## Original Articles

# Age and anemia management: relationship of hemoglobin levels with mortality might differ between elderly and nonelderly hemodialysis patients

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### ABSTRACT

**Background.** The elderly hemodialyzed population is growing. However, little is known about the relationship between hemoglobin level and survival according to age. We investigated the effect of age on the relationship between hemoglobin and survival within the Japan Dialysis Outcomes and Practice Patterns Study (DOPPS) cohort.

**Methods.** We enrolled the entire Japan DOPPS phases 3 and 4 population. Patients were divided by the age of 75 years into two groups. Cox's proportional hazard model was used with hemoglobin at every 4 months treated as a time-dependent variable. The interaction of age and hemoglobin was analyzed.

**Results.** We included 3341 patients in the analyses. The primary outcome occurred in 567 patients during the median follow-up of 2.64 years. Hemoglobin of entire population was $10.3 \pm 1.3$ g/dL. The median of epoetin dose was 3000 IU/week. Interaction was found between ages stratified by the age of 75 years and hemoglobin values ($P = 0.045$) with use of Cox's proportional hazard model. The nonelderly population had poorer prognosis with hemoglobin <10 g/dL, while elderly population only with hemoglobin <9 g/dL. For both hemoglobin strata <9, ≥9 and <10 g/dL, interactions between age and hemoglobin were significant. Subgroup analysis indicated that interaction between age and Hb levels was observed only in the nondiabetic nephropathy group. Several sensitivity analyses demonstrated a similar trend with the original analyses and reinforced the robustness.

**Conclusions.** The elderly population might tolerate low hemoglobin levels. Our findings open the way for further investigation of individualized anemia management.

**Keywords:** aged population, anemia management, individualized therapy, mortality

## INTRODUCTION

Low hemoglobin (Hb) levels have been associated with cardiovascular events [1], mortality [2, 3], health-related quality of life [4, 5] or physical activities [6, 7] in many observational studies on hemodialysis (HD) patients, although randomized controlled trials have indicated that normal Hb values were not necessarily associated with better survival among the HD population [8] and predialysis patients [9–11]. Therefore, anemia control is one of the most important factors in the management of HD patients.

The Dialysis Outcomes and Practice Patterns Study (DOPPS) is an international observational study [12, 13]. The

cohort has provided a wide range of information concerning clinical outcomes, practice patterns and HD treatment itself [14, 15]. The DOPPS has included several studies on anemia management [16–18], which have indicated that low Hb levels may be associated with adverse outcomes [16, 18].

The epidemiology of the HD population has been changing worldwide. The elderly HD population is growing [19]. Old people experience a high incidence of cardiovascular complications [20, 21] and reduced level of activity in daily life [22]. It is known that increased Hb does not necessarily improve prognosis in patients with cardiovascular disease [23]. Moreover, many elderly patients have low Hb levels [24] despite the high doses of erythropoiesis-stimulating agent (ESA) received [25]. Thus, there could be some specific differences in the Hb target for such HD patients.

Therefore, we aimed to elucidate whether the Hb target for optimal anemia control in the elderly population differs from that in the nonelderly HD population.

## MATERIALS AND METHODS

### Target population

The DOPPS phases 3 and 4 cohort was the potential target population for the present investigation. The characteristics of the population and data collection methods were as described previously [12, 13]. Within the DOPPS cohort, patients who were treated in Japan were considered the target population. The exclusion criteria were as follows: missing critical demographic or laboratory data such as age, vintage of dialysis, sex, primary diagnoses of end-stage renal disease (ESRD) and baseline Hb values. Data were collected at the outset and every 4 months, namely the facility round number (FRN) periods. Written informed consent for inclusion into DOPPS was obtained from all the subjects. The protocol of DOPPS is compliant to the Declaration of Helsinki.

### Exposure

Hb values were used as exposure variables: Hb values at the initiation of each phase as well as at each FRN. The Hb values were divided according to increments of 1 g/dL: <9, ≥9 and <10, ≥10 and <11, ≥11 and <12, and ≥12 g/dL. We made imputations for missing Hb for each FRN value other than the initial values using the last observation carried forward (LOCF) method. This method imputed the missing Hb values from the last observed Hb values.

The population was divided into two groups according to the age of 75 years to investigate the effect of age. For sensitivity analysis, we performed the same series of analyses using the age of 70 years as the cutoff value. Several cutoff points were reported to define the 'aged' population [17, 26, 27]. The average age of prevalent HD patients in Japan is ~70 years [22]. The modes of the incident population are 70–74 and 75–79 years for male and female patients, respectively [22]. Moreover, by dividing the population according to the age of 75 years, the number of outcomes between the two groups was almost balanced, which maximized the statistical power of the present study.

### Outcome

Death was considered the primary outcome of the present study. All causes of death were recorded.

### Statistical analyses

Descriptive analyses were performed to summarize the baseline data and the demographic characteristics for both the entire population and the groups stratified by baseline Hb values and age. Continuous variables were expressed as mean and standard deviation, whereas categorical variables were expressed as proportions to the entire population.

ESA responsiveness index was calculated as the dose of epoetin (in IU/week) divided by Hb and dry weight. The ESA responsiveness index was expressed in median and interquartile range.

