ORIGINAL RESEARCH

Association of Anemia and Iron Parameters With Mortality Among Patients Undergoing Prevalent Hemodialysis in Taiwan: The AIM-HD Study

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***Background*—**The Taiwan Health Insurance Bureau has conducted a bundled payment system for hemodialysis reimbursement since 1995. The maximum dose of erythropoiesis-stimulating agents allowed by insurance is capped at 20 000 U of epoetin or 100 μg of darbepoetin alfa per month. Nephrologists have avoided the use of high dosages of erythropoiesis-stimulating agents to achieve a hemoglobin level of 10 to 11 g/dL by iron supplementation. The clinical impact of these policies on patients' outcomes is unknown. The authors aimed to assess the AIM-HD (Association of Anemia, Iron parameters, and Mortality among the prevalent Hemodialysis patients) Study in Taiwan.

***Methods and Results*—**The AIM-HD study was conducted based on the Taiwan Renal Registry Data System. From 2001 to 2008, the authors enrolled 42 230 patients undergoing hemodialysis who were older than 20 years and had received hemodialysis for more than 12 months. Patient follow-ups occurred until death or December 31, 2008. During a study period of 8 years, 12 653 (30.0%) patients died. After multivariate adjustment, the authors found that a hemoglobin level <10 g/dL was significantly associated with higher risk for all-cause and cardiovascular deaths. Moreover, a serum ferritin level between 300 and 800 ng/mL and transferrin saturation value between 30% and 50% were associated with the lowest all-cause mortality.

***Conclusions*—**The authors recommend avoiding a low hemoglobin level and maintaining serum ferritin between 300 and 800 ng/mL and transferrin saturation between 30% and 50%, which were associated with lower risks of all-cause mortality among patients undergoing hemodialysis receiving the restricted erythropoiesis-stimulating agent doses but prompt intravenous iron supplementation in Taiwan. **(*J Am Heart Assoc*. 2018;7:e009206. DOI: 10.1161/JAHA.118.009206.)**

Key Words: anemia • erythropoietin • hemodialysis • hemoglobin • iron

Anemia is frequently encountered in chronic kidney disease (CKD) and is associated with cardiovascular outcomes in patients with CKD.[1] Correcting anemia usually requires erythropoiesis-stimulating agents (ESAs). However, the use of ESAs to normalize hemoglobin levels has repeatedly been shown to be associated with an increased risk of

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Accompanying Tables S1 through S6 and Figures S1 through S3 are available at http://jaha.ahajournals.org/content/7/15/e009206/DC1/embed/inline-supplementary-material-1.pdf

*A complete list of the Taiwan Society of Nephrology Renal Registry Data System members can be found in the Appendix at the end of the article.

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Clinical Perspective

What Is New?

- A bundled payment system for hemodialysis was first developed by Taiwan in 1995. This study investigates the optimal hemoglobin, serum ferritin, and transferrin saturation levels on mortality in patients undergoing hemodialysis after the implementation of a bundled payment system in Taiwan.
- Remarkably, a hemoglobin level <10 g/dL was significantly associated with higher risk for all-cause and cardiovascular deaths. Moreover, serum ferritin levels between 300 and 800 ng/mL and transferrin saturation values between 30% and 50% were associated with the lowest all-cause mortality.

What Are the Clinical Implications?

- In view of economic concerns, restricted dosages for erythropoiesis-stimulating agents were prescribed to achieve a hemoglobin level >10 g/dL, with the aid of prompt iron supplementation in Taiwan.
- Study of optimal serum ferritin and transferrin saturation levels will provide important information to improve future anemia management and iron supplementation for patients undergoing hemodialysis.

cardiovascular events and death.[2–5] The use of iron with ESAs is prerequisite for optimal management of anemia in patients with CKD.[6] Intravenous (IV) iron therapy reduces ESA requirements and increases hemoglobin levels.[7]

Taiwan is the first country in the world to develop a bundled payment system for hemodialysis because of economic concerns.[8] The strategy for the management of anemia in patients with CKD is different from that in many other parts of the world. In 1996, the National Health Insurance Administration of Taiwan applied more restrictive reimbursement criteria for ESA use in patients with stage 5 CKD. According to the criteria, ESAs are to be initiated when nondialysis patients with CKD have a serum creatinine level >6 mg/dL and a hematocrit level <28% to maintain a hematocrit level not exceeding 30%. The maximum dose allowed by insurance is capped at 20 000 U of epoetin-α or β and 100 μg of darbepoetin alfa or methoxy polyethylene glycol-epoetin beta per month. The target hemoglobin range and dose limitation for ESAs are the same for patients undergoing dialysis. Moreover, IV iron supplementation was encouraged earlier in Taiwan in 1996 when nephrology experts reached a consensus regarding the diagnostic criteria for iron deficiency (serum ferritin <300 ng/mL and/or transferrin saturation [TSAT] <30%). Thereafter, nephrologists in Taiwan avoided the use of disproportionately high doses of ESAs to achieve a hemoglobin level of 10 to 11 g/dL by iron supplementation.[8] The clinical impact of these policies is unknown. Using data from the TWRDS (Taiwan Renal Registry Data System),[9] we aimed to assess the association of anemia and iron parameters with mortality among patients with prevalent hemodialysis in Taiwan. In the AIM-HD (Anemia and Iron Parameters With Mortality Among the Prevalent Hemodialysis Patients) study, the authors assessed the effects of optimal hemoglobin, serum ferritin, and TSAT values on mortality in patients undergoing hemodialysis after bundled payment systems were implemented in Taiwan.

Methods

Data Source

The data and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure because access to these data is contractually controlled by the Taiwan Society of Nephrology and Taiwan National Health Research Institutes. Only analytic methods are available on request. A request for the analytic methods should be sent to the corresponding author.

The TWRDS integrated the records of all patients with end-stage renal disease requiring chronic hemodialysis from hospitals and dialysis clinics in Taiwan.[9,10] The TWRDS database includes demographic, disease-associated conditions, initial dialysis date, dialysis type, residual renal function, and laboratory data of each patient undergoing dialysis in Taiwan. Annual reports of dialysis facilities, including dialysis dosages, treatment quality, laboratory data, and clinical outcomes, were collected. The percentage of reports received from dialysis centers each year has been 100% since 1997.[9,10]

Design and Study Participants

We conducted a cohort study based on the TWRDS and identified all patients with incident end-stage renal disease in Taiwan from January 1, 2001, to June 30, 2008. The cohort was described in our previous study.[11] Patients treated by peritoneal dialysis, recipients of kidney transplantation, those with incomplete biochemistry data, and those younger than 20 years at dialysis initiation were excluded. All enrolled patients were divided into subgroups according to the time-averaged hemoglobin, serum ferritin, and TSAT values, respectively, and were followed up until death or December 31, 2008, whichever came first. Mortality records were retrieved from the Taiwan Death Registry at the Taiwan Ministry of Health and Welfare. The outcomes included all-cause mortality, cardiovascular mortality, and mortality caused by ischemic stroke and infection. The institutional review board of Taipei Veterans General Hospital approved the study protocol. The AIM-HD study was performed in

accordance with the approved protocol and the Declaration of Helsinki. Informed consent was waived as a result of the deidentification of any personal information in this database.

Statistical Analysis

All values are expressed as means and SDs unless otherwise specified. The patients' characteristics were compared by ANOVA or chi-square tests. In a multivariable Cox regression model, the effects of hemoglobin, ferritin, and TSAT values were adjusted for age, sex, diabetes mellitus, hypertension, dialysis adequacy, residual renal function by estimated glomerular filtration rate at the start of dialysis, white blood cell counts, normalized protein catabolic rate, serum albumin, cholesterol, triglyceride, calcium, phosphate, alkaline phosphatase, intact parathyroid hormone, uric acid, ESA dose, and IV iron use. The results are expressed as Kaplan–Meier plots or as hazard ratios (HRs) and 95% confidence intervals (CIs). For the incomplete cases in this study, we used the expectation-maximization algorithm to impute and to replace each missing value. The restricted cubic spline curves used to examine nonlinear associations of hemoglobin, ferritin, and TSAT values with all-cause mortality for fitness, adjusted for the aforementioned confounding variables, further characterized the nature of the relationships between hemoglobin, ferritin, and TSAT values with all-cause mortality. Five knots were chosen because this number produced a curve that appeared adequately smooth. Plots of the restricted splines were constructed using STATA version 15 (StataCorp). All *P* values were 2-sided, and the significance level was set at 0.05. All analyses, except for special circumstances, were performed using commercially available software (SAS version 9.4, SAS Institute Inc.).

Results

Patient Characteristics

Figure 1 shows the flowchart of patient selection from the TWRDS during 2001 to 2008. Ultimately, 42 230 stable patients undergoing hemodialysis were enrolled for analysis. All patients were divided into 5 groups according to hemoglobin level (<9, 9–9.9, 10–10.9, 11–11.9, and ≥12 g/dL) (Table 1), 4 groups according to ferritin level (<300, 300–499, 500–799, and ≥800 ng/mL) (Table 2), and 5 groups according to TSAT value (<20, 20–29, 30–49, 50–69, and ≥70%) (Table 3). The data revealed statistically significant differences among the groups in all measured parameters (Tables 1 through 3). In Table 1, compared with patients with a hemoglobin level >10 g/dL, the patients undergoing hemodialysis with a hemoglobin level <10 g/dL were older and predominantly women and had higher serum ferritin and mean ESA administered doses but lower serum albumin and IV iron administration rates. In addition, in Table 2, compared with patients with a ferritin level <800 ng/dL, the patients undergoing hemodialysis with a ferritin level ≥800 ng/dL were older and predominantly women and had higher mean ESA administered doses but lower serum albumin and IV iron administration rates. Finally, in Table 3, compared with patients with a TSAT value of 30% to 50%, the patients undergoing hemodialysis with TSAT values <20% and ≥70% were predominantly women and had higher hypoalbuminemia and dialysis inadequacy rates. Especially, the patients with a TSAT value >50% were older and had lower serum albumin but higher serum ferritin and mean ESA administered doses.

Associations of Hemoglobin With Mortality in Patients Undergoing Hemodialysis

During a median follow-up of 41 months (a maximum follow-up of 95 months), 12 653 (30.0%) patients died. Figure 2 shows the crude HRs and adjusted HRs (aHRs) for mortality according to different hemoglobin categories in these patients. The results showed that patients with a hemoglobin level <10 g/dL had increased risk of all-cause, cardiovascular, ischemic stroke, and infection-related mortality. A hemoglobin level >11 g/dL was associated with lower risk for all-cause and cardiovascular mortality but not ischemic stroke or infection-related mortality. In a multivariate Cox proportional hazard model, the aHRs were 1.78 (95% CI, 1.66–1.89) for all-cause mortality, 1.68 (95% CI, 1.55–1.82) for cardiovascular mortality, 2.24 (95% CI, 1.40–3.59) for ischemic stroke mortality, and 1.67 (95% CI, 1.15–2.42) for infection-related mortality in patients with a hemoglobin level <9 mg/dL (Table 4). In contrast, the aHRs were 0.82 (95% CI, 0.76–0.90) for all-cause mortality and 0.86 (95% CI, 0.78–0.95) for cardiovascular mortality in patients with a hemoglobin level of 11 to 12 g/dL and consistent in those with a hemoglobin level >12 g/dL (Table 4). Moreover, the results were similar in all ESA-treated patients undergoing hemodialysis (Table S1).

