RENAL FAILURE
2022, VOL. 44, NO. 1, 1801–1810
https://doi.org/10.1080/0886022X.2022.2106873

Taylor & Francis
Taylor & Francis Group

CLINICAL STUDY

OPEN ACCESS Check for updates

Synergistic deterioration of prognosis associated with decreased grip strength and hyporesponse to erythropoiesis-stimulating agents in patients undergoing hemodialysis

Shizuka Kobayashi[a]*, Kentaro Tanaka[b], Junichi Hoshino[c]*, Shigeko Hara[d], Akifumi Kushiyama[e], Yoshihide Tanaka[f], Shuta Motonishi[g], Ken Sakai[h] and Takashi Ozawa[a]

[a]Internal Medicine, Kodaira Kitaguchi Clinic, Tokyo, Japan; [b]Internal Medicine, Higashikurume Ekimae Clinic, Tokyo, Japan; [c]Nephrology Center, Toranomon Hospital, Tokyo, Japan; [d]Okinaka Memorial Institute for Medical Research, Toranomon Hospital, Tokyo, Japan; [e]Department of Pharmacotherapy, Meiji Pharmaceutical University, Tokyo, Japan; [f]Internal Medicine, Kumegawa Touseki Naika Clinic, Tokyo, Japan; [g]Internal Medicine, Higashiyamato Nangai Clinic, Tokyo, Japan; [h]Department of Nephrology, Faculty of Medicine, Toho University, Tokyo, Japan

ABSTRACT

Introduction: We examined the combined effect of erythropoietin (EPO) hyporesponsiveness and low handgrip strength (HGS) on the prognosis of patients undergoing hemodialysis (HD).

Methods: We recruited patients with chronic kidney disease (CKD) Stage 5, who were undergoing HD at our dialysis clinic between January 2015 and March 2015 ($n = 182$). Patients of ≥20 years of age and who had been undergoing HD for ≧3 months at enrollment were eligible for inclusion. Seven patients treated with epoetin-β pegol were excluded. First, the erythropoietin resistance index (ERI) and HGS were measured. The patients were stratified by the ERI of 9.44 (U/kg/week/g/dL), and by the HGS of 28 kg for men and 18 kg for women. We then observed death and cardiovascular disease (CVD), composite endpoint (deaths or CVD) for a median of 2 years.

Results: A total of 175 patients (male, $n = 122$; female, $n = 53$; age, 34–92 years) were included in the analysis. During the observation period of 24 months, 57 events (14 deaths and 43 CVD) were observed. High ERI and low HGS were associated with a high incidence of endpoints compared to low ERI and high HGS. Among the four groups classified by ERI and HGS values, the highest risk group was the high ERI/low HGS group (HR: 4.20 95% CI 2.12–8.33).

Conclusions: EPO hyporesponsiveness combined with low HGS were found to be significant predictors of a poor outcome, and the synergistic effects of the two factors had stronger predictive ability than either single factor.

ARTICLE HISTORY
Received 30 March 2022
Revised 20 July 2022
Accepted 21 July 2022

KEYWORDS
Erythropoietin hyporesponsiveness; hand grip strength; all-cause mortality; hemodialysis

Introduction

The cardiovascular risk in patients with chronic kidney disease (CKD) appears to be far greater than that in the general population [1]. Despite improvements in dialysis technology, the cardiovascular mortality of this population remains high [2]. In addition, renal anemia is an important complication of hemodialysis (HD) and is a factor that influences the mortality rate due to circulatory and other complications [3]. Renal anemia is mainly attributable to decreased erythropoietin (EPO) production by the kidneys.

Presently, the main treatment for renal anemia is EPO replacement; erythropoiesis-stimulating agent (ESA) therapy has been used for the treatment of anemia in patients undergoing HD. ESA therapy has many benefits for patients, including an improved quality of life (QoL), greater exercise capacity, and reduced need for blood transfusion [4]; however, 12.5% of patients undergoing HD who receive ESA therapy are reported to exhibit ESA hyporesponsiveness, where the patient does not achieve the desired hemoglobin (Hb) concentration, despite receiving a higher ESA dose than usual [5]. Recent studies have demonstrated that the ESA dose and achieved Hb levels were associated with mortality in patients undergoing HD; additionally, hyporesponsiveness to ESA therapy was reported to be one of the poor prognostic factors in HD patients [6–8].

CONTACT Junichi Hoshino jhoshinoind@gmail.com Nephrology Center, Institute/University/Hospital, Toranomon Hospital, 2-2-2 Toranomon, Tokyo 105-8470, Japan
*Additional affiliation: Department of Nephrology, Tokyo Women's Medical University, Tokyo, Japan.

Focus has also been placed on handgrip strength (HGS) for patients with HD as an indicator of muscle function in recent research [8]. HGS can also be a good indicator of overall muscle strength, as it is related to the strength of other muscle groups [9]. HGS is a strong predictor of cardiovascular mortality and a moderately strong predictor of incident cardiovascular disease [10]. Generally, HGS is a simple and inexpensive risk stratification method for all-cause mortality or cardiovascular disease [10,11]. Many studies have reported that reduced muscle strength measured through HGS was associated with increased mortality and cardiovascular disease [10,11], and the diagnostic criteria for sarcopenia and frailty also include HGS ($<$28 kg for males and $<$18 kg for females) [12].

Associations between anemia, muscle weakness, and motor impairment have been reported [9,13]. Low muscle strength, one of frailty traits, is recognized as one of the major problems experienced by aging patients undergoing HD [13,14]. HGS is an independent predictor of all-cause mortality, even in patients undergoing maintenance HD [10]. The 2018 guidelines of the Japanese Society of Renal Rehabilitation state that frailty-like condition is reversible and may be restored close to normality with appropriate rehabilitation intervention [15]. Additionally, an increase in Hb led to an improvement in QoL, whereas a meta-analysis stated that $a \geq 10$ g/dL improvement in Hb in patients undergoing HD resulted in a significant improvement in malaise [16]. Improvement in vitality and malaise associated with the improvement of anemia are expected to be beneficial when performing exercise therapy [15].

As such, ESA hyporesponsiveness and low HGS appear to be risk factors for all-cause mortality and cardiovascular disease; however, no studies have investigated the prognostic impact of ESA hyporesponsiveness in association with low HGS. Thus, this study investigated the combined effect of ESA hyporesponsiveness and HGS in patients undergoing HD on the prognosis for death and cardiovascular disease.

Materials and methods

Research design

This was a two-year prospective observational cohort study conducted across four clinics of our medical institution (Kodaira Kitaguchi Clinic, Higashikurume Clinic, Kumegawa Touseki Naika Clinic, and Higashiyamato Nangai Clinic). The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Review Board (No. 2014-7). All participants provided their written informed consent.