Cox's proportional hazard models were employed to analyze the relationship between Hb values and mortality. Covariates were age, sex, years on dialysis, diabetic nephropathy as primary diagnoses of ESRD, smoking status (current or not current), body mass index, single-pool Kt/V, C-reactive protein, albumin-adjusted calcium, serum phosphate, total cholesterol, ferritin, use of epoetin dose of >3000 IU/week (median of epoetin), as well as 13 comorbid conditions (coronary artery disease, cancer, other cardiovascular disease, cerebrovascular disease, congestive heart failure, diabetes, gastrointestinal bleeding, hypertension, lung disease, neurological disorder, psychological disorder, peripheral vascular disease and recurrent cellulitis). All covariates were divided into categorical groups; three categories were created for continuous variables by means of tertile. We used laboratory data or comorbidities at the beginning of follow-up for adjustment. Hb values at each FRN were treated as time-dependent variables.

We examined the differences of optimal target Hb by age in three steps. First, we examined type 3 P-values for heterogeneity between the two groups. Second, we performed a trend analysis that investigated the heterogeneity in Hb values within each group. Lastly, we compared the relative risks in each Hb category between the two age groups. Differences for optimal Hb values were considered to exist only when both type 3 P-values and the differences between the two groups in any given Hb categories reached significance.

### Sensitivity analyses

**Inverse propensity treatment weighting method adjustment for estimated ESA doses.** The propensity scores for the prescribing epoetin dose of ≥3000 IU/week or <3000 IU/week were derived as a function of all baseline covariates shown in Table 1 except HIV. The dose of 3000 IU/week was the median of the entire population and was selected for the cutoff. The scores were incorporated as the inverse propensity treatment weight (IPTW) in statistical models to compensate for potential confounding by indications [28]. The fitting of these models was evaluated by C-statistics for the propensity score.

**The effect of cutoff age and primary disease.** The same series of analyses were performed for sensitivity analysis also with the age of 65 and 70 years as the cutoff values. We also

**Table 1. Patient characteristics and baseline data stratified by hemoglobin levels**

| Variables | All (n = 3341) | Hb <9 g/dL (n = 491) | 9≤ Hb <10 g/dL (n = 767) | 10 ≤Hb <11 g/dL (n = 1041) | 11 ≤Hb <12 g/dL (n = 735) | Hb ≥12 g/dL (n = 307) |
|---|---|---|---|---|---|---|
| Age (years) | 63.6 ± 12.7 | 66.0 ± 13.0 | 64.7 ± 12.2 | 63.6 ± 12.1 | 62.0 ± 12.9 | 60.5 ± 13.3 |
| Sex (male) (%) | 63.2 | 57.4 | 60.4 | 62.0 | 67.5 | 73.6 |
| Years on dialysis (years) | 5.5 ± 6.8 | 4.2 ± 6.4 | 5.6 ± 6.7 | 5.7 ± 6.8 | 5.9 ± 6.8 | 6.2 ± 7.5 |
| Primary disease (DM) (%) | 33.9 | 37.3 | 32.6 | 33.1 | 33.6 | 35.2 |
| Current smoker (%) | 13.8 | 12.0 | 12.4 | 14.4 | 13.7 | 18.2 |
| Comorbidities (%) | | | | | | |
|   Coronary artery disease | 25.5 | 28.1 | 25.4 | 26.5 | 21.6 | 27.4 |
|   Cancer, other than skin | 9.5 | 11.0 | 9.4 | 9.6 | 9.3 | 7.5 |
|   Other CVD | 24.9 | 25.3 | 23.6 | 24.8 | 25.0 | 27.4 |
|   Cerebrovascular disease | 13.4 | 15.7 | 13.0 | 13.9 | 11.4 | 13.7 |
|   Congestive heart failure | 19.9 | 25.9 | 18.9 | 18.4 | 18.2 | 22.2 |
|   DM | 39.4 | 45.0 | 38.5 | 37.9 | 38.8 | 39.1 |
|   Gastrointestinal bleeding | 3.5 | 6.3 | 3.3 | 2.6 | 3.1 | 3.9 |
|   HIV | 0.4 | 1.2 | 0.5 | 0.1 | 0.4 | 0.0 |
|   Hypertension | 74.0 | 75.4 | 75.4 | 75.6 | 72.0 | 67.8 |
|   Lung disease | 3.0 | 3.5 | 3.4 | 2.3 | 3.3 | 2.6 |
|   Neurologic disorder | 12.4 | 15.1 | 11.2 | 11.8 | 12.2 | 13.0 |
|   Psychological disorder | 4.4 | 5.3 | 4.2 | 4.2 | 4.0 | 4.9 |
|   Peripheral vascular disease | 14.3 | 17.5 | 12.3 | 15.4 | 12.8 | 14.3 |
|   Recurrent cellulitis | 3.7 | 4.5 | 3.7 | 3.7 | 3.0 | 3.9 |
| BMI (kg/m$^2$) | 21.2 ± 3.4 | 20.8 ± 3.4 | 21.1 ± 3.4 | 21.3 ± 3.4 | 21.3 ± 3.3 | 21.7 ± 3.4 |
| Kt/V | 1.30 ± 0.30 | 1.25 ± 0.34 | 1.30 ± 0.29 | 1.31 ± 0.29 | 1.30 ± 0.29 | 1.27 ± 0.28 |
| Adjusted calcium (mg/dL) | 9.20 ± 0.86 | 9.16 ± 0.90 | 9.22 ± 0.86 | 9.21 ± 0.84 | 9.16 ± 0.83 | 9.30 ± 0.94 |
| Serum phosphorus (mg/dL) | 5.43 ± 1.48 | 5.00 ± 1.57 | 5.35 ± 1.40 | 5.48 ± 1.41 | 5.60 ± 1.52 | 5.78 ± 1.51 |
| Albumin (g/mL) | 3.72 ± 0.48 | 3.40 ± 0.55 | 3.68 ± 0.47 | 3.78 ± 0.45 | 3.84 ± 0.41 | 3.82 ± 0.42 |
| C-reactive protein (mg/mL) | 0.13 (0.06, 0.40) | 0.30 (0.10, 1.35) | 0.12 (0.06, 0.41) | 0.11 (0.05, 0.32) | 0.10 (0.05, 0.30) | 0.14 (0.07, 0.30) |
| Total cholesterol (mg/mL) | 157.2 ± 37.5 | 153.4 ± 38.4 | 157.9 ± 37.6 | 156.2 ± 36.0 | 159.5 ± 38.6 | 159.1 ± 37.9 |
| Hb (g/dL) | 10.3 ± 1.3 | 8.2 ± 0.7 | 9.5 ± 0.3 | 10.5 ± 0.3 | 11.4 ± 0.3 | 12.7 ± 0.7 |
| Ferritin (ng/mL) | 247.3 ± 412.7 | 342.3 ± 580.0 | 234.3 ± 367.6 | 251.7 ± 455.5 | 219.3 ± 283.0 | 180.4 ± 256.7 |
| ESA dose (IU/week) | 3868 ± 3483 | 5491 ± 4376 | 4425 ± 3409 | 3600 ± 3075 | 3174 ± 2984 | 2451 ± 3286 |
| ERI [IU/week · (g/dL)$^{-1}$/kg] | 7.7 (4.5, 13.7) | 13.8 (7.9, 20.5) | 9.5 (5.6, 15.5) | 7.0 (4.2, 11.6) | 5.7 (3.5, 9.4) | 5.3 (2.4, 8.8) |

BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; Hb, hemoglobin; ESA, erythropoiesis-stimulating agents; ERI, ESA responsiveness index. Values are reported as mean ± standard deviation, percentage or median (interquartile range).

stratified the population by the patients' primary causes of ESRD, i.e. the diabetic and nondiabetic nephropathy, and repeated the series of analyses.

**The effect of anemia therapy including ESA and iron pre-scription.** We investigated the same analysis only in the population on ESA. Iron use was categorized into three groups: not prescribed, oral iron supplementation and injectable iron use. We incorporated iron use into the time-dependent model as one of the covariates to adjust iron prescription status.

### Multiple imputation

Missing covariate values were imputed multiple times using the chained equation method in PROC MI in SAS. The results from five such imputed data sets were combined for the final analysis using the Rubin formula in PROC MIANALYZE in SAS. The proportion of missing data was <10% for all imputed covariates, with the exception of Kt/V (18%), C-reactive protein (34%), ferritin (32%) and total cholesterol (18%).

Statistical significance was defined as $P < 0.05$ with two-tailed tests. All analyses were conducted using the SAS software, version 9.2 (SAS Institute, Inc., Cary, NC, USA).

## RESULTS

### Target population

The total number of patients in the potential population, with J-DOPPS phases 3 and 4 combined, was 3423; phase 3 included 2326 patients, among them 1121 patients continued to be followed into phase 4, while 1097 patients were newly recruited during the phase 4 period (Figure 1). We excluded 82 patients because of missing data on age, sex, years on dialysis and baseline Hb level. Eventually, 3341 patients were included in the further analyses.

### Patient characteristics

The baseline characteristics of patients stratified by their Hb values are shown in Table 1. Patients with lower Hb tended to be older, more likely to have diabetic nephropathy as a cause of ESRD, and have fewer years of dialysis and more co-morbidities than patients with higher Hb levels. Additionally, a large number of these patients were female. Table 2 lists the baseline data stratified by age group. Based on the cutoff age of 75 years, there were 2651 nonelderly (<75 years old) and 690 elderly (≥75 years old) patients. The elderly group had lower Hb levels, similar ferritin levels and higher epoetin doses compared with the nonelderly group.

### ESA responsiveness index

ESA responsiveness index was 7.7 (4.5–13.7) IU/week (g/dL)$^{-1}$/kg [median (IQR)] for entire population. ESA responsiveness index by Hb groups was 13.8 (7.9–20.5), 9.5 (5.6–15.5), 7.0 (4.2–11.6), 5.7 (3.5–9.4) and 5.3 (2.4–8.8) IU/week (g/dL)$^{-1}$/kg [median (IQR)] for Hb groups of <9, ≥9 and <10, ≥10 and <11, ≥11 and <12, and ≥12 g/dL, respectively.

### Outcome

The primary end point of death occurred in 567 patients (Table 3). The causes of death are shown in Table 4. In accordance with the registry data of Japan [22], many patients died from cardiac or vascular causes.