Associations of Iron Parameters With Mortality in Patients Undergoing Hemodialysis

The associations between different ferritin categories and mortality were also evaluated, as shown in Figure 3 and Table 4. In a multivariate Cox proportional hazard model, the aHRs were 1.13 (95% CI, 1.06–1.20) for all-cause mortality and 1.16 (95% CI, 1.07–1.25) for cardiovascular mortality in patients with a serum ferritin level <300 ng/mL but not for ischemic stroke mortality (1.04; 95% CI: 0.66–1.63) and infection-related mortality (1.16; 95% CI, 0.81–1.68) (Table 4). On the other hand, the aHRs for all-cause mortality (1.08; 95% CI, 1.01–1.15) and infection-related mortality

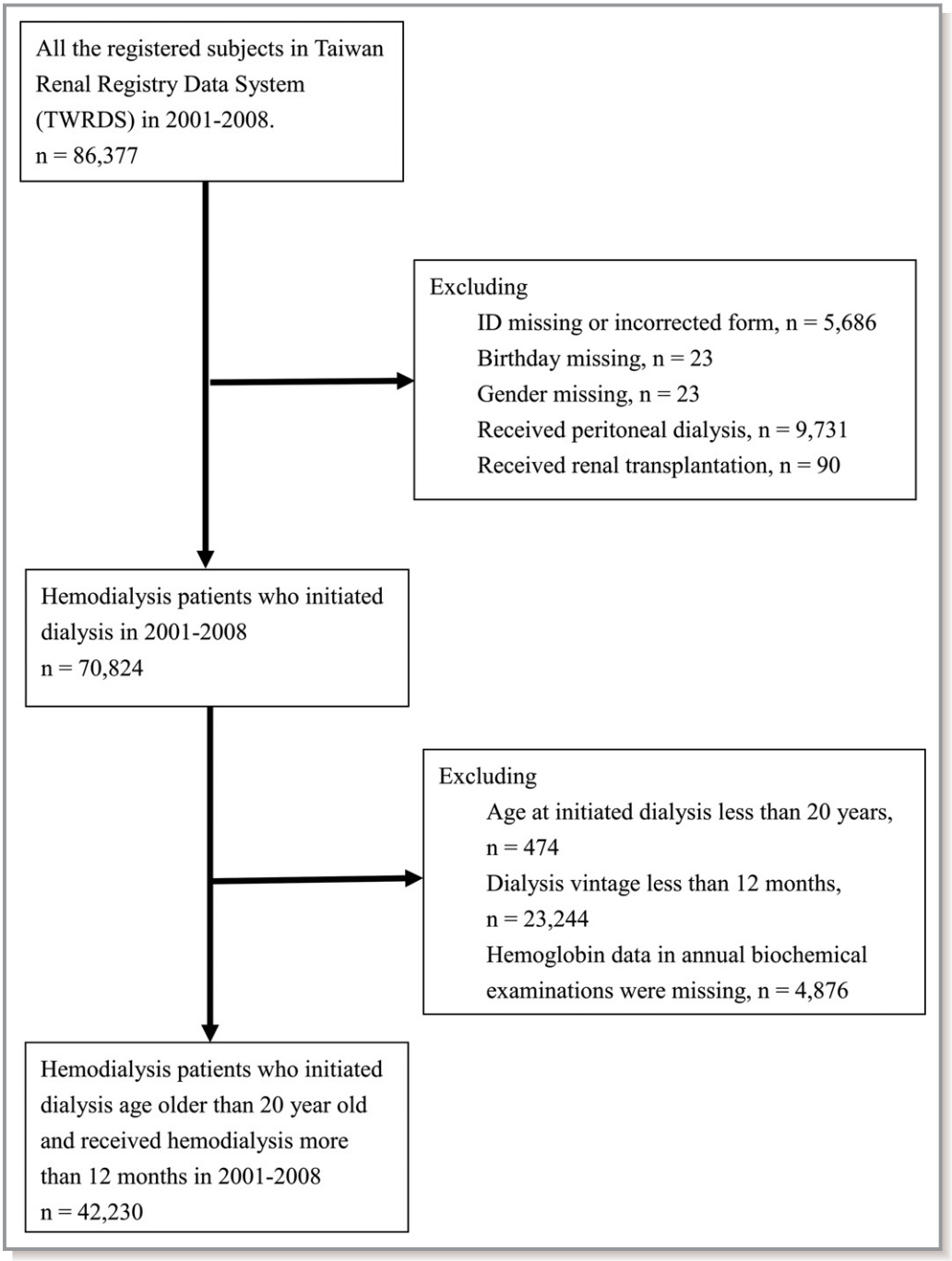

Figure 1. Flowchart of patient selection.

(1.59; 95% CI, 1.11–2.30) were significantly higher in those with a serum ferritin level ≥800 ng/mL.

Figure 4 and Table 4 show the associations between different TSAT categories and mortality. In a multivariate Cox proportional hazard model, the aHRs for all-cause (1.57; 95% CI, 1.46–1.68), cardiovascular (1.63; 95% CI, 1.49–1.77), and ischemic stroke (2.01; 95% CI, 1.21–3.35) mortality were significantly higher in those with a serum TSAT level <20% but modest for infection-related mortality (1.48; 95% CI, 0.97–2.23). On the other hand, the aHR for all-cause mortality was significantly increased in those with a TSAT level ≥50%. In addition, TSAT in a range of 30% to 50% was associated with lower risk for mortality. Figure 5 shows cubic spline curves for the associations of hemoglobin, ferritin, and TSAT with the risk of all-cause mortality. The findings had similar trends shown in Figures 2A, 3A, and 4A. Finally, in terms of all-cause mortality, the trends of optimal hemoglobin, ferritin, and TSAT values are similar in patients with or without iron supplementation. The only difference is that all-cause mortality in patients with serum ferritin

Table 1. Time-Averaged Characteristics of Patients Undergoing Hemodialysis Stratified by 5 Hemoglobin Concentration Groups

Characteristics	Hemoglobin, g/dL					*P* Value
	<9	9 to 9.9	10 to 10.9	11 to 11.9	≥12	
No.	6530	13 754	14 609	5719	1618	
Age, y	63.6 (13.5)	62.3 (13.1)	60.7 (13.4)	59.1 (13.4)	55.3 (13.4)	<0.0001
Age group, y						
20 to 39, No. (%)	322 (4.9)	688 (5.0)	943 (6.5)	462 (8.1)	205 (12.7)	<0.0001
40 to 64, No. (%)	2755 (42.2)	6535 (47.5)	7433 (50.9)	309 (54.0)	960 (59.3)	<0.0001
65 to 74, No. (%)	1964 (30.1)	3924 (28.5)	3898 (26.7)	1457 (25.5)	325 (20.1)	<0.0001
75+, No. (%)	1489 (22.8)	2607 (19.0)	2335 (16.0)	711 (12.4)	128 (7.9)	<0.0001
Sex						
Female, No. (%)	3784 (58.0)	7983 (58.0)	7169 (49.1)	2100 (36.7)	343 (21.2)	<0.0001
Diabetes mellitus, No. (%)	2940 (45.0)	6183 (45.0)	6617 (45.3)	2725 (47.7)	717 (44.3)	0.0074
Hypertension, No. (%)	2152 (33.0)	6127 (44.6)	7176 (49.1)	2751 (48.1)	715 (44.2)	<0.0001
Kt/V	1.6 (0.3)	1.7 (0.3)	1.7 (0.3)	1.6 (0.3)	1.5 (0.3)	<0.0001
Kt/V <1.2, No. (%)	773 (11.8)	796 (5.8)	563 (3.9)	241 (4.2)	118 (7.3)	<0.0001
eGFR at the start of dialysis (MDRD)	7.0 (3.9)	6.4 (5.6)	6.2 (2.6)	6.3 (2.5)	6.2 (3.0)	<0.0001
WBC, $\times 10^3/\mu L$	6.8 (2.3)	6.9 (1.9)	7.0 (1.8)	7.1 (1.8)	7.3 (2.0)	<0.0001
Hemoglobin, g/dL	8.6 (0.3)	9.7 (0.5)	10.5 (0.4)	11.3 (0.5)	12.6 (0.9)	<0.0001
Ferritin, ng/dL	710.2 (488.6)	572.5 (356.9)	503.4 (294.4)	448.5 (284.5)	332.9 (278.8)	<0.0001
TSAT, %	33.6 (17.0)	31.9 (12.1)	32.2 (11.0)	32.5 (11.0)	31.7 (11.8)	<0.0001
Serum calcium, mg/dL	9.1 (0.8)	9.2 (0.7)	9.3 (0.6)	9.3 (0.6)	9.4 (0.6)	<0.0001
Serum phosphate, mg/dL	4.6 (1.4)	4.8 (1.2)	4.9 (1.2)	4.9 (1.1)	5.2 (1.2)	<0.0001
Alkaline phosphatase, U/L	119.0 (65.7)	110.7 (60.2)	103.9 (55.7)	104.7 (57.3)	106.1 (55.0)	<0.0001
Intact PTH, pg/L	190.1 (220.3)	200.2 (211.4)	200.4 (202.2)	211.0 (208.7)	238.9 (232.8)	<0.0001
Uric acid, mg/dL	7.1 (1.5)	7.1 (1.3)	7.2 (1.2)	7.3 (1.3)	7.6 (1.3)	<0.0001
Cholesterol, mg/dL	163.6 (40.6)	174.3 (36.9)	177.4 (34.5)	176.8 (34.3)	175.8 (34.0)	<0.0001
Triglyceride, mg/dL	163.6 (113.4)	166.5 (102.5)	163.0 (92.6)	167.5 (93.4)	172.3 (89.2)	0.0002
nPCR	1.1 (0.3)	1.1 (0.3)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)	<0.0001
Albumin, g/dL	3.6 (0.5)	3.8 (0.4)	3.9 (0.3)	3.9 (0.3)	4.0 (0.3)	<0.0001
Albumin <3 g/dL, No. (%)	786 (12.0)	454 (3.3)	227 (1.6)	61 (1.1)	23 (1.4)	<0.0001
ESA dose, U/mo	18 087 (12 713)	17 124 (9674)	15 018 (8299)	12 912 (8373)	9235 (10 235)	<0.0001
IV iron, No. (%)	2463 (37.7)	7369 (53.6)	8986 (61.5)	3459 (60.5)	837 (51.7)	<0.0001

All values are expressed as mean (SD) unless otherwise specified. eGFR indicates estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; IV, intravenous; Kt/V, dialysis adequacy; MDRD, Modification of Diet in Renal Disease equation; nPCR, normalized protein catabolic rate; PTH, parathyroid hormone; TSAT, transferrin saturation; WBC, white blood cell count.

≥800 ng/mL became modest in patients without IV iron supplementation (Table S2).