Subjects

Participation recruitment was conducted from January to March 2015. Among patients on maintenance dialysis attending our medical institution, 175 consenting patients were included in the study and baseline data were obtained in April 2015. Patients who were $\geq$20 years of age, and who had been receiving HD three times a week for $\geq$3 months at enrollment were eligible for inclusion in this study. Patients who used epoetin-β pegol and those admitted during the month of enrollment were excluded from the study.

Methods

ESA responsiveness was estimated using the EPO resistance index (ERI) for human recombinant EPO (rHuEPO) (U)/week/dry weight (kg)/Hb (g/dl) [5,7,17,18]. To demonstrate the use of rHuEPO and darbepoetin α (DA), the ratio of rHuEPO to DA was calculated as 200:1 [5,7,18]. HGS measurements were obtained as motor function measurements using a Smedley digital dynamometer (Takei Scientific Instruments Co., Ltd., Niigata, Japan). After adjusting for hand size, HGS was measured in a sitting position with arms hanging at the sides. HGS measurements were obtained twice on each side. For our study, we used the maximum HGS values obtained from both hands. HGS measurements were performed before the dialysis session.

All causes of death were defined as all-cause mortality. Cardiovascular disease was defined as ischemic cardiovascular events (angina, myocardial infarction, arteriosclerosis obliterans, cerebral hemorrhage, and cerebral infarction), or nonischemic heart disease events (heart failure). In the survival analysis, if a patient experienced both events, the first event took precedence. The observation period was 2 years. In our study, we observed events with a composite endpoint. However, we performed a separate multivariate analysis for all-cause mortality and cardiovascular disease. Angina pectoris and myocardial infarction were diagnosed using coronary angiography and myocardial scintigraphy, while arteriosclerosis obliterans was screened with ankle-brachial index (ABI) and diagnosed by a specialist using lower extremity ultrasound, contrast-enhanced computed tomography (CT), or magnetic resonance imaging (MRI). Cerebral hemorrhage and infarction were diagnosed based on imaging findings, such as CT and MRI.

Complete blood counts and biochemical data, such as serum urea nitrogen, creatinine (Cr), C-reactive protein, albumin, electrolytes, β2-microglobulin, parathyroid hormone (i-PTH) were measured for various test values, and the Geriatric Nutrition Index (GNRI) and dialysis efficiency (Kt/V) were calculated. Blood sampling and Kt/V were measured prior to the first HD of the week, 2 d after the previous dialysis.

Statistical analysis

Data were presented as percentage, mean ± standard deviation, or median (interquartile range), as appropriate. Kaplan–Meier survival curves were used to assess all-cause mortality and cardiovascular events, and Spearman's correlation coefficient was used to determine the relationship between ERI and HGS.

The previously reported cutoff value of ERI (i.e., 9.44) [19] and cutoff value of HGS for low muscle strength as defined in The Asian Working Group for Sarcopenia (AWGS) 2019 (i.e., 28 kg in males and 18 kg in females) were used to investigate the impact of the composite effects of ERI and HGS on all-cause mortality and cardiovascular events. Then, these were combined and stratified into four groups: low ERI/low HGS ($n = 69$), high ERI/low HGS ($n = 34$), low ERI/high HGS ($n = 61$), and high ERI/high HGS ($n = 11$). A Kaplan–Meier survival curve was used to examine the effects on all-cause mortality and cardiovascular events, while differences between groups were compared using the logarithmic rank test; additionally, a univariate Cox regression analysis was performed to compare risks among the four groups. To examine the association between prognosis and groups combining ERI and HGS, a multivariate Cox regression analysis was performed with adjustment for age, dialysis history, body mass index (BMI) (median), sex, and diabetes mellitus (DM). Statistical significance was set at $p < 0.05$. All statistical analyses were performed using the JMP software program version 16 (SAS Institute Inc., Cary, NC).

Results

Characteristics of the study patients according to the baseline

As shown in Figure 1, 175 subjects were included in the analysis. The baseline characteristics of the study population are shown in Table 1. The subjects included 122 (69.7%) males and 53 (30.3%) females, with a mean age and dialysis history of 68.1 ± 11.4 years and 7.7 ± 10.1 years, respectively. The primary diseases were diabetic nephropathy ($n = 79$, 45.1%), nephrosclerosis ($n = 14$, 8.0%), chronic glomerulonephritis (focal glomerulosclerosis [focal segmental glomerular sclerosis], IgA-nephropathy, ANCA-associated nephritis,

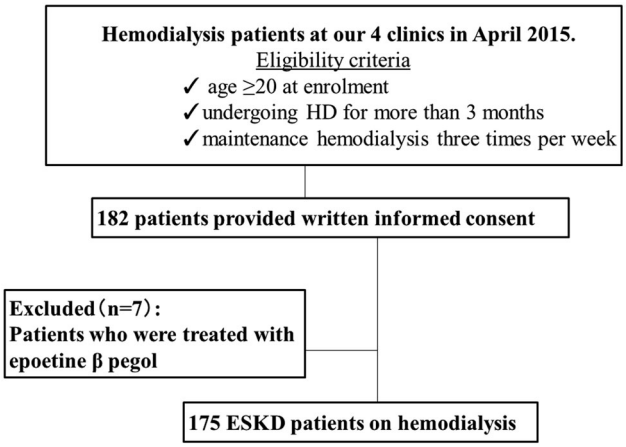

Figure 1. Patient recruitment flow diagram. HD: hemodialysis; ESKD: end-stage kidney disease.

Table 1. Baseline characteristics of patients on hemodialysis.

	All patients ($n = 175$)
Male: Female (*n*)	122/53
Age (years)	68.13 ± 11.40
Duration of dialysis (years)	7.71 ± 10.12
BMI (kg/m^2)	22.12 ± 3.93
BW pre HD (kg)	60.51 ± 13.15
Grip strength (kg)	24.04 ± 7.62
ESA dose (U)	4414.29 ± 4348.21
ERI (ESA dose/kg/g/dL/week)	7.45 ± 7.99
Kt/V	1.48 ± 0.23
GNRI	94.70 ± 5.49
EP[a] *n* (%)	57 (32.57%)
IHD *n* (%)	66 (37.71%)
Cerebrovascular disease *n* (%)	34 (19.43%)
Diabetes *n* (%)	88 (50.29%)
Exercise habits *n* (%)	108 (61.71%)
Blood urea nitrogen (mg/dL)	64.38 ± 14.16
Creatinine (mg/dl)	10.64 ± 2.55
Albumin (g/dl)	3.74 ± 0.28
Uric acid (mg/dl)	6.92 ± 1.58
TG (mg/dl)	109.79 ± 80.98
HDL-Cho (mg/dl)	43.26 ± 13.21
LDL-Cho (mg/dl)	81.70 ± 25.55
CRP (mg/dl)	0.11 (0.05–0.32)
β2MG (mg/dl)	26.31 ± 5.51
CK (IU/L)	97.27 ± 73.83
Phosphorus (mg/dL)	5.34 ± 1.19
Calcium (mg/dL)	8.73 ± 0.69
PTH-intact (pg/mL)	138 (76–196)
Hemoglobin (g/dL)	10.87 ± 0.83
Hematocrit (%)	33.90 ± 2.69
Serum iron (μg/dL)	56.67 ± 21.65
Ferritin (ng/mL)	136.85 ± 123.61
TSAT (%)	23.67 ± 9.47

n: number; ERI: erythropoietin resistance index; HGS: hand grip strength; BMI: body mass index; BW: body weight; HD: hemodialysis; ESA: erythropoiesis-stimulating agents; Kt/V: normalized dialysis dose; GNRI: geriatric nutritional risk index; EP: end point; IHD: ischemic heart disease; TG: triglyceride; HDL-Cho: high-density lipoprotein cholesterol; LDL-Cho: low-density lipoprotein cholesterol; CRP: C-reactive protein; β2MG: beta2-microglobulin; CK: creatine kinase; PTH: parathyroid hormone; TSAT: transferrin saturation.