### Cox's proportional hazard models for baseline Hb values

Table 5 lists the results of Cox models that investigated the relationship of baseline Hb values with mortality. Hb <9 g/dL tended to relate to poorer survival without significance after adjustment in fully adjusted models.
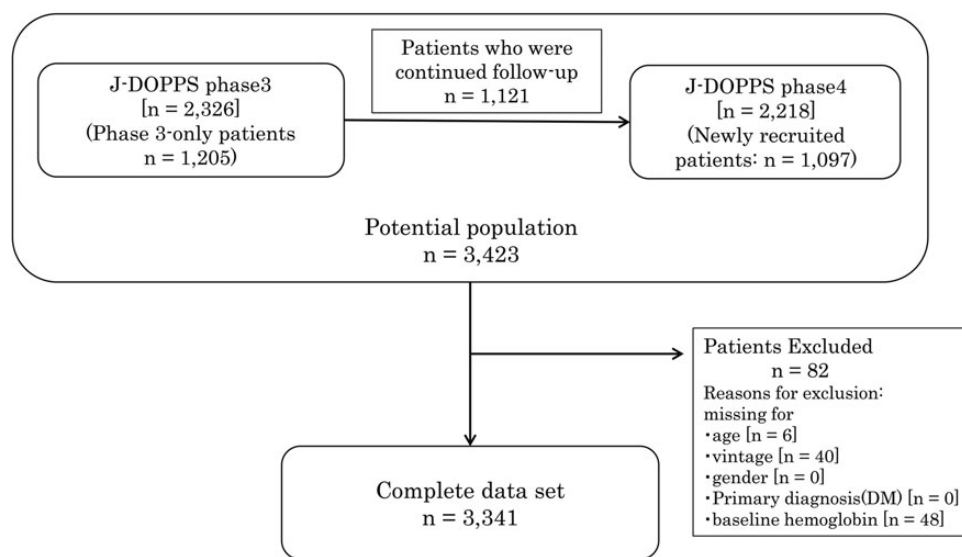
**FIGURE 1:** Flow diagram of the analyzed population. J-DOPPS phases 3 and 4 were potential population for the present study. Among phase 3 patients, 1121 patients were continuously followed-up into the phase 4 period. After exclusion, a complete data set was created for 3341 patients. J-DOPPS: the Japan Dialysis Outcomes and Practice Patterns Study.

**Table 2.** Patient characteristics and baseline data stratified by age

| Variables | All ($n = 3341$) | Nonelderly (<75 years old) ($n = 2651$) | Elderly (≥75 years old) ($n = 690$) |
|---|---|---|---|
| Age (years) | 63.6 ± 12.7 | 59.3 ± 10.4 | 80.1 ± 4.5 |
| Sex (male) (%) | 63.2 | 64.7 | 57.4 |
| Years on dialysis (years) | 5.5 ± 6.8 | 6.0 ± 7.2 | 3.6 ± 4.6 |
| Primary disease (DM) (%) | 33.9 | 34.5 | 31.5 |
| Current smoker (%) | 13.8 | 16.1 | 4.8 |
| Comorbidities (%) | | | |
| Coronary artery disease | 25.5 | 23.2 | 34.5 |
| Cancer, other than skin | 9.5 | 8.1 | 14.8 |
| Other CVD | 24.9 | 22.0 | 36.1 |
| Cerebrovascular disease | 13.4 | 11.9 | 19.1 |
| Congestive heart failure | 19.9 | 18.1 | 27.0 |
| DM | 39.4 | 39.5 | 39.1 |
| Gastrointestinal bleeding | 3.5 | 3.4 | 4.2 |
| HIV | 0.4 | 0.5 | 0.3 |
| Hypertension | 74.0 | 73.6 | 75.5 |
| Lung disease | 3.0 | 2.7 | 4.1 |
| Neurological disorder | 12.4 | 9.7 | 22.5 |
| Psychological disorder | 4.4 | 4.2 | 4.9 |
| Peripheral vascular disease | 14.3 | 13.2 | 18.7 |
| Recurrent cellulitis | 3.7 | 3.7 | 3.5 |
| BMI (kg/m$^2$) | 21.2 ± 3.4 | 21.4 ± 3.4 | 20.4 ± 2.9 |
| Kt/V | 1.30 ± 0.30 | 1.30 ± 0.30 | 1.28 ± 0.29 |
| Adjusted calcium (mg/dL) | 9.20 ± 0.86 | 9.23 ± 0.88 | 9.09 ± 0.79 |
| Serum phosphorus (mg/dL) | 5.43 ± 1.48 | 5.57 ± 1.49 | 4.92 ± 1.34 |
| Albumin (g/mL) | 3.72 ± 0.48 | 3.76 ± 0.47 | 3.55 ± 0.48 |
| C-reactive protein (mg/mL) | 0.13 (0.06, 0.40) | 0.11 (0.05, 0.37) | 0.20 (0.08, 0.68) |
| Total cholesterol (mg/mL) | 157.2 ± 37.5 | 157.8 ± 37.7 | 155.1 ± 36.8 |
| Hb (g/dL) | 10.3 ± 1.3 | 10.4 ± 1.3 | 10.1 ± 1.3 |
| Ferritin (ng/mL) | 247.3 ± 412.7 | 245.8 ± 429.3 | 252.8 ± 346.3 |
| ESA dose (IU/week) | 3868 ± 3483 | 3784 ± 3440 | 4189 ± 3631 |
| ERI [(IU/week · (g/dL)$^{-1}$/kg] | 7.7 (4.5, 13.7) | 7.3 (4.4, 13.1) | 9.1 (5.3, 16.0) |

DM, diabetes mellitus; CVD, cardiovascular disease; HIV, human immunodeficiency virus; BMI, body mass index; Hb, hemoglobin; ESA, erythropoiesis-stimulating agents; ERI, ESA responsiveness index. Values are reported as mean ± SD, percentage or median (inter-quartile range).