Associations of Iron Status and Iron Supplementation With the Risk of Death

We further validated the association of iron status and iron supplementation with the risk of all-cause mortality. The patients undergoing hemodialysis were divided into 3 groups: serum ferritin <800 ng/mL and TSAT <50% receiving iron supplementation (group 1, n=20 038), serum ferritin <800 ng/mL and TSAT <50% without iron supplementation (group 2, n=13 005), and serum ferritin ≥800 ng/mL or TSAT ≥50% (group 3, n=9187) (Table S3). Compared with patients in group 1, patients in groups 2 and 3 were older and predominantly women and had lower serum albumin but a higher dialysis inadequacy rate. Kaplan–Meier (Figure S1) and Cox proportional hazard (Figure S2) of survival curves demonstrated that patients in groups 2 and 3 were associated with a significantly higher risk for all-cause death, as compared with patients in group 1. In a

Table 2. Time-Averaged Characteristics of Patients Undergoing Hemodialysis Stratified by 4 Serum Ferritin Concentration Groups

Characteristics	Ferritin, ng/mL				*P* Value
	<300	300 to 499	500 to 799	≥800	
No.	10 305	12 658	12 765	6502	
Age, y	59.3 (14.3)	60.5 (13.3)	61.8 (12.9)	64.6 (12.5)	<0.0001
Age group, y					
20 to 39, No. (%)	965 (9.4)	808 (6.4)	616 (4.8)	231 (3.6)	<0.0001
40 to 64, No. (%)	5262 (51.1)	6527 (51.6)	6315 (49.5)	2668 (41.0)	<0.0001
65 to 74, No. (%)	2467 (23.9)	3332 (26.3)	3649 (28.6)	2120 (32.6)	<0.0001
75+, No. (%)	1611 (15.6)	1991 (15.7)	2185 (17.1)	1483 (22.8)	<0.0001
Sex					
Female, No. (%)	4502 (43.7)	6094 (48.1)	6946 (54.4)	3837 (59.0)	<0.0001
Diabetes mellitus, No. (%)	4674 (45.4)	5827 (46.0)	5773 (45.2)	2908 (44.7)	0.0016
Hypertension, No. (%)	4237 (41.1)	6111 (48.3)	6139 (48.1)	2434 (37.4)	<0.0001
Kt/V	1.6 (0.3)	1.6 (0.3)	1.7 (0.3)	1.7 (0.3)	
Kt/V <1.2, No. (%)	1126 (10.9)	527 (4.2)	397 (3.1)	441 (6.8)	<0.0001
eGFR at the start of dialysis (MDRD)	6.5 (3.4)	6.2 (2.5)	6.3 (5.6)	6.9 (3.5)	<0.0001
WBC, $\times 10^3/\mu L$	7.0 (2.0)	6.9 (1.8)	6.9 (1.8)	7.1 (2.2)	<0.0001
Hemoglobin, g/dL	10.4 (1.3)	10.3 (1.0)	10.1 (0.9)	9.6 (1.1)	<0.0001
Ferritin, ng/dL	185.8 (77.4)	403.4 (57.1)	624.6 (82.9)	1174.7 (400.1)	<0.0001
TSAT, %	27.7 (12.1)	30.9 (9.9)	33.1 (10.4)	40.6 (16.7)	<0.0001
Serum calcium, mg/dL	9.2 (0.8)	9.2 (0.7)	9.3 (0.7)	9.3 (0.8)	<0.0001
Serum phosphate, mg/dL	5.0 (1.3)	4.8 (1.2)	4.8 (1.1)	4.6 (1.3)	<0.0001
Alkaline phosphatase, U/L	107.4 (60.2)	105.5 (56.7)	107.1 (57.2)	119.3 (64.8)	<0.0001
Intact PTH, pg/L	227.2 (236.3)	202.5 (202.4)	195.9 (199.2)	173.9 (201.1)	<0.0001
Uric acid, mg/dL	7.2 (1.4)	7.2 (1.3)	7.2 (1.3)	7.0 (1.4)	<0.0001
Cholesterol, mg/dL	174.0 (37.4)	174.8 (34.3)	176.0 (36.3)	169.4 (39.2)	<0.0001
Triglyceride, mg/dL	157.1 (95.2)	161.5 (93.2)	168.2 (98.6)	179.1 (115.3)	<0.0001
nPCR	1.1 (0.3)	1.1 (0.2)	1.1 (0.2)	1.1 (0.3)	<0.0001
Albumin, mg/dL	3.8 (0.4)	3.9 (0.4)	3.8 (0.4)	3.7 (0.5)	<0.0001
Albumin <3 g/dL, No. (%)	483 (4.7)	232 (1.8)	325 (2.6)	511 (7.9)	<0.0001
ESA dose, U/mo	13 603 (9584)	15 620 (9269)	16 580 (9378)	17 276 (11 604)	<0.0001
Iron IV, No. (%)	5178 (50.3)	8205 (64.8)	7585 (59.4)	2146 (33.0)	<0.0001

All values are expressed as the mean (SD) unless otherwise specified. eGFR indicates estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; IV, intravenous; Kt/V, dialysis adequacy; MDRD, Modification of Diet in Renal Disease equation; nPCR, normalized protein catabolic rate; PTH, parathyroid hormone; TSAT, transferrin saturation; WBC, white blood cell count.

multivariate Cox proportional hazard model (Table S4), compared with patients in group 1 (reference group), the aHRs for all-cause mortality were significantly higher in patients in group 2 (1.77; 95% CI, 1.67–1.86) and patients in group 3 (1.64; 95% CI, 1.55–1.74).

Associations of ESA Doses With Mortality in Patients Undergoing Hemodialysis

Table S5 shows the entire range of ESA administered doses in the studied patients undergoing hemodialysis. In a multivariate Cox proportional hazard model, patients who had received a monthly ESA dose <10 000 U were associated with higher risk of all-cause mortality. Moreover, the low monthly ESA administered doses were also associated with higher risk of cardiovascular mortality but not ischemic stroke or infection-related mortality. Finally, the interaction of hemoglobin level and ESA doses on the risk of all-cause death were analyzed (Table S6). We found that in the patients with a hemoglobin level <10 g/dL, lower ESA doses (<10 000 U/mo) were associated with higher mortality as

Table 3. Time-Averaged Characteristics of Patients Undergoing Hemodialysis Stratified by 5 TSAT Percentage Groups

Characteristics	TSAT, %					*P* Value
	<20	20 to 29	30 to 49	50 to 69	≥70	
No.	5474	15 726	17 910	2384	736	
Age, y	61.4 (13.9)	61.0 (13.2)	61.2 (13.5)	62.2 (13.9)	64.3 (13.1)	<0.0001
Age group, y						
20 to 39, No. (%)	362 (6.6)	954 (6.1)	1135 (6.3)	143 (6.0)	26 (3.5)	0.0186
40 to 64, No. (%)	2615 (47.8)	7984 (50.8)	8796 (49.1)	1077 (45.2)	300 (40.8)	<0.0001
65 to 74, No. (%)	1459 (26.7)	4304 (27.4)	4910 (27.4)	671 (28.2)	224 (30.4)	<0.2295
75+, No. (%)	1038 (19.0)	2484 (15.8)	3069 (17.1)	493 (20.7)	186 (25.3)	<0.0001
Sex						
Female, No. (%)	2906 (53.1)	8268 (52.6)	8691 (48.5)	1137 (47.7)	377 (51.2)	<0.0001
Diabetes mellitus, No. (%)	2867 (52.4)	8017 (51.0)	7240 (40.4)	812 (34.1)	246 (33.4)	0.0001
Hypertension, No. (%)	1964 (35.9)	7577 (48.2)	8336 (46.5)	867 (36.4)	177 (24.1)	<0.0001
Kt/V	1.6 (0.3)	1.6 (0.3)	1.7 (0.3)	1.7 (0.3)	1.6 (0.3)	
Kt/V <1.2, No. (%)	836 (15.3)	780 (5.0)	637 (3.6)	147 (6.2)	91 (12.4)	<0.0001
eGFR at the start of dialysis (MDRD)	7.0 (4.1)	6.4 (5.2)	6.2 (2.6)	6.5 (3.0)	7.2 (3.7)	<0.0001
WBC, $\times 10^3/\mu L$	7.7 (2.4)	7.1 (1.8)	6.6 (1.7)	6.4 (1.9)	6.5 (2.4)	<0.0001
Hemoglobin, g/dL	10.0 (1.3)	10.2 (1.0)	10.2 (1.0)	9.9 (1.2)	9.2 (1.3)	<0.0001
Ferritin, ng/dL	390.8 (321.7)	469.4 (276.1)	579.4 (321.9)	881.1 (542.9)	1222.0 (717.9)	<0.0001
TSAT, %	16.2 (3.6)	25.4 (2.8)	37.0 (5.2)	57.1 (5.4)	83.0 (9.5)	<0.0001
Serum calcium, mg/dL	9.2 (0.8)	9.3 (0.7)	9.3 (0.7)	9.2 (0.7)	9.2 (0.8)	<0.0001
Serum phosphate, mg/dL	4.9 (1.5)	4.9 (1.2)	4.8 (1.1)	4.6 (1.2)	4.5 (1.5)	<0.0001
Alkaline phosphatase, U/L	113.1 (62.5)	106.9 (57.5)	106.6 (58.1)	117.6 (64.4)	133.0 (70.6)	<0.0001
Intact PTH, pg/L	206.0 (232.6)	204.6 (216.3)	200.4 (198.9)	193.5 (211.7)	170.1 (188.7)	<0.0001
Uric acid, mg/dL	7.2 (1.5)	7.2 (1.3)	7.1 (1.2)	7.1 (1.3)	7.0 (1.5)	<0.0001
Cholesterol, mg/dL	174.9 (41.3)	177.4 (36.2)	173.3 (34.4)	163.8 (37.9)	154.8 (39.9)	<0.0001
Triglyceride, mg/dL	171.7 (109.1)	174.3 (104.1)	158.0 (91.2)	147.9 (92.7)	157.4 (107.7)	<0.0001
nPCR	1.1 (0.3)	1.1 (0.2)	1.1 (0.2)	1.1 (0.3)	1.1 (0.3)	<0.0001
Albumin, g/dL	3.7 (0.5)	3.8 (04)	3.9 (0.4)	3.7 (0.4)	3.6 (0.5)	<0.0001
Albumin <3 g/dL, No. (%)	488 (8.9)	419 (2.7)	410 (2.3)	138 (5.8)	96 (13.0)	<0.0001
ESA dose, U/mo	14 532 (12 653)	15 733 (9216)	15 890 (9364)	15 926 (9309)	16 724 (11 951)	<0.0001
IV iron, No. (%)	2249 (41.1)	9408 (59.8)	10 368 (57.9)	946 (39.7)	143 (19.4)	<0.0001

All values are expressed as the mean (SD) unless otherwise specified. eGFR indicates estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; IV, intravenous; Kt/V, dialysis adequacy; MDRD, Modification of Diet in Renal Disease equation; nPCR, normalized protein catabolic rate; PTH, parathyroid hormone; TSAT, transferrin saturation; WBC, white blood cell count.

compared with patients with a hemoglobin level <10 g/dL but higher ESA doses (≥10 000 U/mo).

Discussion

Taiwan has a high prevalence of CKD (11.9%).[12] Compared with international data using the United States Renal Data System, the incidence and prevalence of end-stage renal disease in Taiwan ranked first in the world from 2002 to 2014.[13] Anemia is a common problem in Taiwanese patients with CKD. Wen et al[12] reported that 58.8% of patients with stage 4 CKD in Taiwan are anemic, and the prevalence of anemia increases to 92.5% in patients with stage 5 CKD. On March 1, 1995, Taiwan's government launched the National Health Insurance (NHI) system, which ensures the right to health care for all residents and provides free access to medical services and total coverage of medical expenses for renal replacement therapy. Meanwhile, the NHI implemented