[a]EP: all-cause death and cardiovascular disease. Data are expressed as the median (interquartile range) or number (percentage).

membranoproliferative glomerulonephritis: $n = 44$, 25.1%), polycystic kidney disease ($n = 8$, 4.6%), unknown ($n = 18$, 10.3%), and others ($n = 12$, 6.9%). The type of ESA was rHuEPO in 93 cases (53.1%) and DA in 61 cases (34.9%). At the time of enrollment, 21 patients (12.0%) were ESA-naive.

Outcomes

During the follow-up period (24 months), all-cause death or cardiovascular events were observed in 57 (32.5%) of the 175 patients undergoing HD. There were 43 cardiovascular events and 14 deaths. Of these, there were 10 deaths from non-cardiovascular causes.

Characteristics of the study patients according to HGS or ERI

The low HGS group was characterized by older age and lack of exercise habits, while the high ERI group was characterized by anemia, iron deficiency, low grip strength, and light weight (Table 2). Table 3 shows the patient characteristics stratified into four groups according to the ERI and HGS cutoff values. The Kruskal–Wallis test and Pearson's test were used to compare the four groups; there were no differences in HD duration, Kt/V, exercise habits, secondary hyperparathyroidism, cerebrovascular disease, DM, or history of angina pectoris.

Association of ERI and HGS with composite endpoints, respectively

ERI and HGS were significantly associated with all-cause mortality or cardiovascular disease, respectively. The high ERI group was at high risk for all-cause mortality or cardiovascular disease (Figure 2(a) Log rank, $p < 0.0001$). Regarding HGS, the low HGS group showed a higher risk of all-cause death or cardiovascular disease (Figure 2(b) Log rank, $p = 0.007$).

Table 2. Characteristics of 175 HD patients (high ERI subcohort and low HGS subcohort).

	Low ERI ($n = 130$)	High ERI ($n = 45$)	*p* Value	Low HGS ($n = 103$)	High HGS ($n = 72$)	*p* Value
Male: Female (*n*)	95/35	27/18	0.09	74/29	48/24	0.46
Age (years)	67.22 ± 11.26	70.78 ± 11.42	0.07	71.60 ± 10.00	63.17 ± 11.47	<0.0001
Duration of dialysis (years)	7.12 ± 6.74	9.41 ± 16.21	0.19	7.95 ± 11.88	7.37 ± 6.82	0.71
BMI (kg/m^2)	22.72 ± 4.04	20.40 ± 3.01	0.0006	21.75 ± 3.80	22.66 ± 4.05	0.13
BW pre HD (kg)	62.80 ± 13.59	53.92 ± 8.98	<0.0001	58.17 ± 11.76	63.87 ± 14.27	0.004
Grip strength (kg)	25.09 ± 7.69	21.02 ± 6.54	0.001	19.92 ± 4.97	29.94 ± 6.84	<0.0001
ESA dose (U)	2476.92 ± 1823.84	10,011.11 ± 4663.68	<0.0001	5288.84 ± 4942.23	3163.19 ± 2890.11	0.001
ERI (ESA dose/kg/g/dL/week)	3.79 ± 2.72	18.04 ± 8.73	<0.0001	9.09 ± 9.14	5.10 ± 5.14	0.001
Kt/V	1.47 ± 0.24	1.50 ± 0.21	0.45	1.47 ± 0.21	1.49 ± 0.26	0.65
GNRI	95.36 ± 5.12	92.80 ± 6.07	0.006	93.65 ± 5.75	96.21 ± 4.71	0.002
EP[a] *n* (%)	32 (22.33)	25 (55.56)	0.0001	42 (40.78)	15 (20.83)	0.005
IHD, *n* (%)	25 (19.23)	10 (22.22)	0.66	23 (22.33)	12 (16.67)	0.35
Cerebrovascular disease, *n* (%)	49 (37.69)	17 (37.78)	0.99	38 (36.89)	28 (38.89)	0.78
Diabetes, *n* (%)	69 (53.98	19 (42.22)	0.20	57 (55.34)	31 (43.06)	0.10
Exercise habits n(%)	81 (62.31)	27 (60)	0.78	55 (53.40)	53 (73.6)	0.006
Blood urea nitrogen(mg/dL)	63.26 ± 13.65	67.64 ± 15.05	0.07	63.75 ± 14.99	65.29 ± 12.81	0.48
Creatinine (mg/dL)	10.81 ± 2.73	10.13 ± 1.85	0.12	10.05 ± 2.18	11.48 ± 2.79	0.0002
Albumin (g/dL)	3.76 ± 0.26	3.71 ± 0.32	0.32	3.69 ± 0.27	3.83 ± 0.26	0.001
Uric acid (mg/dL)	6.84 ± 1.49	7.15 ± 1.81	0.26	6.83 ± 1.66	7.05 ± 1.45	0.36
TG (mg/dL)	116.27 ± 87.83	91.07 ± 52.36	0.07	92.78 ± 50.45	134.13 ± 106.26	0.0008
HDL-Cho (mg/dL)	43.5 ± 12.55	42.56 ± 14.93	0.68	43.94 ± 13.81	42.28 ± 12.22	0.41
LDL-Cho (mg/dL)	81.29 ± 25.66	82.87 ± 25.22	0.72	80.58 ± 24.91	83.29 ± 26.37	0.49
CRP (mg/dL)	0.11 (0.05–0.26)	0.15 (0.05–0.58)	0.01	0.14 (0.05–0.39)	0.09 (0.05–0.26)	0.07
β2MG (mg/dL)	25.83 ± 5.59	27.70 ± 5.01	0.04	26.65 ± 5.72	25.82 ± 5.15	0.32
CK (IU/L)	98.63 ± 68.12	93.33 ± 88.14	0.68	94.05 ± 78.75	101.88 ± 0.49	0.49
Phosphorus (mg/dL)	5.34 ± 1.26	5.37 ± 0.98	0.88	5.16 ± 1.15	5.60 ± 1.20	0.01
Calcium (mg/dL)	8.73 ± 0.69	8.74 ± 0.70	0.97	8.67 ± 0.73	8.83 ± 0.63	0.14
PTH-intact (pg/mL)	140 (76–197.25)	134 (74–188.5)	0.28	131 (72–181)	152.5 (94–209)	0.42
Hemoglobin (g/dL)	10.98 ± 0.80	10.53 ± 0.84	0.001	10.86 ± 0.84	10.88 ± 0.82	0.83
Hematocrit (%)	34.07 ± 2.70	33.39 ± 2.59	0.14	34.02 ± 2.75	33.73 ± 2.59	0.49
Serum iron (μg/dL)	60.27 ± 22.55	46.24 ± 14.41	0.0001	55.72 ± 23.05	58.01 ± 19.39	0.49
Ferritin (ng/mL)	143.93 ± 132.10	116.40 ± 91.88	0.20	142.86 ± 122.94	128.26 ± 124.06	0.44
TSAT (%)	25.21 ± 9.88	19.23 ± 6.31	0.0002	23.66 ± 10.37	23.70 ± 8.01	0.97