**Table 3.** Numbers of death and observed Hb values stratified by Hb groups and age

| | Hb groups | | | | | Total |
|---|---|---|---|---|---|---|
| | Hb <9 g/dL | 9 ≤Hb <10 g/dL | 10 ≤Hb <11 g/dL | 11 ≤Hb <12 g/dL | Hb ≥ 12 g/dL | |
| Nonelderly | 87 (2558) | 75 (5786) | 83 (9445) | 52 (6412) | 38 (2834) | 335 (27 035) |
| Elderly | 57 (685) | 46 (1318) | 69 (1741) | 42 (1057) | 18 (371) | 232 (5172) |

The numbers of death and observed Hb values (included in parentheses) were indicated. Although the observed numbers of Hb values were almost one-fifth in the elderly group, the outcome numbers were moderately balanced across age groups.

### Time-dependent Cox's proportional hazard models

We performed survival analysis treating Hb values measured every 4 months as time-dependent variables, whereas missing values were imputed by means of the LOCF method. Table 6 shows that either Hb <9 g/dL or >12 g/dL was related to poor prognosis after full adjustment.

### Effect of age on the relationship between Hb values and survival

We conducted time-dependent Cox's proportional hazard analyses for the elderly and nonelderly groups (Figure 2A). The type 3 P-value indicating the existence of an interaction was 0.045 for the entire model. Trend analyses within both groups revealed a significant relationship between Hb and survival. In the nonelderly group, high mortality rates were observed either for the Hb <9 g/dL category [hazards ratio (HR) 3.74, 95% confidence interval (CI) 2.75–5.08; reference, 10–11 g/dL Hb] or for the 9–10 g/dL Hb category (HR: 1.46, 95% CI: 1.07–2.00; reference, 10–11 g/dL Hb). On the other hand, in the elderly group, only Hb <9 g/dL category exhibited higher mortality (HR: 1.90, 95% CI: 1.31–2.75; reference, 10–11 g/dL Hb). The interaction of age and Hb was significant for both categories (P = 0.023 and 0.044, <9g/dL and 9–10 g/dL Hb, respectively). Table 7 demonstrates the HR for each covariate.

**Table 4. Causes of death (total events: _n_ = 567)**

| Main causes of death | % (no. of events) |
|---|---|
| Cardiac | 27.3% (155) |
| Vascular | 11.1% (63) |
| Infection | 16.1% (91) |
| Liver disease | 1.2% (7) |
| Gastrointestinal | 2.7% (15) |
| Metabolic | 0.5% (3) |
| Other | 18.7% (106) |
| Unknown | 22.4% (127) |

_Cardiac_: myocardial infarction (acute), pericarditis including cardiac tamponade, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest (cause unknown), valvular heart disease, pulmonary edema due to exogenous fluid. _Vascular_: hemorrhagic stroke, ischemic brain damage, anoxic encephalopathy, hemorrhage from vascular access, other hemorrhage, mesenteric infarction, ischemic bowel. _Infection_: septicemia due to vascular access, peritonitis (complication of peritoneal dialysis), septicemia due to peripheral vascular disease, gangrene, other septicemia, pulmonary infection, other infection. _Liver disease_: liver failure (cause unknown or other), cirrhosis, hepatitis C. _Gastrointestinal_: gastrointestinal hemorrhage, perforation of peptic ulcer. _Metabolic_: hyperkalemia.

**Table 5. Cox proportional hazard models for baseline hemoglobin values (result of multi-imputation analysis)**

| Hb range | Hazard ratio | 95% CI | P-value |
|---|---|---|---|
| Hb <9 g/dL | 1.26 | 0.98–1.63 | 0.076 |
| 9≤ Hb <10 g/dL | 0.85 | 0.67–1.08 | 0.176 |
| 10≤ Hb <11 g/dL | | Reference | |
| 11≤ Hb <12 g/dL | 0.96 | 0.76–1.22 | 0.761 |
| Hb ≥12 g/dL | 1.02 | 0.73–1.43 | 0.919 |

The HR of mortality for patients in each Hb group versus reference was assessed using Cox models adjusted for age, sex, years on dialysis, primary disease (diabetic nephropathy), smoking, 13 comorbidities (coronary artery disease, cancer, other cardiovascular disease, cerebrovascular disease, congestive heart failure, diabetes, gastrointestinal bleeding, hypertension, lung disease, neurological disorder, psychological disorder, peripheral vascular disease and recurrent cellulitis), body mass index, single-pool Kt/V, albumin, C-reactive protein, adjusted Ca, serum P, total cholesterol, ferritin and high-dose erythropoiesis-stimulating agents (≥4500 IU/week). Hb, hemoglobin; 95% CI, 95% confidence interval.

