferritin <100 ng/ml, iron administration is recommended in dialysis patients.[12] The reason partly lies in the fact that intravenous administration of a certain iron preparation increases oxidative stress.[13] Some Japanese nephrologists do not recommend iron administration to patients with

functional iron deficiency[14] characterized with high ferritin and low TSAT, because of a possibility of iron accumulation in such organs as liver, leukocytes, and cardiovascular system, leading to liver toxicity, impaired immunity, and atherosclerosis, respectively. In fact, bolus iron injection is reported to increase the risk of infection-related hospitalization.[15] Therefore, Japanese guidelines have recommended iron administration exclusively to the patients with absolute iron deficiency. However, evidences of the cutoffs of iron parameters reflecting absolute iron deficiency are very scarce in Japanese hemodialysis (HD) patients. Given that serum ferritin distribution ranges of Japanese maintenance HD patients are much lower than those of Western countries,[16] the data in Europe and North America cannot be extrapolated to Japanese patients.

The aims of this Japanese nationwide cross-sectional study are (1) to elucidate the cutoff of TSAT or ferritin levels under which Hb levels decrease (the cutoff of absolute iron deficiency) in Japanese maintenance HD patients and (2) to examine the ranges of iron parameters where ESA responsiveness is best. The latter might give us some insights of the cutoff values of iron markers showing relative hyporesponsiveness to ESA.

RESULTS

Characteristics of the study subjects

As shown in Figure 1, we excluded a total of 89,841 patients, due to missing values in the key variables for anemia in the survey: Hb, type of ESA, Fe, total iron-binding capacity, and ferritin. Eventually, 142,339 in-center maintenance HD patients were enrolled. Table 1 summarizes the characteristics of the study subjects. The median (interquartile range (IQR)) levels were 23.7 (16.8–32.0)% for TSAT, 73 (31–158) ng/ml for ferritin, 1.0 (1.0–4.0) mg/l for C-reactive protein (CRP), and 126 (68–206) pg/ml for parathyroid hormone (PTH). Compared with HD patients in Western countries, the study population had a longer duration of dialysis, lower levels of body mass index, ferritin, CRP, and PTH, probably due to different clinical practice patterns. There were 33,352 (23.4%) subjects treated with epoetin alpha or beta (Epo A/B), 61,992 (43.6%) with darbepoetin (Darb), 17,338 (12.2%) with epoetin beta pegol (Pegol), and less than 10% with other ESAs, including epoetin kappa. The remaining subjects (11.9%) did not receive any ESA. There were no clinically meaningful differences between the subjects we analyzed and the population that met the inclusion criteria but was not included in the analyses due to missing data.

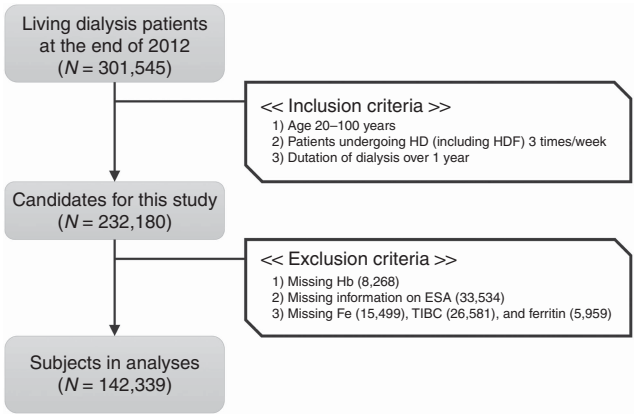

Figure 1 | Flowchart of the subject selection process in this study. Briefly, 142,339 in-center maintenance hemodialysis patients, undergoing 3 sessions per week, aged 20–100 years, with duration of dialysis of 12 months or more, and without missing data in the key variables for anemia, were selected from the original data set that comprised of 301,545 living dialysis patient records. ESA, erythropoiesis-stimulating agent; Fe, serum iron; Hb, hemoglobin; HD, hemodialysis; HDF, hemodiafiltration; TIBC, total iron-binding capacity.

Distributions of TSAT and ferritin

The distributions of TSAT, ferritin, and CRP were right-skewed (Figure 2a–c). The proportions of the subjects who met the criteria of TSAT $<20\%$, ferritin <100 ng/ml, and both were 36.3, 60.2, and 28.0%, respectively. When divided by the CRP level at 10 mg/l, which was in the 87th percentile

Table 1 | Characteristics of the study subjects

	Study subjects	Patients who met with inclusion criteria
Number	142,339	232,180
Female (%)	37.4	37.4
Age (years)	66.8 ± 12.3	66.8 ± 12.3
Duration of dialysis (years)	6.5 (3.3–11.8)	6.6 (3.3–11.9)
Diabetes (%)	36.5	36.4
BMI (kg/m^2)	21.5 ± 3.8	21.4 ± 3.8
Serum albumin (g/dl)	3.7 ± 0.4	3.7 ± 0.4
Hemoglobin (g/dl)	10.7 ± 1.2	10.6 ± 1.2
TSAT (%)	23.7 (16.8–32.0)	23.6 (16.8–32.0)
Ferritin (ng/ml)	73 (31–158)	75 (31–162)
CRP (mg/l)	1.0 (1.0–4.0)	1.0 (1.0–4.0)
Intact PTH (pg/ml)	126 (68–206)	126 (66–207)
Kt/V	1.44 (1.27–1.64)	1.44 (1.26–1.64)
Past history of CVDs (%)		
Myocardial infarction	9.7	9.8
Cerebral infarction	18.2	18.5
Cerebral hemorrhage	6.0	6.1
Amputation of the extremities	3.5	2.0
Blood pressure (mm Hg)		
Systolic	152 ± 24	152 ± 24
Diastolic	78 ± 15	78 ± 15
Antihypertensive drug use (%)	66.9	66.3
Current smoking (%)	13.4	13.3
ESAs (%)		
No ESA	11.9	12.2
Epoetin alpha/beta	23.4	23.2
Darbepoetin	43.6	42.9
Epoetin beta pegol	12.2	12.2
Others	8.9	9.5

Abbreviations: BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; ESA, erythropoiesis-stimulating agent; HD, hemodialysis; IQR, interquartile range; PTH, parathyroid hormone; TSAT, transferrin saturation.
The values are expressed as mean ± s.d. or median (IQR).