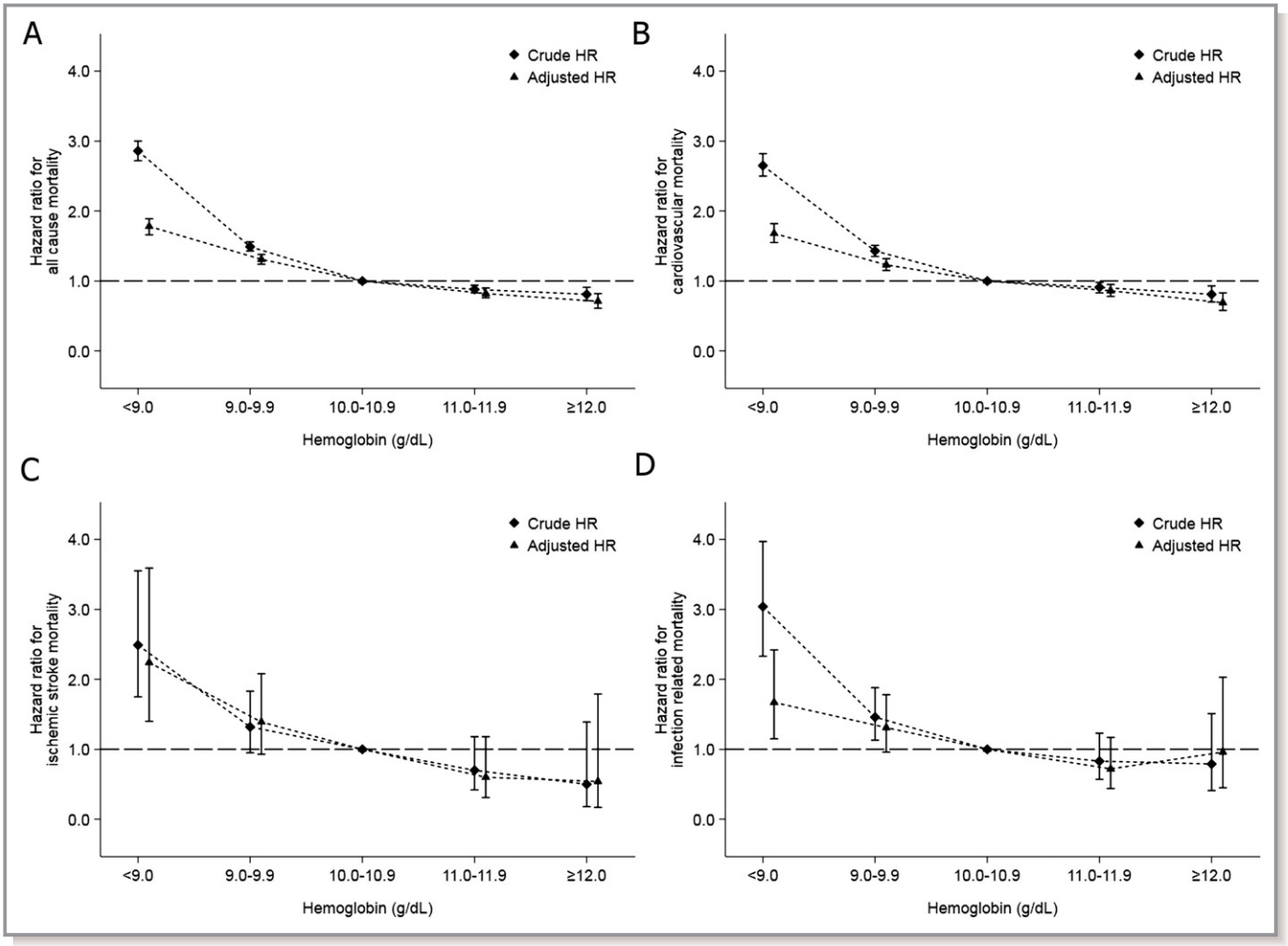

Figure 2. Associations between hemoglobin values and all-cause (A), cardiovascular (B), ischemic stroke (C), and infection-related (D) mortality in 42 230 patients undergoing maintenance hemodialysis. HR indicates hazard ratio.

a fully bundled payment system for hemodialysis expenses, including the actual cost of dialysis, the cost of dialysis-related laboratory tests, and the costs of using ESAs, IV iron, calcium-containing phosphate binders, and active vitamin D. Later, in 1996, the NHI applied more restrictive reimbursement criteria for ESA use targeting a lower hematocrit level in nondialysis and hemodialysis patients with stage 5 CKD. ESAs are to be initiated when patients with dialysis-dependent CKD have a hematocrit level <28% to maintain a hematocrit level at 30%. The maximum dose allowed by insurance is capped at 20 000 U of epoetin-α or -β and 100 μg of darbepoetin alfa or methoxy polyethylene glycol-epoetin beta per month. However, the conservative hematocrit target of 30% for patients with CKD set by the NHI of Taiwan was related to economic concerns but not evidence-based. The optimal hemoglobin, serum ferritin, and TSAT values required to improve survival rates among patients undergoing hemodialysis after the implementation of bundled payment systems in Taiwan warranted further assessment.

According to our previous report,[8] the mean hemoglobin value has been steady since 2000 in Taiwanese patients undergoing hemodialysis. We, therefore, analyzed the data from TWRDS to examine the associations of anemia and iron parameters with mortality in patients undergoing hemodialysis during 2001 to 2008. In addition, because the blood hemoglobin concentration changes longitudinally in patients undergoing hemodialysis as a result of treatment measures and disease status, using a single baseline hemoglobin level does not provide an accurate assessment of individual patients' exposure to the effects of anemia over time.[14] To account for this, we analyzed the time-averaged hemoglobin value in each patient, which allows validation of the longitudinal burden of anemia by averaging all individual measurements and considering the duration of any individual measurement value.[14] Our results showed that a lower hemoglobin level was associated with significantly higher all-cause mortality in patients undergoing hemodialysis: with a hemoglobin of 10.0 to 10.9 g/dL as a reference, the adjusted

Table 4. Hemoglobin Value, Iron Parameters, and the Risks of All-Cause, Cardiovascular, Ischemic Stroke, and Infection-Related Mortality Among Patients Undergoing Chronic Hemodialysis

	Events	IR	cHR	aHR
Hemoglobin, g/dL*				
All-cause mortality				
<9	3338	159.06	2.86 (2.72–3.00), *P*=0.001	1.78 (1.66–1.89), *P*=0.001
9 to 9.9	4512	87.78	1.49 (1.43–1.56), *P*=0.001	1.31 (1.24–1.38), *P*=0.001
10 to 10.9	3334	59.35	1.0 (reference)	1.0 (reference)
11 to 11.9	1143	52.29	0.88 (0.83–0.94), *P*=0.001	0.82 (0.76–0.90), *P*=0.001
≥12	326	49.06	0.81 (0.72–0.91), *P*=0.001	0.71 (0.61–0.82), *P*=0.001
Cardiovascular mortality				
<9	2093	99.73	2.65 (2.50–2.82), *P*=0.001	1.68 (1.55–1.82), *P*=0.001
9 to 9.9	2913	56.67	1.43 (1.35–1.51), *P*=0.001	1.23 (1.15–1.32), *P*=0.001
10 to 10.9	2250	40.05	1.0 (reference)	1.0 (reference)
11 to 11.9	791	36.19	0.91 (0.83–0.98), *P*=0.016	0.86 (0.78–0.95), *P*=0.003
≥12	219	32.96	0.81 (0.70–0.93), *P*=0.002	0.69 (0.58–0.83), *P*=0.001
Ischemic stroke mortality				
<9	58	2.76	2.49 (1.75–3.55), *P*=0.001	2.24 (1.40–3.59), *P*=0.001
9 to 9.9	79	1.54	1.32 (0.95–1.83), *P*=0.10	1.39 (0.93–2.08), *P*=0.11
10 to 10.9	66	1.17	1.0 (reference)	1.0 (reference)
11 to 11.9	18	0.82	0.70 (0.42–1.18), *P*=0.18	0.60 (0.31–1.18), *P*=0.14
≥12	4	0.60	0.50 (0.18–1.39), *P*=0.18	0.54 (0.17–1.79), *P*=0.31
Infection-related mortality				
<9	112	5.34	3.04 (2.33–3.97), *P*=0.001	1.67 (1.15–2.42), *P*=0.007
9 to 9.9	139	2.70	1.46 (1.13–1.88), *P*=0.003	1.31 (0.96–1.78), *P*=0.09
10 to 10.9	105	1.87	1.0 (reference)	1.0 (reference)
11 to 11.9	34	1.56	0.83 (0.57–1.23), *P*=0.36	0.72 (0.44–1.17), *P*=0.19
≥12	10	1.51	0.79 (0.41–1.51), *P*=0.48	0.96 (0.45–2.03), *P*=0.92
Ferritin, ng/mL†				
All-cause mortality				
<300	3190	89.91	1.38 (1.32–1.45), *P*=0.001	1.13 (1.06–1.20), *P*=0.001
300 to 499	3168	66.78	1.0 (reference)	1.0 (reference)
500 to 799	3419	67.23	0.99 (0.94–1.04), *P*=0.63	0.90 (0.85–0.96), *P*=0.001
≥800	2876	123.50	1.88 (1.78–1.97), *P*=0.001	1.08 (1.01–1.15), *P*=0.027
Cardiovascular mortality				
<300	2145	60.46	1.41 (1.33–1.50), *P*=0.001	1.16 (1.07–1.25), *P*=0.001
300 to 499	2089	44.03	1.0 (reference)	1.0 (reference)
500 to 799	2244	44.12	0.98 (0.93–1.04), *P*=0.59	0.89 (0.83–0.96), *P*=0.002
≥800	1788	76.78	1.77 (1.66–1.88), *P*=0.001	1.04 (0.95–1.13), *P*=0.40
Ischemic stroke mortality				
<300	53	1.49	1.12 (0.78–1.61), *P*=0.53	1.05 (0.67–1.64), *P*=0.84
300 to 499	65	1.37	1.0 (reference)	1.0 (reference)
500 to 799	66	1.30	0.93 (0.66–1.31), *P*=0.69	0.92 (0.61–1.40), *P*=0.71
≥800	41	1.76	1.30 (0.88–1.93), *P*=0.18	0.71 (0.41–1.21), *P*=0.20

Continued

Table 4. Continued

	Events	IR	cHR	aHR
Infection-related mortality				
<300	97	2.73	1.47 (1.10–1.95), *P*=0.009	1.17 (0.82–1.69), *P*=0.39
300 to 499	91	1.92	1.0 (reference)	1.0 (reference)
500 to 799	101	1.99	1.02 (0.77–1.35), *P*=0.91	0.88 (0.63–1.23), *P*=0.45
≥800	111	4.77	2.52 (1.91–3.33), *P*=0.001	1.59 (1.11–2.30), *P*=0.013
TSAT, %‡				
All-cause mortality				
<20	2403	143.93	2.49 (2.37–2.62), *P*=0.001	1.57 (1.46–1.68), *P*=0.001
20 to 29	4427	76.28	1.23 (1.18–1.28), *P*=0.001	1.16 (1.10–1.22), *P*=0.001
30 to 49	4524	63.63	1.0 (reference)	1.0 (reference)
50 to 69	873	98.08	1.57 (1.46–1.69), *P*=0.001	1.17 (1.07–1.28), *P*=0.001
≥70	426	182.73	3.11 (2.82–3.43), *P*=0.001	1.46 (1.27–1.68), *P*=0.001
Cardiovascular mortality				
<20	1647	98.65	2.68 (2.52–2.85), *P*=0.001	1.63 (1.49–1.77), *P*=0.001
20 to 29	2991	51.53	1.30 (1.24–1.37), *P*=0.001	1.20 (1.12–1.27), *P*=0.001
30 to 49	2878	40.48	1.0 (reference)	1.0 (reference)
50 to 69	503	56.51	1.42 (1.29–1.56), *P*=0.001	1.07 (0.95–1.21), *P*=0.24
≥70	247	105.95	2.83 (2.49–3.23), *P*=0.001	1.32 (1.09–1.59), *P*=0.004
Ischemic stroke mortality				
<20	48	2.88	3.19 (2.21–4.61), *P*=0.001	2.01 (1.21–3.35), *P*=0.007
20 to 29	79	1.36	1.41 (1.02–1.95), *P*=0.036	1.37 (0.93–2.02), *P*=0.11
30 to 49	70	0.98	1.0 (reference)	1.0 (reference)
50 to 69	20	2.25	2.32 (1.41–3.81), *P*=0.001	2.01 (1.07–3.77), *P*=0.029
≥70	8	3.43	3.75 (1.81–7.80), *P*=0.001	2.57 (0.99–6.70), *P*=0.053
Infection-related mortality				
<20	67	4.01	2.10 (1.57–2.80), *P*=0.001	1.30 (0.85–1.97), *P*=0.23
20 to 29	145	2.50	1.22 (0.97–1.53), *P*=0.09	1.16 (0.88–1.53), *P*=0.30
30 to 49	149	2.10	1.0 (reference)	1.0 (reference)
50 to 69	27	3.03	1.48 (0.98–2.22), *P*=0.06	0.73 (0.41–1.29), *P*=0.28
≥70	12	5.15	2.65 (1.47–4.77), *P*=0.001	0.81 (0.32–2.03), *P*=0.66

cHR indicates crude hazard ratio; IR, incidence rate per 1000 patient-years.