**Table 6. Time-dependent Cox proportional hazard models for LOCF hemoglobin values (result of multi-imputation analysis)**

| Hb range | Hazard ratio | 95% CI | P-value |
|---|---|---|---|
| Hb <9 g/dL | 2.82 | 2.23–3.56 | <0.001 |
| 9≤ Hb <10 g/dL | 1.14 | 0.90–1.45 | 0.287 |
| 10≤ Hb <11 g/dL | | Reference | |
| 11≤ Hb <12 g/dL | 0.99 | 0.77–1.29 | 0.966 |
| Hb ≥12 g/dL | 1.37 | 1.01–1.87 | 0.045 |

The HR of mortality for patients in each Hb group versus reference was assessed using Cox models adjusted for age, sex, years on dialysis, primary disease (diabetic nephropathy), smoking, 13 comorbidities (coronary artery disease, cancer, other cardiovascular disease, cerebrovascular disease, congestive heart failure, diabetes, gastrointestinal bleeding, hypertension, lung disease, neurological disorder, psychological disorder, peripheral vascular disease and recurrent cellulitis), body mass index, single-pool Kt/V, albumin, C-reactive protein, adjusted Ca, serum P, total cholesterol, ferritin and high-dose erythropoiesis-stimulating agents (≥4500 IU/week). LOCF, last observation carried forward; Hb, hemoglobin; 95% CI, 95% confidence interval.

### Sensitivity analyses

**Inverse propensity treatment weighting method adjustment for estimated ESA doses.** We employed the IPTW method as a sensitivity analysis by incorporating the values estimated the propensity for use of epoetin doses of ≥3000 IU/week to build the 'pseudo-population' for adjusting confounding by indication for ESA use. Fitting of the logistic regression models was evaluated by _C_-statistic (0.668–0.674) and Hosmer–Lemeshow's P-value (0.112–0.660). As shown in Figure 2B, time-dependent Cox's proportional hazard models adjusted by IPTW indicated that similar trends in the categories of Hb <10 g/dL in both groups unadjusted by IPTW. The interactions between age and Hb values among the <10 g/dL Hb categories were all significant.

**Effects of cutoff for age.** We performed the same analyses with or without IPTW adjustment for the groups that were divided according to the cutoff age of 70 years. We obtained results similar to what we observed in the aforementioned analyses that used the age of 75 years as the cutoff, although the interaction of age and Hb levels was less pronounced; only the interaction for the <9 g/dL Hb category was significant (data not shown). When we applied 65 years old as the cutoff age, the interaction of age and Hb levels on mortality almost disappeared (data not shown).

**Effect of diabetes.** The interactions were also investigated in population groups that were stratified by whether the patients' primary diagnoses of ESRD were diabetic nephropathy or not.

The analyses, performed using the cutoff age of 75 years and adjusted by IPTW, indicated that there was significant interaction between age and overall Hb only in the nondiabetic nephropathy group (Figure 3A) but not in the diabetic nephropathy group (Figure 3B).

**The effect of anemia therapy including ESA and iron prescription.** We investigated the same analyses only confined in the population who are treated by any doses of ESA. The analysis on such population did not virtually differ from the results of the original analyses (data not shown). The model to which iron prescription was added as a covariate also did not demonstrate significant changes in the results of the trend (data not shown).

## DISCUSSION

There were differences in the effect of Hb on survival between the elderly and nonelderly populations. Nonelderly patients had increased risk if they had Hb <10 g/dL, whereas only for the <9 g/dL Hb category among the elderly population. The present study is the first to demonstrate the direct relationship between age and Hb levels from the viewpoints of mortality.

Many of the existing guidelines [29–32] recommend the same target Hb across all ages. Only the Japanese guideline [33] suggests that a high Hb might be beneficial for young patients with high physical activity.

The current study demonstrated that the relationship between low Hb and poorer survival was lessened in the elderly population.