n: number; ERI: erythropoietin resistance index; HGS: hand grip strength; BMI: body mass index; BW: body weight; HD: hemodialysis; ESA: erythropoiesis-stimulating agents; Kt/V: normalized dialysis dose; GNRI: geriatric nutritional risk index; EP: end point; IHD: ischemic heart disease; TG: triglyceride; HDL-Cho; high-density lipoprotein cholesterol; LDL-Cho: low-density lipoprotein cholesterol; CRP: C-reactive protein; β2MG: beta2-microglobulin; CK: creatine kinase; PTH: parathyroid hormone; TSAT: transferrin saturation.

[a]EP: all-cause death and cardiovascular disease. Data are expressed as the median (interquartile range) or number (percentage). Statistical significance was estimated with Kruskal–Wallis test.

Table 3. Characteristics of 175 HD patients (comparison of the 4 groups).

	Low ERI/low HGS ($n = 69$)	High ERI/low HGS ($n = 34$)	Low ERI/high HGS ($n = 61$)	High ERI/high HGS ($n = 11$)	p Value
Male: Female (n)	50/19	24/10	45/16	3/8	0.017
Age (years)	70.9 ± 9.69	73.03 ± 10.46	63.05 ± 11.46	63.82 ± 11.46	<0.0001
Duration of dialysis (years)	7.03 ± 6.36	9.81 ± 18.45	7.23 ± 7.15	8.14 ± 4.52	0.59
BMI (kg/m^2)	22.47 ± 3.86	20.29 ± 3.21	23.00 ± 4.20	20.74 ± 2.29	0.005
BW pre HD (kg)	60.57 ± 12.08	53.31 ± 9.35	65.33 ± 14.72	55.8 ± 7.38	0.0001
Grip strength (kg)	20.15 ± 4.92	19.45 ± 5.05	30.68 ± 6.31	25.86 ± 8.09	<0.0001
ESA dose (U)	2721.01 ± 1873.02	10500 ± 5132.08	2200.82 ± 1725.42	8500.00 ± 2132.00	<0.0001
ERI (ESA dose/kg/g/dL/week)	4.21 ± 2.71	19.00 ± 9.58	3.30 ± 2.65	15.09 ± 4.00	<0.0001
Kt/V	1.47 ± 0.21	1.47 ± 0.21	1.47 ± 0.26	1.59 ± 0.18	0.43
GNRI	94.51 ± 5.29	91.91 ± 6.22	96.32 ± 4.73	95.55 ± 4.56	0.002
EP[a] n (%)	19 (27.54)	23 (67.65)	13 (21.31)	2 (18.18)	<0.0001
IHD n (%)	16 (23.19)	7 (20.59)	9 (14.75)	3 (27.27)	0.60
Cerebrovascular disease n (%)	25 (36.23)	13 (38.24)	24 (39.34)	4 (36.36)	0.98
Diabetes n (%)	40 (57.97)	17 (50.0)	29 (47.54)	2 (18.18)	0.09
Exercise habits n (%)	36 (52.17)	19 (55.88)	45 (73.77)	8 (72.73)	0.058
Blood urea nitrogen (mg/dL)	62.27 ± 14.56	66.76 ± 15.40	64.37 ± 12.45	70.35 ± 13.56	0.21
Creatinine (mg/dL)	10.15 ± 2.37	9.83 ± 1.71	11.56 ± 2.91	11.04 ± 1.95	0.002
Albumin (g/dL)	3.70 ± 0.26	3.67 ± 0.30	3.82 ± 0.24	3.84 ± 0.34	0.01
Uric acid (mg/dL)	6.69 ± 1.52	7.11 ± 1.90	7.01 ± 1.44	7.25 ± 1.49	0.45
TG (mg/dL)	95.16 ± 50.94	87.94 ± 49.08	140.15 ± 111.50	100.73 ± 60.37	0.003
HDL-Cho (mg/dL)	44.88 ± 12.78	42.03 ± 15.52	41.93 ± 12.09	44.18 ± 12.78	0.57
LDL-Cho (mg/dL)	78.64 ± 24.48	84.53 ± 25.30	84.30 ± 26.61	77.73 ± 24.26	0.51
CRP (mg/dL)	0.13 (0.05–0.25)	0.16 (0.06–0.69)	0.09 (0.05–0.3)	0.05 (0.05–0.26)	0.01
β2MG (mg/dL)	26.32 ± 6.00	27.33 ± 5.04	25.27 ± 5.02	28.85 ± 4.74	0.12
CK (IU/L)	91.74 ± 66.59	98.74 ± 98.77	106.43 ± 68.98	76.64 ± 35.49	0.53
Phosphorus (mg/dL)	5.16 ± 1.24	5.17 ± 0.97	5.54 ± 1.26	5.98 ± 0.74	0.06
Calcium (mg/dl)	8.70 ± 0.73	8.60 ± 0.70	8.76 ± 0.64	9.15 ± 0.48	0.14
PTH-intact (pg/mL)	131(71–182)	132 (70.25–184.75)	152 (93.5–207)	153 (103–241)	0.60
Hemoglobin (g/dL)	10.97 ± 0.80	10.64 ± 0.87	11.00 ± 0.79	10.20 ± 0.65	0.006
Hematocrit (%)	34.14 ± 2.74	33.76 ± 2.73	34.00 ± 2.64	32.35 ± 1.64	0.18
Serum iron (μg/dL)	60.81 ± 25.18	45.38 ± 12.79	59.66 ± 19.12	48.91 ± 18.31	0.002
Ferritin (ng/mL)	158.12 ± 131.46	111.89 ± 96.33	127.88 ± 130.99	130.36 ± 74.78	0.29
TSAT (%)	26.01 ± 11.21	18.88 ± 6.05	24.31 ± 8.04	20.30 ± 6.94	0.001

n: number; ERI: erythropoietin resistance index; HGS: hand grip strength; BMI: body mass index; BW: body weight; HD: hemodialysis; ESA: erythropoiesis-stimulating agents; Kt/V: normalized dialysis dose; GNRI: geriatric nutritional risk index; EP: end point; IHD: ischemic heart disease; TG: triglyceride; HDL-Cho: high-density lipoprotein cholesterol; LDL-Cho: low-density lipoprotein cholesterol; CRP: C-reactive protein; β2MG: beta2-microglobulin; CK: creatine kinase; PTH: parathyroid hormone; TSAT: transferrin saturation.