*Adjusted hazard ratios (aHRs) were adjusted for age, sex, diabetes mellitus, hypertension, dialysis adequacy (Kt/V), estimated glomerular filtration rate (eGFR) at the start of dialysis (Modification of Diet in Renal Disease equation [MDRD]), white blood cell count (WBC), normalized protein catabolic rate (nPCR), serum albumin, cholesterol, triglyceride, ferritin, transferrin saturation, calcium, phosphate, alkaline phosphatase, intact parathyroid hormone (PTH), uric acid, erythropoiesis-stimulating agent (ESA) dose, and intravenous iron use.

†aHRs were adjusted for age, sex, diabetes mellitus, hypertension, Kt/V, eGFR at the start of dialysis (MDRD), WBC, nPCR, serum albumin, cholesterol, triglyceride, hemoglobin, transferrin saturation, calcium, phosphate, alkaline phosphatase, intact PTH, uric acid, ESA dose, and intravenous iron use.

‡aHRs were adjusted for age, sex, diabetes mellitus, hypertension, Kt/V, eGFR at the start of dialysis (MDRD), WBC, nPCR, serum albumin, cholesterol, triglyceride, ferritin, hemoglobin, calcium, phosphate, alkaline phosphatase, intact PTH, uric acid, ESA dose, and intravenous iron use.

§Cardiovascular mortality defined by *International Classification of Diseases, 9th Revision* (*ICD-9*) codes 250, 261 to 263, 280 to 285, 410 to 414, 401 to 405, 440, 430 to 432, and 580 to 589. Ischemic stroke mortality defined by *ICD-9* codes 433 to 434 and 436. Infection-related mortality defined by *ICD-9* codes 001 to 139, 420 to 429, 320 to 322, 326, 510 to 513, 567, 590, 599, 711, 730, 460 to 466, 480 to 487, 490 to 493, and 680 to 686.

death HRs for hemoglobin levels of <9.0 and 9.0 to 9.9 g/dL were 1.74 (1.66–1.89) and 1.31 (1.24–1.38), respectively. In contrast, the aHRs of all-cause mortality for hemoglobin levels of 11.0 to 11.9 and ≥12.0 g/dL were 0.82 (0.76–0.90) and 0.71 (0.61–0.82), respectively. More intriguingly, when hemoglobin was modeled as a continuous predictor, mortality was lowest for hemoglobin values ≈12 g/dL according to a cubic spline plot (Figure 4). Regidor et al[15] have reported a U-shaped curve relationship between hemoglobin and all-cause mortality in patients undergoing hemodialysis. In

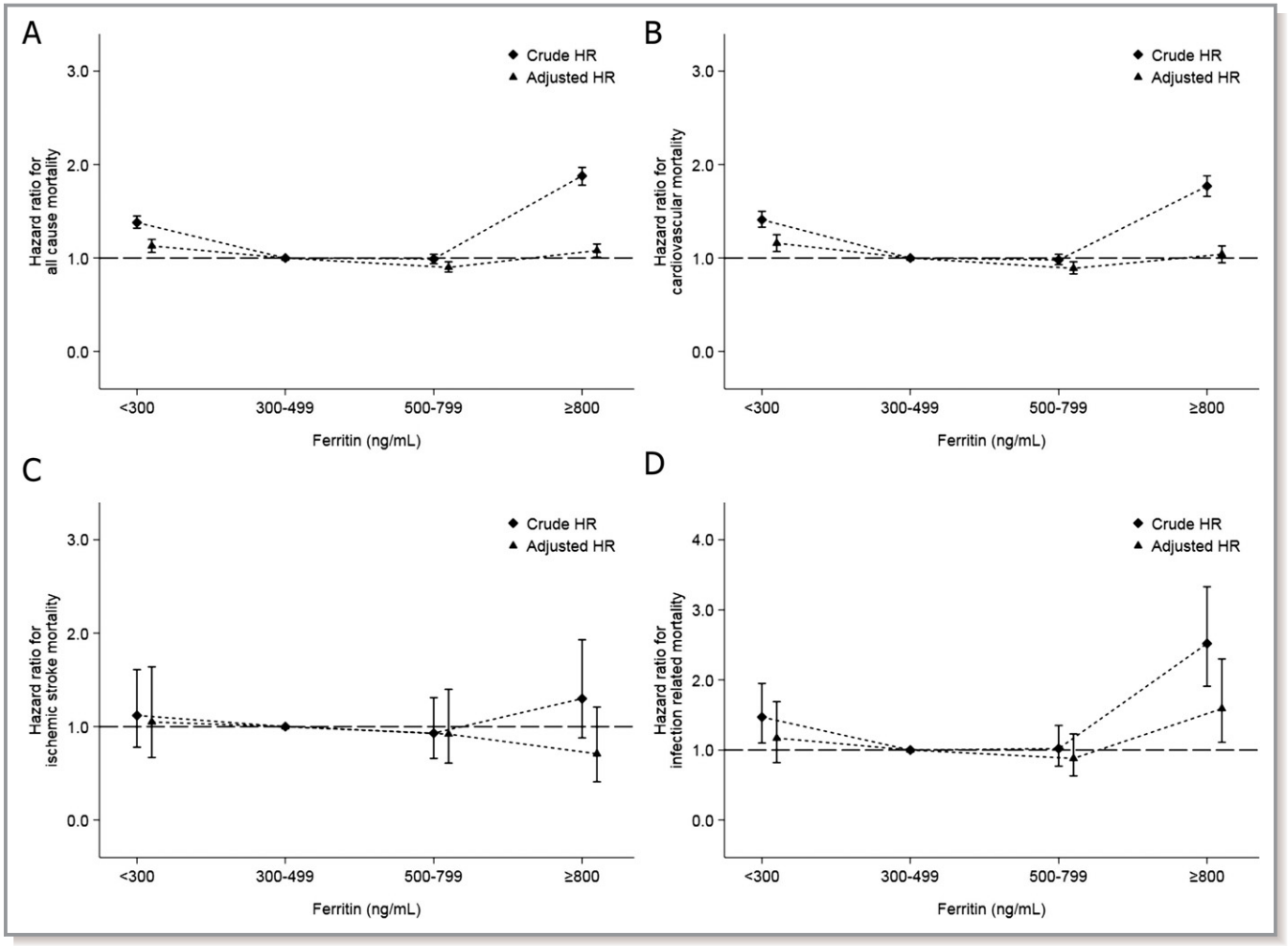

Figure 3. Associations between serum ferritin levels and all-cause (A), cardiovascular (B), ischemic stroke (C), and infection-related (D) mortality in 42 230 patients undergoing maintenance hemodialysis. HR indicates hazard ratio.

contrast, the results of our study were biased toward the left side of the U-shaped curve, which were similar to those of previous studies on nondialysis and peritoneal dialysis patients with CKD.[14,16] However, the higher the hemoglobin level (>13.5 g/dL) the higher the mortality, as reported by Regidor et al.[15] The reasons for this discrepancy are mainly a result of low ESA toxicity with lower administered doses, adequate iron supplementation, prompt ESA response with low inflammatory and well-nourished status (Table 1), and limited cases with hemoglobin >12.0 g/dL (3.8% of patients) in the AIM-HD study.

The greatest impact of the bundle system in anemia management is the use of IV iron. Nephrology experts in Taiwan reached a consensus regarding the diagnostic criteria for iron deficiency in 1996. They recommended that iron supplementation be considered for patients undergoing dialysis with a ferritin level <300 ng/mL and/or a TSAT level <30% to maintain a ferritin level of 300 to 500 ng/mL and a TSAT of 30% to 50%. The consensus was mainly based on our previous studies performed in Taiwan, which provided the guidance on the use of IV iron supplementation in the management of CKD-related anemia.[17–20] However, the impact of these recommendations for iron supplementation and iron parameters on patients' outcomes was unknown at that time. Kalantar-Zadeh et al[21] reported no significant differences in the risks of all-cause and cardiovascular mortality among patients undergoing hemodialysis with serum ferritin levels of 200 to 1200 ng/mL, whereas those with a serum ferritin level ≥1200 ng/mL were associated with increased mortality rate.[21] In contrast, we found that a serum ferritin level <300 ng/mL was associated with higher risks of all-cause and cardiovascular mortality. Iimori et al[22] demonstrated that iron-deficiency anemia was associated with all-cause mortality in patients with CKD, and Xu et al[23] further reported that myocardial iron depletion was associated with left ventricular dysfunction. These findings[22,23] are corroborated by our observations. Galić et al[24] reported that the incidences of sepsis and vascular access infection were higher among patients undergoing hemodialysis with a serum

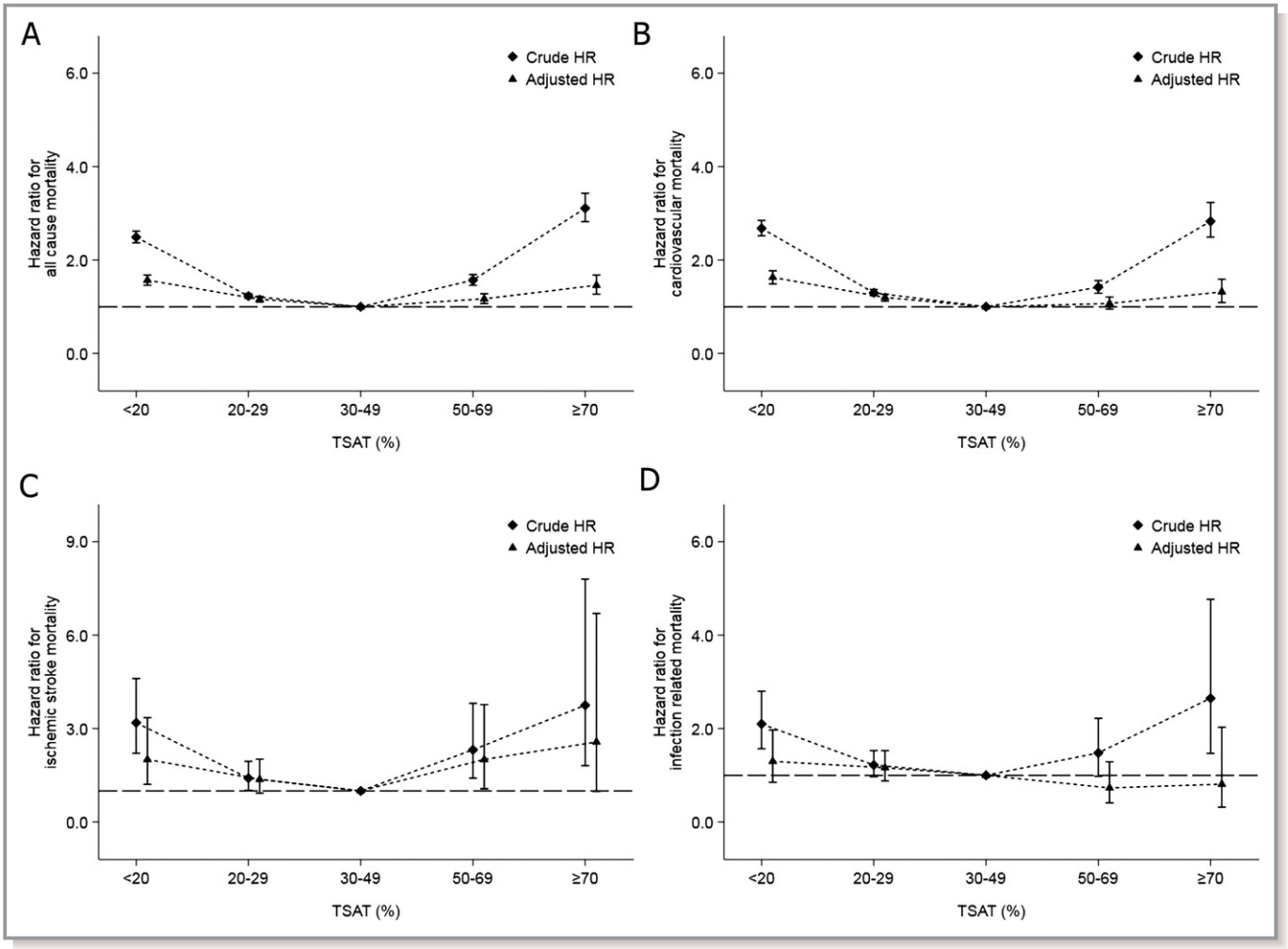

Figure 4. Associations between transferrin saturation (TSAT) values and all-cause (A), cardiovascular (B), ischemic stroke (C), and infection-related (D) mortality in 42 230 patients undergoing maintenance hemodialysis. HR indicates hazard ratio.