The reason why low Hb had a weaker link to poorer survival could be related to the reduced activity in the elderly patients. Gait speed or chair-rising time was reportedly slow in
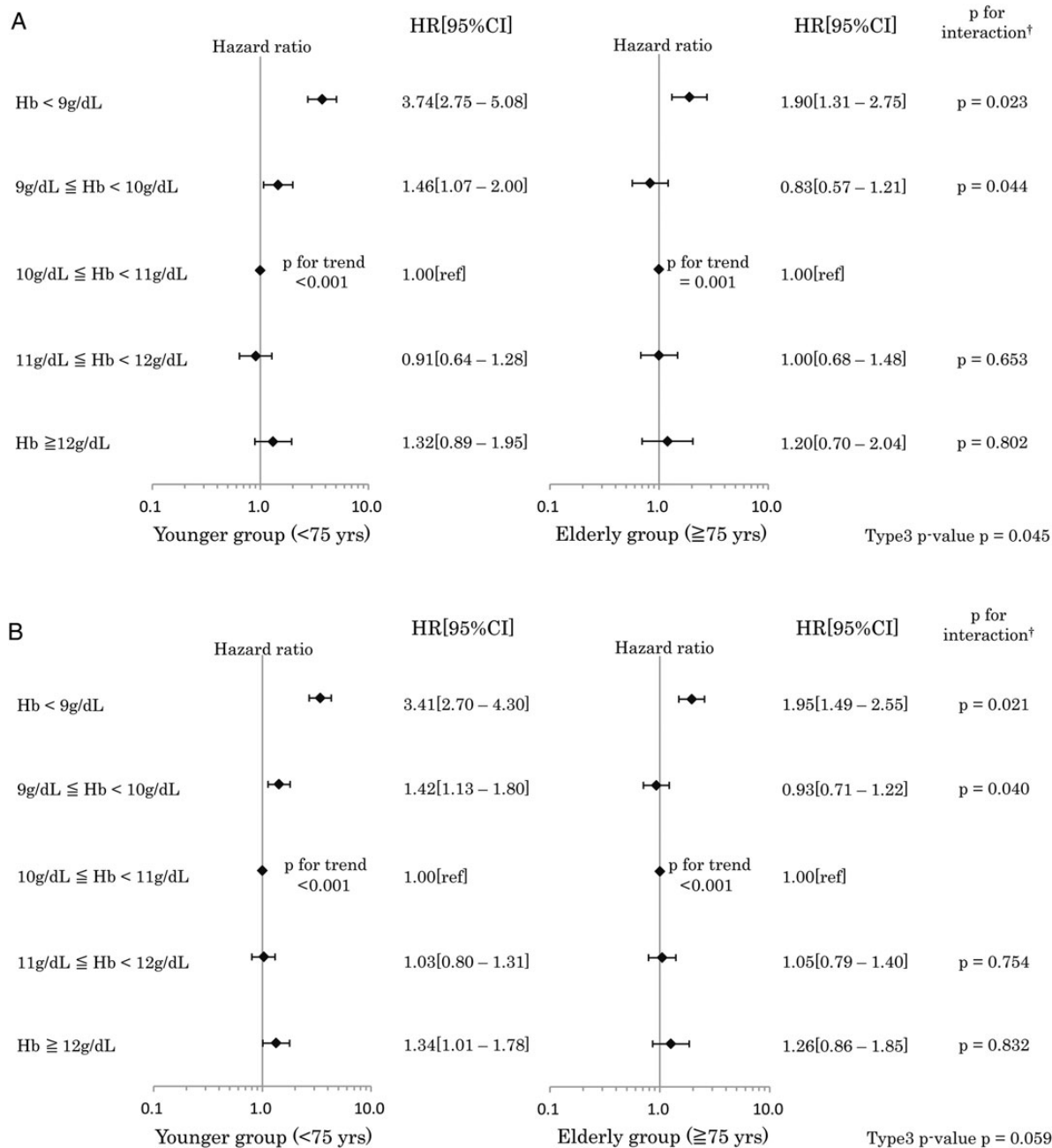
**FIGURE 2:** Effect of age on optimal Hb target ranges (cutoff age: 75 years). The HR of mortality for patients in each Hb group versus reference was assessed using Cox models adjusted for sex, years on dialysis, primary disease (diabetic nephropathy), smoking, 13 comorbidities (coronary artery disease, cancer, other cardiovascular disease, cerebrovascular disease, congestive heart failure, diabetes, gastrointestinal bleeding, hypertension, lung disease, neurologic disorder, psychological disorder, peripheral vascular disease and recurrent cellulitis), body mass index, single-pool Kt/V, albumin, C-reactive protein, adjusted Ca, serum P, total cholesterol, ferritin and epoetin dose of ≥4500 IU/week without (**A**) or with (**B**) inverse propensity treatment weighting. P for trend indicates the significance across Hb strata within each age group, whereas P for interaction indicates the significance between both age groups in each Hb strata. Hb, hemoglobin; HR, hazard ratio; 95% CI, 95% confidence interval.

the elderly HD population [34]. Oxygen consumption in the elderly population is reported to be lower than that in the younger people [35], as well as exercise capacity measured by peak exercise oxygen uptake [36]. The sedentary characteristics of this population [37] might be permissive of the reduced oxygen delivery due to low Hb levels. On the other hand, decreased physical activity itself can be related to poorer prognosis [38, 39]. Therefore, the exact reasons require further

considerations or investigations. The results of ESA responsiveness indicated that patients with lower Hb levels required relatively higher doses of ESA to maintain Hb levels, which suggested that such patients might have higher ESA resistance compared with those with higher Hb levels. This might offer a clue for elucidating the causes of differences.

The interaction of Hb and age on mortality was observed only in a time-variable model not in a baseline model. We

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**Table 7. Complete results of Cox's proportional hazard models**