[a]EP: all-cause death and cardiovascular disease. Data are expressed as the median (interquartile range) or number (percentage). Statistical significance was estimated with Kruskal–Wallis test.

Next, we assessed whether there was an association between ERI and HGS. ERI and HGS showed a negative correlation (Spearman's rank correlation coefficient: $rs = -0.28$; $p = 0.0002$) (Figure 3).

Association between the level of ERI, HGS, and mortality/cardiovascular disease

The evaluation of the Kaplan-Meier survival curve demonstrated that, among the four groups, the high ERI/low HGS group showed significantly higher rates of death and cardiovascular disease (Figure 4(a) Log rank, $p < 0.0001$); this group tended to be older and had a higher dose of ESA, lower BMI and lower GNRI, while blood sampling data indicated low levels of Cr, albumin, triglycerides, serum iron, and TSAT (Fe/TIBC). The Kaplan-Meier survival curve, which separated outcomes into death and CVD events, similarly showed that the high ERI/low HGS group was at highest risk (Figure 4(b) Log rank, $p = 0.006$, Figure 4(c) Log rank, $p = 0.0002$). A subsequent univariate analysis using the low ERI/high HGS group as a reference revealed that among the four groups, the high ERI/low HGS group was at the highest risk for all-cause death or cardiovascular disease (HR: 4.2, 95% CI: 2.13–6.20). The single effect of EPO responsiveness or HGS on all-cause death or cardiovascular disease was milder than the composite effect (Table 4).

Multivariate analysis

Finally, multivariate analysis demonstrated that older age (HR: 1.79, 95% CI: 1.01–3.15), DM (HR: 1.64, 95% CI: 0.94–2.84), and the high ERI/low HGS group (HR: 3.52, 95% CI 2.00–6.20) were associated with the risk of all-cause mortality or cardiovascular disease (Table 4). After adjusting for age, diabetes, HD history, BMI, and sex, the high ERI/low HGS group remained a high-risk group for all-cause death or cardiovascular disease. We also

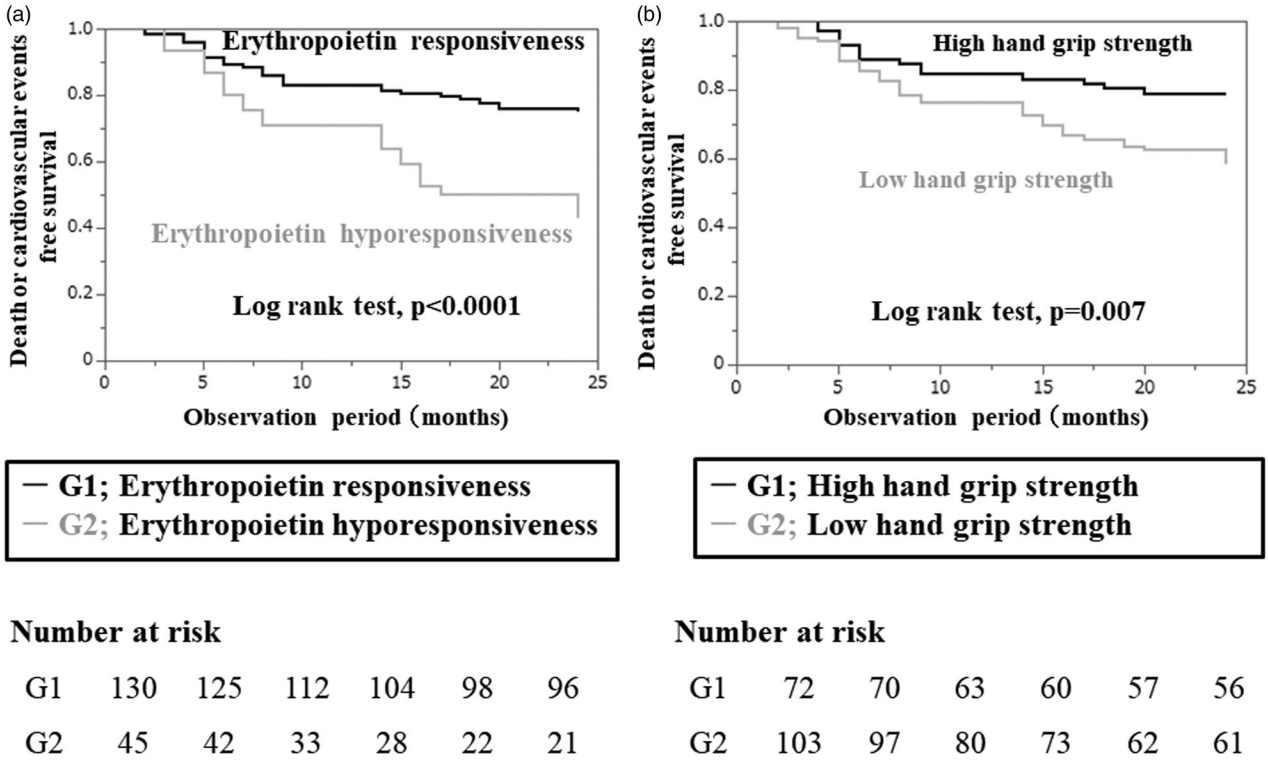

Figure 2. Effect of erythropoietin responsiveness and hand grip strength on death or cardiovascular events in HD patients. 2a. The Kaplan–Meier curves for erythropoietin responsiveness to death or cardiovascular events in HD patients. ESA hyporesponsive patients compared to ESA responsive patients, log-rank p value < 0.0001. 2b. Kaplan–Meier curves of HGS for death or cardiovascular events in HD patients. Low HGS patients compared to high HGS patients, log-rank p value $= 0.007$. HD: hemodialysis; ESA: erythropoiesis-stimulating agents; HGS: hand grip strength.