ferritin level >500 ng/mL. However, this association with infection-related mortality was not observed in their multivariate analysis. In contrast, we found that a serum ferritin level ≥800 ng/mL was significantly associated with infection-related mortality among patients with prevalent hemodialysis. Fortunately, beginning in 2005, the Taiwan Society of Nephrology for accreditation of hemodialysis units proposed that IV iron supplementation should not be used when serum ferritin exceeds 800 ng/mL.[8] Accordingly, the proportion of patients undergoing hemodialysis with a serum ferritin level >800 ng/mL gradually decreased from 1995 to 2012 (Figure S3). The recommended 800-ng/mL threshold as the upper level for serum ferritin in anemia management in Taiwanese patients undergoing hemodialysis could be based on epidemiological evidence according to our results. Finally, the AIM-HD study demonstrated that TSAT between 30% and 50% was associated with the lowest all-cause and cardiovascular mortality. Our study mutually supported the recommendations by both the 1996 Taiwan practice guidelines[8] and the 2012 Kidney Disease: Improving Global Outcomes (KDIGO)[25] clinical practice guideline for anemia management in CKD.

Study Strengths and Limitations

From a clinical perspective, several issues warrant discussion in this study. Our study was notable for its large sample size, its nationally representative nature, and the fact that the study cohort was validated by strict Taiwan NHI reimbursement regulations. Nevertheless, several limitations of our study should be addressed. First, our study was observational in nature and cannot prove causality. In testing the hypothesis that anemia decreased survival by affecting cardiovascular-related factors, we found that the effect of anemia on all-cause mortality was similar to the trend for cardiovascular mortality. Second, the therapeutic effects of ESAs could not be directly measured. We found that a lower time-averaged hemoglobin was associated with higher all-cause and cardiovascular mortality in all ESA-treated patients undergoing hemodialysis

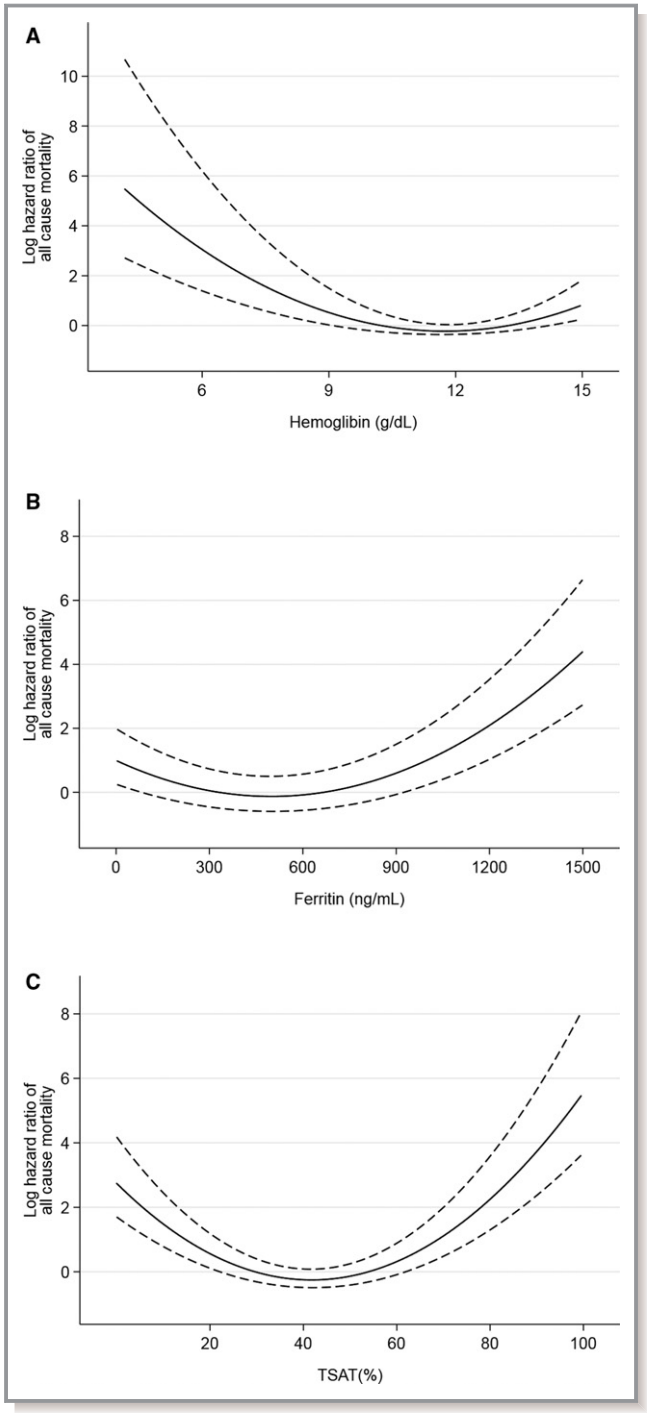

Figure 5. Cubic spline and 95% confidence level of all-cause mortality for hemoglobin (A), serum ferritin (B), and transferrin saturation (TSAT) (C) in 42 230 patients undergoing maintenance hemodialysis.

(Table S1), and the results were also similar in all patients undergoing hemodialysis (Table 4), revealing the protective effects of modest but not high ESA administered doses in our patients (Table S5). Third, in TWRDS, potential cofounders such as malignancy, coronary artery disease, and heart failure were not available for analysis. Fourth, inflammatory markers such as C-reactive protein and interleukin 6 were not available in the AIM-HD study. However, we did use data on serum albumin, transferrin, ferritin, and white blood cells as malnutrition-inflammation complex markers to adjust potential bias. Finally, we excluded patients younger than 20 years and those who died or could not undergo a follow-up within 1 year after the initiation of hemodialysis, therefore our patients may not represent the entire hemodialysis population.

Conclusions

A lower (<10 g/dL), time-averaged hemoglobin value was associated with higher risk of death among patients receiving inadequately low ESA administered doses in the bundled payment system. In addition, a serum ferritin level <300 ng/mL was associated with higher risk of all-cause and cardiovascular mortality and a serum ferritin level >800 ng/mL was associated with all-cause and infection-related mortality. A TSAT value between 30% and 50% was associated with lower risk of all-cause and cardiovascular mortality. Therefore, we recommend avoiding a low hemoglobin value and maintaining a ferritin level between 300 and 800 ng/mL and a TSAT level between 30% and 50% in patients with prevalent hemodialysis receiving the restricted ESA doses but prompt IV iron supplementation based on the findings of the AIM-HD study.

Appendix

Members of the Taiwan Society of Nephrology Renal Registry Data System Research Group include Der-Cherng Tarng, Wei-Cheng Tseng, Ming-Tsun Tsai, Shuo-Ming Ou, Chih-Yu Yang, Yao-Ping Lin (Taipei Veterans General Hospital, Taipei); Yi-Sheng Lin (Taipei City Hospital, Taipei); Szu-Chun Hung, Ko-Lin Kuo (Taipei Tzu Chi Hospital, Taipei); Tung-Po Hung (Wei Gong Memorial Hospital, Miaoli); Chih-Cheng Hsu, Jia-Sin Liu, Ming-Huang Lin (National Health Research Institutes, Zhunn).

Author Contributions

K.L.K., S.C.H., and D.C.T. designed the study; K.L.K., J.S.L., and M.H.L. performed experiments; W.C.T., M.T.T., J.S.L., and M.H.L. analyzed the data; J.S.L. and M.H.L. made the figures; C.C.H. and D.C.T. drafted and revised the article; and all authors approved the final version of the article.

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Disclosures

None.

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Supplemental Material

Table S1. Hemoglobin and all-cause, cardiovascular, ischemic stroke and infection-related mortality risks among hemodialysis patients treated with erythropoiesis stimulating agents (n=38,801).

Hemoglobin (g/dL)	Events	IR	cHR	aHR
All-cause mortality				
< 9.0	2,962	154.35	2.90 (2.76-3.05), p=0.001	1.79 (1.67-1.92), p=0.001
9.0-9.9	4,144	85.49	1.52 (1.45-1.59), p=0.001	1.33 (1.25-1.41), p=0.001
10.0-10.9	3,022	56.77	1.0 (reference)	1.0 (reference)
11.0-11.9	992	49.06	0.87 (0.81-0.93), p=0.001	0.83 (0.76-0.90), p=0.001
≥12.0	226	42.98	0.74 (0.64-0.84), p=0.001	0.67 (0.56-0.79), p=0.001
Cardiovascular mortality				
< 9.0	1,849	96.35	2.66 (2.50-2.84), p=0.001	1.68 (1.54-1.83), p=0.001
9.0-9.9	2,659	54.85	1.44 (1.36-1.52), p=0.001	1.24 (1.16-1.33), p=0.001
10.0-10.9	2,051	38.53	1.0 (reference)	1.0 (reference)
11.0-11.9	685	33.88	0.88 (0.81-0.96), p= 0.004	0.85 (0.77-0.95), p=0.003
≥12.0	152	28.91	0.73 (0.62-0.86), p= 0.001	0.64 (0.52-0.79), p=0.001
Ischemic stroke mortality				
< 9.0	50	2.61	2.45 (1.68-3.56), p=0.001	2.04 (1.23-3.37), p=0.005
9.0-9.9	70	1.44	1.29 (0.91-1.82), p= 0.15	1.34 (0.88-2.05), p= 0.17
10.0-10.9	60	1.13	1.0 (reference)	1.0 (reference)
11.0-11.9	15	0.74	0.66 (0.37-1.16), p= 0.15	0.62 (0.31-1.25), p= 0.18

≥12.0	3	0.57	0.50 (0.16-1.58), p= 0.24	0.68 (0.21-2.25), p= 0.53
Infection related mortality				
< 9.0	99	5.16	3.05 (2.30-4.04), p=0.001	1.74 (1.17-2.57), p= 0.006
9.0-9.9	126	2.60	1.46 (1.12-1.90), p= 0.005	1.36 (0.98-1.87), p= 0.07
10.0-10.9	96	1.80	1.0 (reference)	1.0 (reference)
11.0-11.9	31	1.53	0.85 (0.57-1.28), p= 0.44	0.80 (0.49-1.31), p= 0.37
≥12.0	9	1.71	0.93 (0.47-1.83), p= 0.83	1.01 (0.45-2.24), p= 0.98

Abbreviations: aHR: adjusted hazard ratio; cHR: crude hazard ratio; IR: incidence rate per 1000 patient-years.

*aHRs were adjusted for adjusted for age, sex, diabetes, hypertension, dialysis adequacy (Kt/V), eGFR at the start of dialysis (MDRD), white blood cell counts, the normalized protein catabolic rate (nPCR), serum albumin, cholesterol, triglyceride, ferritin, transferrin saturation, calcium, phosphate, alkaline phosphatase, intact-PTH, uric acid, erythropoiesis-stimulating agents dose, and intravenous iron use.

**Cardiovascular mortality defined by ICD 9 codes 250, 261-263, 280-285, 410-414, 401-405, 440, 430-432, and 580-589. Ischemic stroke mortality defined by ICD 9 codes 433-434 and 436. Infection-related mortality defined by ICD 9 codes 001-139, 420-429, 320-322, 326, 510-513, 567, 590, 599, 711, 730, 460-466, 480-487, 490-493, and 680-686.

