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...
Anemia Management in Hemodialysis Patients  Kuo et al

**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 were 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. The use of iron with ESAs is prerequisite for optimal management of anemia in patients with CKD. Intravenous (IV) iron therapy reduces ESA requirements and increases hemoglobin levels.

Taiwan is the first country in the world to develop a bundled payment system for hemodialysis because of economic concerns. 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. The clinical impact of these policies is unknown. Using data from the TWRDS (Taiwan Renal Registry Data System), 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. 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.

**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. 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
All the registered subjects in Taiwan Renal Registry Data System (TWRDS) in 2001-2008. n = 86,377

Excluding
ID missing or incorrect form, n = 5,686
Birthday missing, n = 23
Gender missing, n = 23
Received peritoneal dialysis, n = 9,731
Received renal transplantation, n = 90

Hemodialysis patients who initiated dialysis in 2001-2008. n = 70,824

Excluding
Age at initiated dialysis less than 20 years, n = 474
Dialysis vintage less than 12 months, n = 23,244
Hemoglobin data in annual biochemical examinations were missing, n = 4,876

Hemodialysis patients who initiated dialysis age older than 20 year old and received hemodialysis more than 12 months in 2001-2008. n = 42,230

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

| Characteristics | <9 | 9 to 9.9 | 10 to 10.9 | 11 to 11.9 | ≥12 | P Value |
|----------------|----|----------|------------|------------|-----|---------|
| 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 (48.1) | 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, ×10^9/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 (1.8) | 7.0 (1.8) | 7.3 (2.0) | <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.
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...
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%). 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. Anemia is a common problem in Taiwanese patients with CKD. Wen et al 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

| Table 3. Time-Averaged Characteristics of Patients Undergoing Hemodialysis Stratified by 5 TSAT Percentage Groups |
|---------------------------------------------------------------|
| Characteristics | TSAT, % | <20 | 20 to 29 | 30 to 49 | 50 to 69 | ≥70 | P Value |
| 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) | 4034 (27.4) | 4910 (27.4) | 671 (28.2) | 224 (30.4) | <0.0295 |
| 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) | 8869 (48.5) | 1137 (47.7) | 377 (51.2) | <0.0001 |
| Diabetes mellitus, No. (%) | 2867 (52.4) | 8017 (51.0) | 8691 (48.5) | 1137 (47.7) | 377 (51.2) | <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) | <0.0001 |
| 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, ×10^9/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 (0.4) | 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) | 38 (8.5) | 96 (13.0) | <0.0001 |
| ESA dose, U/mo | 14 532 (12 653) | 15 733 (9216) | 15 926 (9309) | 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.

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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

**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.
### 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** |         |     |       |         |
|                      | <9     | 3338| 159.06| 2.86    |
|                      | 9 to 9.9| 4512| 87.78 | 1.49    |
|                      | 10 to 10.9| 3334| 59.35 | 1.0     |
|                      | 11 to 11.9| 1143| 52.29 | 0.88    |
|                      | ≥12    | 326 | 49.06 | 0.81    |
| **All-cause mortality** |         |     |       |         |
|                      | <9     | 2093| 99.73 | 2.65    |
|                      | 9 to 9.9| 2913| 56.67 | 1.43    |
|                      | 10 to 10.9| 2250| 40.05 | 1.0     |
|                      | 11 to 11.9| 791 | 36.19 | 0.91    |
|                      | ≥12    | 219 | 32.96 | 0.81    |
| **Cardiovascular mortality** |         |     |       |         |
|                      | <9     | 2145| 60.46 | 1.41    |
|                      | 9 to 9.9| 2089| 44.03 | 1.0     |
|                      | 10 to 10.9| 2244| 44.12 | 0.98    |
|                      | ≥12    | 1788| 76.78 | 1.77    |
| **Ischemic stroke mortality** |         |     |       |         |
|                      | <9     | 53  | 1.49  | 1.12    |
|                      | 9 to 9.9| 65  | 1.37  | 1.0     |
|                      | 10 to 10.9| 66 | 1.30  | 0.93    |
|                      | ≥12    | 41  | 1.76  | 1.30    |
| **Infection-related mortality** |         |     |       |         |
|                      | <9     | 112 | 5.34  | 3.04    |
|                      | 9 to 9.9| 139 | 2.70  | 1.46    |
|                      | 10 to 10.9| 105 | 1.87  | 1.0     |
|                      | 11 to 11.9| 34 | 1.56  | 0.83    |
|                      | ≥12    | 10  | 1.51  | 0.79    |
| **Ferritin, ng/mL** |         |     |       |         |
|                      | <300   | 3190| 89.91 | 1.38    |
|                      | 300 to 499| 3168| 66.78 | 1.0     |
|                      | 500 to 799| 3419| 67.23 | 0.99    |
|                      | ≥800   | 2876| 123.50| 1.88    |
| **All-cause mortality** |         |     |       |         |
|                      | <300   | 2145| 60.46 | 1.41    |
|                      | 300 to 499| 2089| 44.03 | 1.0     |
|                      | 500 to 799| 2244| 44.12 | 0.98    |
|                      | ≥800   | 1788| 76.78 | 1.77    |
| **Cardiovascular mortality** |         |     |       |         |
|                      | <300   | 53  | 1.49  | 1.12    |
|                      | 300 to 499| 65 | 1.37  | 1.0     |
|                      | 500 to 799| 66 | 1.30  | 0.93    |
|                      | ≥800   | 41  | 1.76  | 1.30    |

Continued
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

| 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 (iPTH), uric acid, erythropoiesis-stimulating agent (ESA) dose, and intravenous iron use.

1aHRs 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.