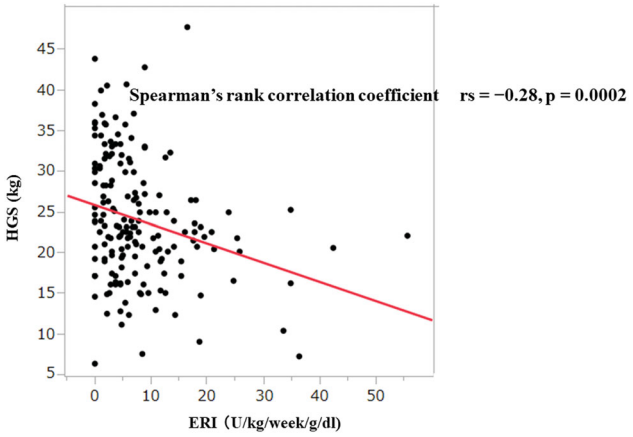

Figure 3. ERI is negatively correlated with HGS. The Y-axis shows the strength of HGS (kg) and the X-axis shows the ERI. Individual patients are shown as dots. ERI: erythropoietin resistance index; HGS: hand grip strength.

performed an additional analysis with the endpoints separated by all-cause mortality and cardiovascular events and found that high ERI/low HGS was a strong risk, as was the composite endpoint (all-cause mortality or cardiovascular disease) (Table 5). The high ERI/low HGS group was associated with the risk of cardiovascular disease (HR: 3.02, 95% CI: 1.55–5.86) and all-cause mortality (HR: 5.51, 95% CI: 1.71–17.78), respectively.

Discussion

ESA hyporesponsiveness, which is caused by iron deficiency, inflammation, dialysis efficiency, nutritional status, hyperparathyroidism, and other conditions, has been reported to be associated with a poor long-term prognosis in dialysis patients [6,19,20]. Three main mechanisms have previously been proposed regarding the use of ESA and the risk of cardiovascular events [8]; increasing blood volume or viscosity as a result of elevation of Hb by ESA therapy, advanced pathology associated with tolerance to ESA and unrelated to ESA pharmacology, or direct toxicity due to ESA, especially at supraphysiological doses. The latter two mechanisms could explain the poor prognosis of subjects in an ESA hyperresponsive state.

Underlying advanced illness in subjects hyporesponsive to ESA has previously been reported [8,19,20], including generalized illness, androgen deficiency, infection and inflammation, increased cytokine signaling, nutritional deficiencies, secondary hyperparathyroidism, malignancy, bone marrow disorders, vitamin

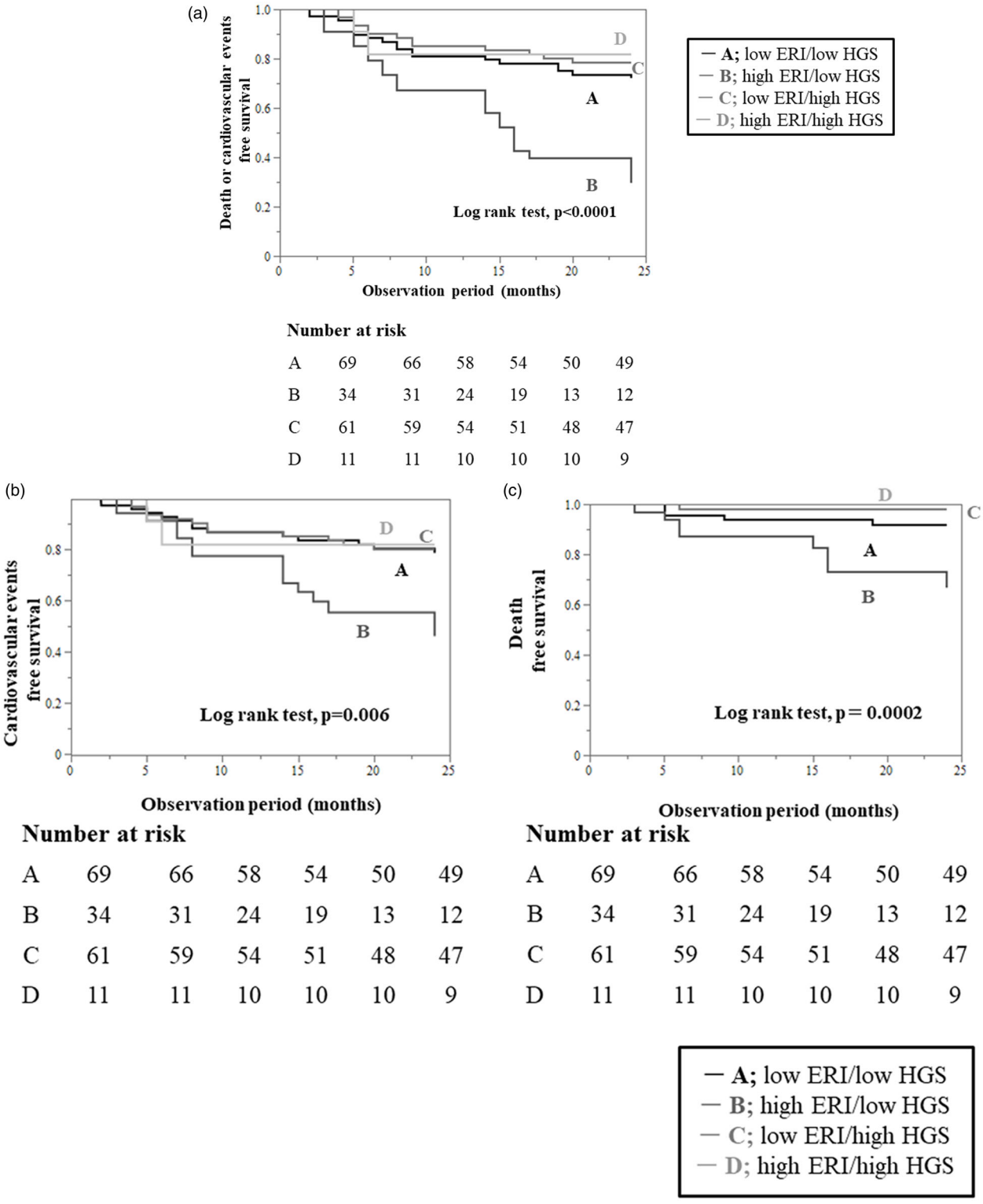

Figure 4. Composite effect on death or cardiovascular events. A; low ERI/low HGS, B; high ERI/low HGS, C; low ERI/high HGS, D; high ERI/high HGS. 4a. Kaplan–Meier curves for ESA responsiveness and HGS to death or cardiovascular events in HD patients. 4b. Kaplan–Meier curves for ESA responsiveness and HGS to cardiovascular events in HD patients. 4c. Kaplan–Meier curves for ESA responsiveness and HGS to death in HD patients. ERI: erythropoietin resistance index; HGS: hand grip strength; ESA: erythropoiesis-stimulating agents; HD: hemodialysis.

B12 and folate deficiencies, inadequate dialysis, and acquired defects in iron transport [21,22]. In our data, iron deficiency, and undernutrition were observed in ESA-hyporesponsive patients with a poor prognosis. As previously reported, a decrease in the ESA response is an appropriate marker of the severity of the

Table 4. Univariate analysis of the four groups and mortality and cardiovascular disease risk based on Cox proportional hazards analyses.