Table S2. Hemoglobin value, iron parameters and the risks of all-cause mortality among chronic hemodialysis patients with or without iron supplementation.

	Events	IR	cHR	aHR
With iron supplementation (n=23,114)				
Hemoglobin (g/dL)[1]				
< 9	813	93.83	2.61 (2.39-2.85), p=0.001	1.97 (1.77-2.20), p=0.001
9-9.9	1,589	55.83	1.47 (1.37-1.58), p=0.001	1.35 (1.24-1.47), p=0.001
10-10.9	1,349	38.23	1.0 (reference)	1.0 (reference)
11-11.9	442	33.41	0.89 (0.80-0.99), p= 0.029	0.84 (0.74-0.95), p= 0.007
≥12	97	28.10	0.71 (0.58-0.87), p= 0.001	0.65 (0.50-0.83), p=0.001
Ferritin (ng/mL)[2]				
< 300	973	52.84	1.21 (1.12-1.31), p=0.001	1.12 (1.02-1.24), p= 0.019
300-499	1,393	44.80	1.0 (reference)	1.0 (reference)
500-799	1,326	42.50	0.91 (0.85-0.98), p= 0.016	0.89 (0.82-0.97), p= 0.011
≥ 800	598	71.28	1.58 (1.43-1.73), p=0.001	1.16 (1.03-1.31), p= 0.013
TSAT (%)[3]				
< 20	647	88.79	2.61 (2.38-2.86), p=0.001	1.74 (1.55-1.96), p=0.001
20-29	1,796	50.64	1.37 (1.29-1.47), p=0.001	1.26 (1.16-1.36), p=0.001
30-49	1,612	38.33	1.0 (reference)	1.0 (reference)
50-69	187	49.69	1.32 (1.13-1.53), p=0.001	1.09 (0.91-1.30), p= 0.37

≥70	48	91.46	2.51 (1.89-3.35), p=0.001	1.48 (1.00-2.18), p= 0.049
Without iron supplementation (n=19,116)				
Hemoglobin (g/dL)[1]				
< 9	2,525	204.94	2.28(2.15-2.42), p=0.001	1.69 (1.56-1.83), p=0.001
9-9.9	2,923	127.43	1.35 (1.28-1.43), p=0.001	1.25 (1.17-1.35), p=0.001
10-10.9	1,985	95.02	1.0 (reference)	1.0 (reference)
11-11.9	701	81.25	0.85 (0.78-0.93), p=0.001	0.82 (0.74-0.92), p=0.001
≥12	229	71.74	0.74 (0.65-0.85), p=0.001	0.73 (0.61-0.88), p= 0.001
Ferritin (ng/mL)[2]				
< 300	2,217	129.92	1.23 (1.15-1.31), p=0.001	1.12 (1.04-1.22), p= 0.005
300-499	1,775	108.56	1.0 (reference)	1.0 (reference)
500-799	2,093	106.47	0.97 (0.91-1.04), p= 0.40	0.90 (0.84-0.98), p= 0.01
≥ 800	2,278	152.92	1.43 (1.35-1.52), p=0.001	1.04 (0.96-1.13), p= 0.31
TSAT (%)[3]				
< 20	1,756	186.64	2.01 (1.89-2.13), p=0.001	1.44 (1.32-1.57), p=0.001
20-29	2,631	116.56	1.18 (1.12-1.25), p=0.001	1.10 (1.03-1.18), p= 0.004
30-49	2,912	100.26	1.0 (reference)	1.0 (reference)
50-69	686	133.52	1.35 (1.25-1.47), p=0.001	1.18 (1.06-1.31), p= 0.003
≥70	378	209.24	2.22 (1.99-2.47), p=0.001	1.43 (1.23-1.66), p=0.001

Abbreviations: aHR: adjusted hazard ratio; cHR: crude hazard ratio; IR: incidence rate per 1000 patient-years

[1]aHRs were adjusted for adjusted for age, sex, diabetes, hypertension, dialysis adequacy (Kt/V), estimated glomerular filtration rate (eGFR) at the start of dialysis (MDRD), white blood cell counts, the normalized protein catabolic rate (nPCR), serum albumin, cholesterol, triglyceride, ferritin, transferrin saturation, calcium, phosphate, alkaline phosphatase, intact-PTH, uric acid, erythropoiesis-stimulating agents dose, and intravenous iron use.

[2]aHRs were adjusted for adjusted for age, sex, diabetes, hypertension, dialysis adequacy (Kt/V), estimated glomerular filtration rate (eGFR) at the start of dialysis (MDRD), white blood cell counts, the normalized protein catabolic rate (nPCR), serum albumin, cholesterol, triglyceride, hemoglobin, transferrin saturation, calcium, phosphate, alkaline phosphatase, intact-PTH, uric acid, erythropoiesis-stimulating agents dose, and intravenous iron use.

[3]aHRs were adjusted for adjusted for age, sex, diabetes, hypertension, dialysis adequacy (Kt/V), estimated glomerular filtration rate (eGFR) at the start of dialysis (MDRD), white blood cell counts, the normalized protein catabolic rate (nPCR), serum albumin, cholesterol, triglyceride, ferritin, hemoglobin, calcium, phosphate, alkaline phosphatase, intact-PTH, uric acid, erythropoiesis-stimulating agents dose, and intravenous iron use.

*Cardiovascular mortality defined by ICD 9 codes 250, 261-263, 280-285, 410-414, 401-405, 440, 430-432, and 580-589. Ischemic stroke mortality defined by ICD 9 codes 433-434 and 436. Infection-related mortality defined by ICD 9 codes 001-139, 420-429, 320-322, 326, 510-513, 567, 590, 599, 711, 730, 460-466, 480-487, 490-493, and 680-686.

Table S3. Characteristics of hemodialysis patients in different iron status by cut-off values of ferritin at 500 ng/mL and transferrin saturation at 50% with or without iron supplementation.

	Groups			
Characteristics	**Group 1: Ferritin < 800 ng/mL and TSAT < 50 % with iron supplementation**	**Group 2: Ferritin < 800 ng/mL and TSAT < 50 % without iron supplementation**	**Group 3: Ferritin ≥ 800 ng/mL or TSAT ≥ 50 %**	***P* value**
n	20,038	13,005	9,187	< 0.001
Age (years)	60.9 (13.3)	62.4 (13.7)	64.9 (13.0)	< 0.001
Age group				
20-39 years, n (%)	1,359 (6.8)	865 (6.7)	396 (4.3)	< 0.001
40-64 years, n (%)	10,643 (53.1)	6,252 (48.1)	3,877 (42.2)	< 0.001
65-74 years, n (%)	5,193 (25.9)	3,518 (27.1)	2,857 (31.1)	< 0.001
75+ years, n (%)	2,843 (14.2)	2,370 (18.2)	2,057 (22.4)	< 0.001
Sex				
Female, n (%)	9,999 (49.9)	6,335 (48.7)	5,045 (54.9)	< 0.001
Diabetes, n (%)	9,262 (46.2)	6,010 (46.2)	3,910 (42.6)	< 0.001
Hypertension, n (%)	12,319 (61.5)	3,386 (26.0)	3,216 (35.0)	< 0.001
KT/V	1.6 (0.3)	1.6 (0.3)	1.7 (0.3)	0.34
Kt/V < 1.2, n (%)	501 (2.5)	615 (4.9)	388 (4.5)	< 0.001
eGFR at the start of dialysis (MDRD)	6.2 (4.6)	6.4 (2.9)	7 (3.9)	< 0.001
WBC ($\times 10^3$ /μl)	6.9 (1.7)	7.0 (2.0)	7.0 (2.3)	< 0.001
Hemoglobin (g/dL)	10.2 (1.0)	10 (1.2)	9.6 (1.2)	< 0.001

Ferritin (ng/dL)	429.4 (177.2)	411.8 (203.1)	1,019.3 (466.3)	< 0.001
TSAT (%)	29.7 (7.8)	28.7 (8.8)	44.5 (18.2)	< 0.001
Serum calcium (mg/dL)	9.3 (0.6)	9.3 (0.7)	9.3 (0.8)	0.59
Serum phosphate (mg/dL)	4.9 (1.1)	4.8 (1.3)	4.6 (1.3)	< 0.001
Alkaline phosphatase (U/L)	104.2 (55.9)	109.1 (59.1)	117.8 (65.2)	< 0.001
Intact-PTH (pg/L)	213.3 (205.2)	198.3 (220.5)	179.3 (204.2)	< 0.001
Uric acid (mg/dL)	7.2 (1.2)	7.2 (1.4)	7 (1.4)	< 0.001
Cholesterol (mg/dL)	175.5 (33.2)	176.1 (38.8)	168.4 (39.5)	< 0.001
Triglyceride (mg/dL)	163.2 (93.1)	165.2 (100.4)	169.9 (110.4)	< 0.001
nPCR	1.1 (0.2)	1.1 (0.3)	1.1 (0.3)	< 0.001
Albumin (g/dL)	3.9 (0.3)	3.8 (0.4)	3.7 (0.5)	< 0.001
Albumin < 3 g/dL, n (%)	226 (1.1)	451 (3.5)	874 (9.6)	< 0.001
ESA dose, (U/month)	16,192.1 (8,381.5)	14,515.6 (10,589.2)	16,173.3 (11,486.0)	< 0.001
Iron IV, n (%)	20,038(100.0)	0 (0.0)	3,076 (33.5)	< 0.001

Abbreviations: ESA: erythropoiesis-stimulating agent; eGFR: estimated glomerular filtration rate; IV: intravenous; nPCR: normalized protein catabolic rate; PTH, parathyroid hormone; TSAT: transferrin saturation; WBC: white blood cell count

Table S4. The risks of all-cause, cardiovascular, ischemic stroke and infection-related mortality among chronic hemodialysis patients in different iron status by cut-off values of ferritin at 800 ng/mL and transferrin saturation at 50% with or without iron supplementation.

Hemoglobin (g/dL)	Events	IR	cHR	aHR
All-cause mortality				
Group 1	3502	45.3	1.0 (reference)	1.0 (reference)
Group 2	5122	107.34	2.41 (2.31-2.51), p=0.001	1.77 (1.67-1.86), p=0.001
Group 3	4029	125.72	2.87 (2.74-3.00), p=0.001	1.64 (1.55-1.74), p=0.001
Cardiovascular mortality				
Group 1	2299	29.74	1.0 (reference)	1.0 (reference)
Group 2	3448	72.26	2.47 (2.34-2.60), p=0.001	1.77 (1.66-1.89), p=0.001
Group 3	2519	78.60	2.73 (2.58-2.89), p=0.001	1.51 (1.41-1.63), p=0.001
Ischemic stroke mortality				
Group 1	68	0.88	1.0 (reference)	1.0 (reference)
Group 2	94	1.97	2.28 (1.67-3.12), p=0.001	1.97 (1.33-2.90), p=0.001
Group 3	63	1.97	2.31 (1.64-3.25), p=0.001	1.42 (0.90-2.23), p= 0.13
Infection-related mortality				
Group 1	116	1.5	1.0 (reference)	1.0 (reference)
Group 2	144	3.02	2.04 (1.60-2.61), p=0.001	1.54 (1.14-2.10), p= 0.005
Group 3	140	4.37	3.00 (2.35-3.84), p=0.001	1.76 (1.28-2.44), p=0.001

Abbreviations: IR: incidence rate per 1000 patient-years, cHR: crude hazard ratio; aHR: adjusted hazard ratio; TSAT: transferrin saturation.