1aHRs 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.

1Cardiovascular 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 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 011 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.
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 al21 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 al22 demonstrated that iron-deficiency anemia was associated with all-cause mortality in patients with CKD, and Xu et al23 further reported that myocardial iron depletion was associated with left ventricular dysfunction. These findings22,23 are corroborated by our observations. Galić et al24 reported that the incidences of sepsis and vascular access infection were higher among patients undergoing hemodialysis with a serum 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.

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.
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. 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 and the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) 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 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.
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.

References
1. Parfrey PS, Foley RN, Wittreich BH, Sullivan DJ, Zagari MJ, Frei D. Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. J Am Soc Nephrol. 2000;16:2180–2189.

2. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, Schwab SJ, Goodkin DA. 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;339:584–590.

3. Singh AK, Szczep L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D; CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006;355:2085–2098.

4. Druieke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, Burger HU, Scherhag A; CREATE Investigators. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med. 2006;355:2071–2084.

5. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, Feyzi JM, Ivanovich P, Kewalramani R, Levey AS, Lewis EF, McGill JB, McMurray JV, Gupta A. Optimization of epoetin therapy with intravenous iron therapy in maintenance hemodialysis patients on erythropoietin therapy. Am J Nephrol. 2006;26:104–108.

6. Hsu WL, Li SY, Liu JS, Huang PH, Lin SJ, Hsu CC, Lin YP, Tarrant DC. High uric acid ameliorates indoxyl sulfate-induced endothelial dysfunction and is associated with lower mortality among hemodialysis patients. Toxins (Basel). 2017;9:E20.

7. Ditto DW, Curtis LF, Kalantar-Zadeh K, Anderson JE, Huang TP. Myocardial iron deficiency to iron overload. Kidney Int. 2001;59:231–237.

8. Hsu WL, Li SY, Liu JS, Huang PH, Lin SJ, Hsu CC, Lin YP, Tarrant DC. High uric acid ameliorates indoxyl sulfate-induced endothelial dysfunction and is associated with lower mortality among hemodialysis patients. Toxins (Basel). 2017;9:E20.

9. Wen CP, Cheng TY, Tsai MK, Chang YC, Chan HT, Tsai SP, Chang PH, Hsu CC, Sung PK, Hsu YH, Wen SF. All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462293 adults in Taiwan. Lancet. 2008;371:2173–2182.

10. United States Renal Data Systems (USRDS) 2014 annual data report. 2016.

11. Kovesdy CP, Trivedi BK, Kalantar-Zadeh K, Anderson JE. Association of anemia with outcomes in men with moderate and severe chronic kidney disease. Kidney Int. 2006;69:560–564.

12. Regidor DL, Kopple JD, Kovesdy CP, Kilpatrick RD, McAllister CJ, Aronovitz J, Greenland S, Kalantar-Zadeh K. Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. J Am Soc Nephrol. 2006;17:1191–1191.

13. Molnar MZ, Mehrotra R, Duong U, Kovesdy CP, Kalantar-Zadeh K. Association of hemoglobin and survival in peritoneal dialysis patients. Clin J Am Soc Nephrol. 2011;6:1973–1981.

14. Tarng DC, Chen TW, Huang TP. Iron metabolism indices for early prediction of the response and resistance to erythropoietin therapy in maintenance hemodialysis patients. Am J Nephrol. 1999;19:230–237.

15. Kovesdy CP, Trivedi BK, Kalantar-Zadeh K, Anderson JE. Iron hyporesponsiveness: a prospective cohort study based on 462293 adults in Taiwan. Lancet. 2008;371:2173–2182.

16. Tarng DC, Huang TP, Chen TW, Yang WC. Incidence, prevalence and mortality trends of dialysis in Taiwan Renal Registry Data System (TWRDS) 2000–2009. Acta Nephrol. 2012;26:104–108.

17. Yang WC, Hwang SJ. Anemia management and mortality risk in newly visiting patients undergoing oral iron therapy. Kidney Int Suppl. 2012;2:279–335.
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 |
| Group      | Cases | aHR | 95% CI             | p-value | cHR | 95% CI             | p-value |
|------------|-------|-----|--------------------|---------|-----|--------------------|---------|
| ≥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 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.
|                          | Events | IR    | cHR                           | aHR                           |
|--------------------------|--------|-------|-------------------------------|-------------------------------|
| **With iron supplementation (n=23,114)** |        |       |                               |                               |
| Hemoglobin (g/dL)<sup>1</sup> |        |       |                               |                               |
| < 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)<sup>2</sup> |        |       |                               |                               |
| < 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 (%)<sup>3</sup>    |        |       |                               |                               |
| < 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     |
| Hemoglobin (g/dL) |
|-------------------|
| ≥70 |
| Without iron supplementation (n=19,116) |
| Without iron supplementation (n=19,116) |
| Ferritin (ng/mL) |
| TSAT (%) |

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

| 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 (× 10³/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 |
| Parameter                        | Group 1      | Group 2      | Group 3      | p Value   |
|----------------------------------|--------------|--------------|--------------|-----------|
| 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 (95% CI) | aHR (95% CI) |
|-------------------|--------|------|-------------|-------------|
| **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) |
| Infection related mortality |  |  |  |  |  |
|-----------------------------|-----|-----|-----|-----|
| ≥20,000                     | 102 | 2.31| 1.03 (0.78-1.36), p= 0.83 | 1.04 (0.74-1.47), p= 0.81 |
| < 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)            |

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

*aHRs were 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 (95% CI) | p-value | aHR (95% CI) | p-value |
|----------------|--------|------|--------------|---------|--------------|---------|
| 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 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).

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 %.

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
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).