	End point; composite endpoint (all-cause death and cardiovascular disease)					
	Non-adjusted			Adjusted		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Group high ERI/low HGS *vs.* others[a]	3.63	(2.13–6.20)	<0.0001	3.52	(2.00–6.20)	<0.0001
High ERI/low HGS *vs.* Ref[b]	4.2	(2.12–8.33)	<0.0001	–	–	–
High ERI/high HGS *vs.* Ref[b]	0.86	(0.19–3.81)	0.84	–	–	–
Low ERI/low HGS *vs.* Ref[b]	1.34	(0.66–2.73)	0.40	–	–	–
Low ERI/high HGS (Ref. Group)	1	NA	NA	–	–	–
Age (years) (>median)	1.79	(1.06–3.11)	0.03	1.79	(1.01–3.15)	0.04
Duration of HD (years) (>median)	1.19	(0.71–2.03)	0.49	1.28	(0.73–2.23)	0.37
BMI (kg/m^2) (>median)	0.91	(0.53–1.53)	0.73	1.22	(0.69–2.17)	0.47
Female *vs.* male	1.28	(0.73–2.19)	0.37	1.4	(0.80–2.56)	0.22
Diabetes	1.52	(0.90–2.62)	0.11	1.64	(0.94–2.84)	0.07

ERI: erythropoietin resistance index; HGS: hand grip strength; HR: Hazard ratio; CI: confidence interval; NA: not assessed; HD: hemodialysis; BMI: body mass index.
[a]Others are low ERI/lowHGS, high ERI/lowHGS, lowERI/highHGS, and high ERI/highHGS. And they are reference.
[b]Using the low ERI/high HGS group as a reference. Effects of ERI and HGS on composite endpoint (all-cause death and cardiovascular disease). Cox proportional hazards analyses (univariate analysis) were performed to examine associations among the 4 groups. Univariate and multivariate analysis of risk factors associated with composite endpoint.

Table 5. Cardiovascular disease risk based on Cox proportional hazards analyses, and mortality risk based on Cox proportional hazards analyses.

	(End point: cardiovascular disease)						(End point: mortality)					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Group high ERI/low HGS *vs.* others[a]	2.89	(1.53–5.43)	0.001	3.02	(1.55–5.86)	0.001	7.09	(2.44–20.61)	0.0003	5.51	(1.71–17.78)	0.004
Age (years) (>median)	1.56	(0.85 –2.87)	0.14	1.74	(0.92–3.29)	0.08	2.83	(0.88–9.04)	0.07	1.63	(0.46–5.72)	0.44
Duration of HD (years) (>median)	1.15	(0.63–2.10)	0.63	1.10	(0.57–2.09)	0.76	1.34	(0.46–3.86)	0.58	1.78	(0.60–5.31)	0.29
BMI (kg/m^2) (>median)	1.16	(0.63–2.11)	0.03	2.20	(1.15–4.21)	0.22	0.40	(0.12–1.30)	0.13	0.64	(0.18–2.31)	0.50
Female *vs.* male	1.88	(1.03–3.44)	0.03	2.20	(1.15–4.21)	0.01	0.18	(0.02–1.39)	0.10	0.17	(0.02–1.39)	0.10
Diabetes	1.58	(0.86–2.92)	0.13	1.69	(0.89–3.19)	0.10	1.36	(0.47–3.94)	0.56	1.23	(0.41–3.70)	0.70

ERI: erythropoietin resistance index; HGS: hand grip strength; HR: Hazard ratio; CI: confidence interval; HD: hemodialysis; BMI: body mass index.
[a]Others are low ERI/lowHGS, high ERI/lowHGS, lowERI/highHGS, and high ERI/highHGS. And they are reference.

pathological condition [4], and corresponds to the results of a cohort study that included dialysis patients in Italy [7]. On the other hand, the importance of the direct toxicity of ESA for cardiovascular risk was repeatedly raised in previous reports [8,23–25], such as the CHIOR study: patients with high-dose ESAs, regardless of Hb level, exhibited a higher cardiovascular risk than patients with high Hb and low exposure to ESAs. Taking these reports into account, high doses of ESA in hyporesponsive patients could be an important cause of poor prognosis in our study population.

Muscle atrophy appears due to decreased oxygenated blood flow to the periphery and oxygen supply to the muscles in patients with anemia [13], suggesting a relationship between anemia and muscle weakness. On the contrary, exercise increased the expression of EPO in skeletal muscle, as well as the release of EPO into the circulation; exercise and skeletal muscle are thought to increase erythropoiesis and promote hematopoiesis [26]. Exercise can increase the survival of bone marrow transplant recipients, and suggest the potential clinical importance of exercise for the hematopoietic system [27]. Several studies have reported the effects of exercise therapy on anemia as well as the relationship between anemia and muscle weakness [26–28]. Treatment of anemia is an important factor in improving frailty in healthy people [13], and resistance training for muscle strength was reported to improve HGS and Hb levels in patients undergoing HD [28].

ESA hyporesponsiveness and low grip strength are related to each other, have an additive impact on the poor prognosis in patients with HD, and are independent of various other risk factors, including old age, and DM. The key to improving this interrelated condition may be the effects of exercise therapy on improved anemia [26–28]. The guidelines for renal rehabilitation, published by the Japanese Society of Renal Rehabilitation in 2018 note that exercise therapy is reported to be effective for improving exercise tolerance, QoL, dialysis efficiency, and ADL, preventing and

improving protein-energy wasting, inhibiting protein catabolism, and preventing cardiovascular disease [15]. To avoid the risk of CVD in patients receiving high-dose ESA treatment [25], improvement of anemia by exercise treatment [26,28] might be useful.

There have been no reports on the degree of improvement in muscle strength and responsiveness to EPO treatment through rehabilitation intervention during dialysis. Whether training that raises HGS or improves ESA responsiveness will change the prognosis is a topic for future research.

This study was associated with several limitations. First, clinical practice for renal anemia differs between Japan and Western countries, including background factors in CKD patients. The ESA dose and Hb level are generally lower in Japan than in other countries; data and results may not be representative of HD patients in other countries. Second, there is no clear unified definition of ESA hyporesponsiveness. The guidelines proposed by the Japanese Society for Dialysis Therapy [17] differ from those of Kidney Disease: Improving Global Outcomes guidelines [29]. Third, mortality includes more than just cardiovascular, and various causes of death may be related to ERI and HGS. Finally, there were differences in the number of cases among the four groups, making intergroup comparisons difficult.

Despite the limitations mentioned above, the synergistic relationship of ESA response and low HGS with a poor prognostic outcome in HD patients should be widely investigated in the future because HD patients are aging and becoming vulnerable.

Conclusion

ESA hyporesponsiveness and low HGS are predictors of poor prognostic outcomes, and their combined effect shows a stronger predictive ability. As a future research theme, we are examining whether an increase in HGS leads to an improvement in ERI.