*aHRs were adjusted for adjusted for age, sex, diabetes, hypertension, dialysis adequacy (Kt/V), GFR at the start of dialysis (MDRD), white blood cell counts, the normalized protein catabolic rate (nPCR), serum albumin, cholesterol, triglyceride, hemoglobin, ferritin, transferrin saturation, calcium, phosphate, alkaline phosphatase, intact-PTH, uric acid, erythropoiesis-stimulating agents dose, and intravenous iron use.

**Cardiovascular mortality defined by ICD 9 codes 250, 261-263, 280-285, 410-414, 401-405, 440, 430-432, and 580-589. Ischemic stroke mortality defined by ICD 9 codes 433-434 and 436. Infection-related mortality defined by ICD 9 codes 001-139, 420-429, 320-322, 326, 510-513, 567, 590, 599, 711, 730, 460-466, 480-487, 490-493, and 680-686.

***Group definition:
Group 1: ferritin < 800 ng/mL and TSAT < 50 % with iron supplementation,
Group 2: ferritin < 800 ng/mL and TSAT < 50 % without iron supplementation,
Group 3: ferritin ≥ 800 ng/mL or TSAT ≥ 50 %.

Table S5. Associations of erythropoiesis stimulating agent dose with all-cause, cardiovascular, ischemic stroke and infection-related mortality among hemodialysis patients.

ESA (units/month)	Events	IR	cHR	aHR
All-cause mortality				
< 5,000	1,859	111.22	1.55 (1.47-1.64), p=0.001	1.18 (1.09-1.28), p=0.001
5,000-9,999	1,375	85.92	1.13 (1.06-1.20), p=0.001	1.18 (1.09-1.27), p=0.001
10,000-14,999	2,703	74.52	0.98 (0.93-1.03), p= 0.34	1.03 (0.97-1.09), p= 0.34
15,000-19,999	3,331	75.76	1.0 (reference)	1.0 (reference)
≥20,000	3,385	76.74	1.03 (0.98-1.08), p= 0.27	0.99 (0.94-1.05), p= 0.77
Cardiovascular mortality				
< 5,000	1,238	74.07	1.60 (1.49-1.72), p=0.001	1.16 (1.06-1.28), p=0.002
5,000-9,999	943	58.92	1.20 (1.11-1.30), p=0.001	1.22 (1.11-1.34), p=0.001
10,000-14,999	1,799	49.60	1.00 (0.94-1.07), p= 0.88	1.04 (0.97-1.112), p= 0.29
15,000-19,999	2,152	48.95	1.0 (reference)	1.0 (reference)
≥20,000	2,134	48.38	1.00 (0.94-1.06), p= 0.94	0.98 (0.91-1.05), p= 0.51
Ischemic stroke mortality				
< 5,000	37	2.21	1.66 (1.10-2.49), p= 0.015	1.56 (0.93-2.61), p= 0.09
5,000-9,999	23	1.44	1.02 (0.63-1.65), p= 0.93	1.14 (0.64-2.06), p= 0.65
10,000-14,999	53	1.46	1.03 (0.71-1.49), p= 0.87	1.16 (0.75-1.79), p= 0.50
15,000-19,999	62	1.41	1.0 (reference)	1.0 (reference)

≥20,000	50	1.13	0.82 (0.56-1.18), p= 0.28	0.68 (0.43-1.08), p= 0.10
Infection related mortality				
< 5,000	59	3.53	1.64 (1.19-2.26), p= 0.003	1.50 (0.98-2.32), p= 0.06
5,000-9,999	54	3.37	1.48 (1.06-2.06), p= 0.02	1.95 (1.30-2.93), p=0.001
10,000-14,999	85	2.34	1.02 (0.77-1.36), p= 0.88	1.13 (0.79-1.62), p= 0.51
15,000-19,999	100	2.27	1.0 (reference)	1.0 (reference)
≥20,000	102	2.31	1.03 (0.78-1.36), p= 0.83	1.04 (0.74-1.47), p= 0.81

Abbreviations: aHR: adjusted hazard ratio; cHR: crude hazard ratio; ESA: erythropoiesis-stimulating agent; IR: incidence rate per 1000 patient-years.

*aHRs were adjusted for adjusted for age, sex, diabetes, hypertension, dialysis adequacy (Kt/V), eGFR at the start of dialysis (MDRD), white blood cell counts, the normalized protein catabolic rate (nPCR), serum albumin, cholesterol, triglyceride, hemoglobin, ferritin, transferrin saturation, calcium, phosphate, alkaline phosphatase, intact-PTH, uric acid, and intravenous iron use.

**Cardiovascular mortality defined by ICD 9 codes 250, 261-263, 280-285, 410-414, 401-405, 440, 430-432, and 580-589. Ischemic stroke mortality defined by ICD 9 codes 433-434 and 436. Infection-related mortality defined by ICD 9 codes 001-139, 420-429, 320-322, 326, 510-513, 567, 590, 599, 711, 730, 460-466, 480-487, 490-493, and 680-686

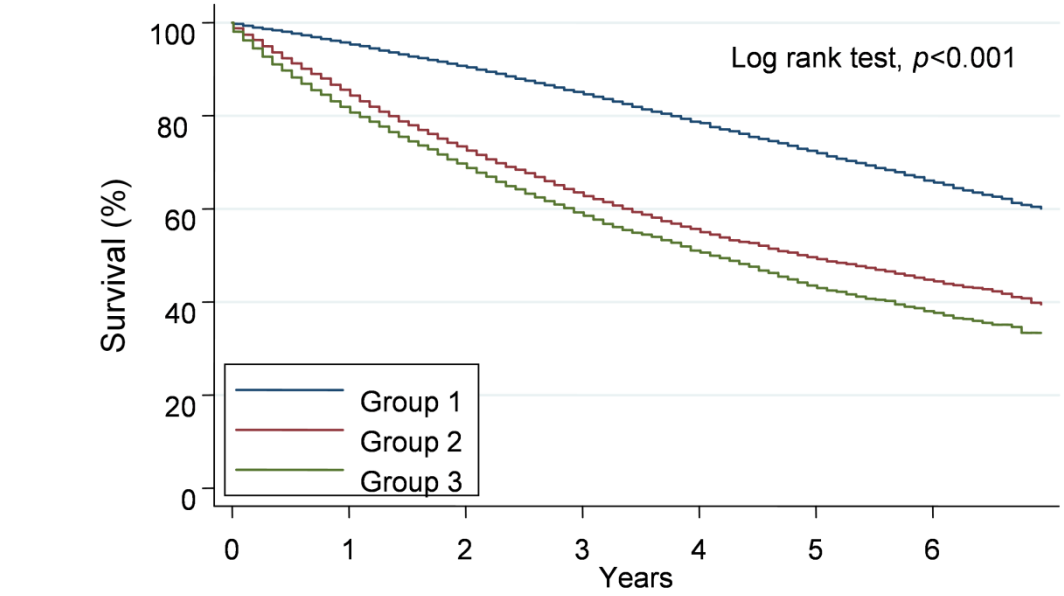
Table S6. The interaction of hemoglobin level and erythropoiesis stimulating agent dose on the risk of all-cause mortality among hemodialysis patients.

	Events	IR	cHR	aHR
Hgb≧10 g/dL & ESA ≧10,000 units/month	3,124	50.36	0.30 (0.28-0.32), p< 0.001	0.58 (0.53-0.63), p< 0.001
Hgb≧10g/dL & ESA < 10,000 units/month	1,679	74.15	0.44 (0.41-0.47), p< 0.001	0.65 (0.60-0.72), p< 0.001
Hgb <10 g/dL & ESA ≧10,000 units/month	6,295	101.03	0.61 (0.58-0.64), p< 0.001	0.88 (0.82-0.95), p= 0.001
Hgb <10 g/dL & ESA < 10,000 units/month	1,555	154.37	1.0 (reference)	1.0 (reference)

Abbreviations: aHR: adjusted hazard ratio; cHR: crude hazard ratio; ESA: erythropoiesis stimulating agent; Hgb: hemoglobin; IR: incidence rate per 1000 patient-years.

aHRs were adjusted for adjusted for age, sex, diabetes, hypertension, dialysis adequacy (Kt/V), eGFR at the start of dialysis (MDRD), white blood cell counts, the normalized protein catabolic rate (nPCR), serum albumin, cholesterol, triglyceride, ferritin, transferrin saturation, calcium, phosphate, alkaline phosphatase, intact-PTH, uric acid, and intravenous iron use.

Figure S1. Kaplan–Meier analysis of survival curve among hemodialysis patients from Taiwan Renal Registry Data System (2001–2008).



Number at risk

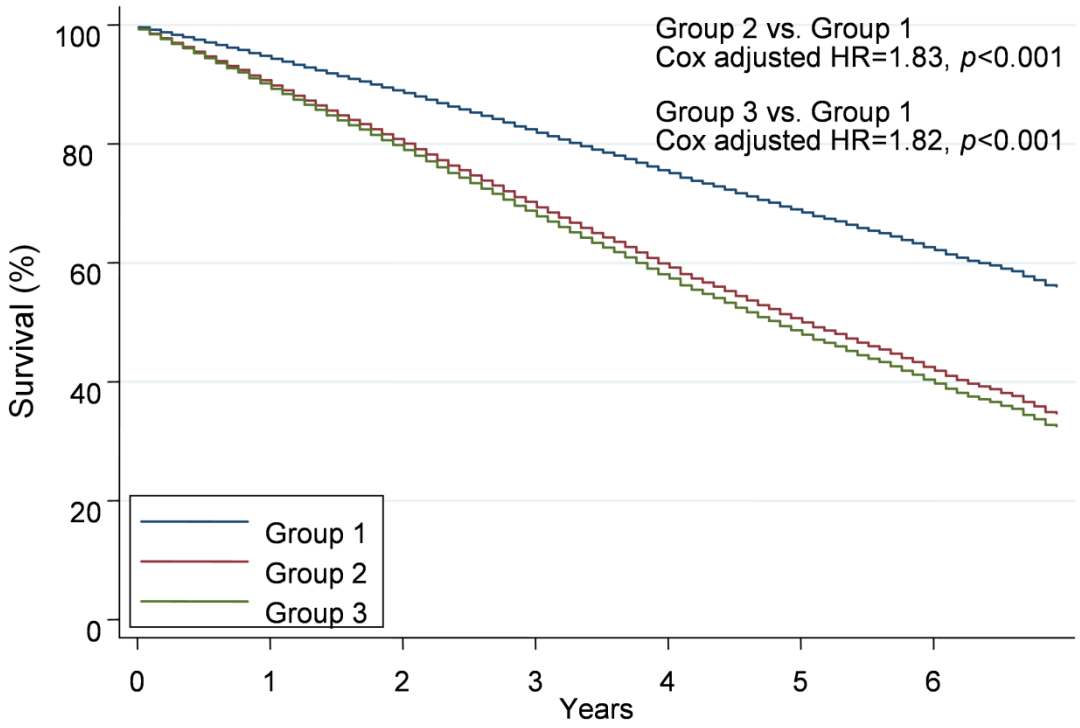
Group 1	20038	16319	12496	8692	5661	3308	1474
Group 2	13005	9704	7155	5151	3594	2250	1093
Group 3	9187	6651	4844	3321	2180	1235	538

Group 1: ferritin < 800 ng/mL and TSAT < 50 % with iron supplementation,

Group 2: ferritin < 800 ng/mL and TSAT < 50 % without iron supplementation,

Group 3: ferritin ≥ 800 ng/mL or TSAT ≥ 50 %.

Figure S2. **Cox proportional hazard of survival curve among hemodialysis patients from Taiwan Renal Registry Data System (2001–2008).**



Group 1: ferritin < 800 ng/mL and TSAT < 50 % with iron supplementation,

Group 2: ferritin < 800 ng/mL and TSAT < 50 % without iron supplementation,

Group 3: ferritin ≥ 800 ng/mL or TSAT ≥ 50 %.

Figure S3. Year trend in distribution of serum ferritin for hemodialysis patients from Taiwan Renal Registry Data System (1995–1999 and 2004-2012).