Acknowledgments

The authors thank all the patients who participated in this study. The authors also thank Yui Izumi, Nao Okumura, and Yukiko Uchiyama for measuring the physical performance of the patients. The authors thank Brian Quinn, Japan Medical Communication (www.japan-mc.co.jp) for editing the English language of this manuscript.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki. Study approval statement: This study protocol was reviewed and approved by the Clinical Research, Ethics Committee of the Institutional Ethics Committee at Medical Tokyo, Japan, approval number 2014-7. Consent to participate statement: All participants provided their written informed consent.

Author contributions

Shizuka Kobayashi (SK) designed the study and wrote the first draft of the article. All authors commented on previous versions of the article. Analysis was performed by SK. Kentaro Tanaka (KT) and Akifumi Kushiyama (AK) contributed to the selection of objects, the collection and analysis of data, and the preparation of articles. Junichi Hoshino (JH) contributed to the interpretation of data and revised the manuscript for key intellectual content. All Authors read and approved the final article.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by Okinaka Memorial Institute for Medical Research.

Data availability statement

Datasets generated and/or analyzed during this study are not publicly available because they are part of the medical records of the patients involved. However, they are available from the corresponding author upon reasonable request.

References

[1] Collins AJ, Kasiske B, Herzog C, United States Renal Data System, et al. Excerpts from the United States renal data system 2004 annual data report: atlas of end-stage renal disease in the United States. Am J Kidney Dis. 2005;45(1):A5–280.

[2] Chirakarnjanakorn S, Navaneethan SD, Francis GS, et al. Cardiovascular impact in patients undergoing maintenance hemodialysis: clinical management considerations. Int J Cardiol. 2017;232:12–23.

[3] Kataoka H, Tsuchiya K, Naganuma T, et al. Relationship between anaemia management at haemodialysis initiation and patient prognosis. Nephrol. 2015;20(4):14–21.

[4] Okazaki M, Komatsu M, Kawaguchi H, et al. Erythropoietin resistance index and the all-cause mortality of chronic hemodialysis patients. Blood Purif. 2014;37(2):106–112.

[5] Hara A, Koshino Y, Kurokawa Y, et al. Relationship between anti-erythropoietin receptor autoantibodies and responsiveness to erythropoiesis-stimulating agents in patients on hemodialysis: a multi-center cross-sectional study. Clin Exp Nephrol. 2020;24(1):88–95.

[6] Ogawa T, Shimizu H, Kyono A, et al. Relationship between responsiveness to erythropoiesis-stimulating agent and long-term outcomes in chronic hemodialysis patients: a single-center cohort study. Int Urol Nephrol. 2014;46(1):151–159.
[7] Panichi V, Rosati A, Bigazzi R, et al. Anaemia and resistance to erythropoiesis-stimulating agents as prognostic factors in haemodialysis patients: results from the RISCAVID study. Nephrol. Dial. Transplant. 2011;26(8):2641–2648.
[8] McCullough PA, Barnhart HX, Inrig JK, et al. Cardiovascular toxicity of epoetin-alfa in patients with chronic kidney disease. Am J Nephrol. 2013;37(6):549–558.
[9] Gi YM, Jung B, Kim KW, et al. Low handgrip strength is closely associated with anemia among adults: a cross-sectional study using Korea national health and nutrition examination survey (KNHANES). PLoS One. 2020;15(3):e0218058.
[10] Vogt BP, Borges MCC, Goés CR, et al. Handgrip strength is an independent predictor of all-cause mortality in maintenance dialysis patients. Clin Nutr. 2016;35(6):1429–1433.
[11] Leong DP, Teo KK, Rangarajan S, et al. Prognostic value of grip strength: findings from the prospective urban rural epidemiology (PURE) study. Lancet. 2015;386(9990):266–273.
[12] Chen LK, Woo J, Assantachai P, et al. Asian working group for sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. J Am Med Direct Assoc. 2020;21(3):300–307.
[13] Ishikawa A, Higuchi K. M abo. Effects of anemia and hypoproteinemia on functional ability in patients receiving hemodialysis who have complications. Tokyo Jikeikai Ika Daigaku Zasshi. 2008;123:231–235.
[14] Heiwe S, Jacobson SH. Exercise training in adults with CKD: a systematic review and Meta-analysis. Am J Kidney Dis. 2014;64(3):383–393.
[15] Yamagata K, Hoshino J, Sugiyama H, et al. Clinical practice guideline for renal rehabilitation: systematic reviews and recommendations of exercise therapies in patients with kidney diseases. Ren Replace Ther. 2019;5:28.
[16] Johansen KL, Finkelstein FO, Dennis DA, et al. Systematic review of the impact of erythropoiesis-stimulating agents on fatigue in dialysis patients. Nephrol Dial Transplant. 2012;27:2418–2425.
[17] Yamamoto H, Nishi S, Tomo T, et al. Japanese society for dialysis therapy: guidelines for renal anemia in chronic kidney disease. Ren Replace Ther. 2015;3:36.
[18] Bae MN, Kim SH, Kim YO, et al. Association of erythropoietin-stimulating agent responsiveness with mortality in hemodialysis and peritoneal dialysis patients. PLoS One. 2015;10(11):e0143348.
[19] Eriguchi R, Taniguchi M, Ninomiya T, et al. Hyporesponsiveness to erythropoiesis-stimulating agent as a prognostic factor in Japanese hemodialysis patients: the Q-Cohort study. J Nephrol. 2015;28(2):217–225.
[20] Singh AK, Himmelfarb J, Szczech LA, et al. Resolved: targeting a higher hemoglobin is associated with greater risk in patients with CKD anemia. J Am Soc Nephrol. 2009;20(7):1436–1443.
[21] Gaweda AE, Goldsmith LJ, Brier ME, et al. Iron, inflammation, dialysis adequacy, nutritional status, and hyperparathyroidism modify erythropoietic response. Clin J Am Soc Nephrol. 2010;5(4):576–581.
[22] Smrzova J, Balla J, Bárány P. Inflammation and resistance to erythropoiesis-stimulating agents–what do we know and what needs to be clarified? Nephrol Dial Transplant. 2005;208(8):viii2–7.
[23] Besarab A, Bolton WK, Browne JK, et al. 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. 1998;339(9):584–590.
[24] Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006;355(20):2085–2098.
[25] Szczech LA, Barnhart HX, Inrig JK, et al. Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved hemoglobin outcomes. Kidney Int. 2008;74(6):791–798.
[26] Baker JM, Parise G. Skeletal muscle erythropoietin expression is responsive to hypoxia and exercise. Med Sci Sports Exerc. 2016;48(7):1294–1301.
[27] De Lisio M, Baker JM, Parise G. Exercise promotes bone marrow cell survival and recipient reconstitution post-bone marrow transplantation, which is associated with increased survival. Exp Hematol. 2013;41(2):143–154.
[28] da Silva V, Corrêa H, Neves R, et al. Impact of low hemoglobin on body composition, strength, and redox status of older hemodialysis patients following resistance training. Front Physiol. 2021;12:619054.
[29] KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney International Supplements. 2012;2:279–335.