| Variables | Nonelderly(<75 years) | | | Elderly(≥75 years) | | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95% CI | P-value | Hazard ratio | 95% CI | P-value |
| Hemoglobin (g/dL) | | | | | | |
| <9 | 3.74 | 2.75–5.08 | <0.001 | 1.90 | 1.31–2.75 | <0.001 |
| ≥9 and <10 | 1.46 | 1.07–2.00 | 0.018 | 0.83 | 0.57–1.21 | 0.337 |
| ≥10 and <11 | Ref. | | | Ref. | | |
| ≥11 and <12 | 0.91 | 0.64–1.28 | 0.581 | 1.00 | 0.68–1.48 | 0.991 |
| ≥12 | 1.32 | 0.89–1.95 | 0.168 | 1.20 | 0.70–2.04 | 0.508 |
| Vintage (per 1 year) | 1.05 | 1.03–1.07 | <0.001 | 1.00 | 0.97–1.03 | 0.913 |
| Gender (female versus male) | 0.60 | 0.45–0.81 | <0.001 | 1.21 | 0.86–1.69 | 0.278 |
| Primary cause of ESRD (DMN versus non-DMN) | 1.11 | 0.73–1.70 | 0.625 | 0.84 | 0.52–1.35 | 0.473 |
| Smoking status | | | | | | |
| Active smoker | 1.01 | 0.73–1.41 | 0.947 | 2.07 | 1.11–3.87 | 0.022 |
| Ex-smoker <1 year | 1.73 | 1.01–2.96 | 0.046 | 0.77 | 0.23–2.58 | 0.677 |
| Ex-smoker >1 year | 1.26 | 0.89–1.78 | 0.191 | 1.45 | 0.93–2.27 | 0.100 |
| Never smoker | Ref. | | | Ref. | | |
| Current status unknown | 1.17 | 0.36–3.76 | 0.792 | 4.28 | 1.40–13.09 | 0.011 |
| Unknown | 1.16 | 0.86–1.57 | 0.332 | 1.41 | 0.98–2.03 | 0.065 |
| Presence of each comorbidity | | | | | | |
| Coronary artery disease | 1.01 | 0.78–1.31 | 0.952 | 1.12 | 0.83–1.52 | 0.458 |
| Cancer, other than skin | 1.30 | 0.91–1.85 | 0.150 | 0.80 | 0.54–1.20 | 0.285 |
| Other CVD | 1.33 | 1.03–1.70 | 0.028 | 1.22 | 0.91–1.64 | 0.189 |
| Cerebrovascular disease | 1.78 | 1.33–2.36 | <0.001 | 1.02 | 0.71–1.47 | 0.898 |
| Congestive heart failure | 1.35 | 1.03–1.77 | 0.031 | 1.25 | 0.91–1.73 | 0.171 |
| Diabetes mellitus | 1.97 | 1.26–3.06 | 0.003 | 1.43 | 0.90–2.25 | 0.129 |
| Gastrointestinal bleeding | 0.90 | 0.52–1.53 | 0.687 | 0.68 | 0.35–1.33 | 0.258 |
| Hypertension | 1.02 | 0.79–1.34 | 0.863 | 0.70 | 0.52–0.94 | 0.019 |
| Lung disease | 1.07 | 0.60–1.90 | 0.824 | 1.23 | 0.66–2.28 | 0.516 |
| Neurological disorder | 1.50 | 1.11–2.02 | 0.009 | 1.60 | 1.15–2.23 | 0.005 |
| Psychological disorder | 1.31 | 0.82–2.09 | 0.267 | 1.18 | 0.62–2.25 | 0.614 |
| Peripheral vascular disease | 1.27 | 0.94–1.71 | 0.116 | 1.07 | 0.74–1.55 | 0.725 |
| Recurrent cellulitis | 1.42 | 0.92–2.21 | 0.115 | 1.25 | 0.61–2.55 | 0.542 |
| Body mass index (kg/m$^2$) | | | | | | |
| <19.64 | Ref. | | | Ref. | | |
| ≥19.64 and <22.27 | 0.74 | 0.56–0.98 | 0.034 | 0.74 | 0.52–1.06 | 0.098 |
| ≥22.27 | 0.74 | 0.55–0.99 | 0.045 | 0.58 | 0.37–0.90 | 0.015 |
| Kt/V | | | | | | |
| <1.163 | Ref. | | | Ref. | | |
| ≥1.163 and <1.411 | 0.87 | 0.64–1.17 | 0.349 | 1.10 | 0.73–1.66 | 0.640 |
| ≥1.411 | 0.94 | 0.66–1.36 | 0.749 | 0.97 | 0.64–1.46 | 0.876 |
| Albumin (g/dL) | | | | | | |
| <3.60 | Ref. | | | Ref. | | |
| ≥3.60 and <3.90 | 0.72 | 0.55–0.95 | 0.019 | 0.74 | 0.53–1.03 | 0.070 |
| ≥3.90 | 0.63 | 0.46–0.85 | 0.002 | 0.92 | 0.59–1.42 | 0.690 |
| Albumin corrected calcium (mg/dL) | | | | | | |
| <8.80 | Ref. | | | Ref. | | |
| ≥8.80 and <9.50 | 1.07 | 0.79–1.45 | 0.646 | 1.40 | 0.97–2.01 | 0.072 |
| ≥9.50 | 1.00 | 0.74–1.37 | 0.992 | 1.71 | 1.17–2.49 | 0.006 |
| Serum phosphate (mg/dL) | | | | | | |
| <4.70 | Ref. | | | Ref. | | |
| ≥4.70 and <5.90 | 0.95 | 0.71–1.26 | 0.707 | 0.88 | 0.64–1.20 | 0.417 |
| ≥5.90 | 1.18 | 0.89–1.56 | 0.247 | 0.84 | 0.57–1.23 | 0.361 |
| C-reactive protein (mg/dL) | | | | | | |
| <0.100 | Ref. | | | Ref. | | |
| ≥0.100 and <0.320 | 1.51 | 1.11–2.05 | 0.008 | 1.33 | 0.88–2.01 | 0.169 |
| ≥0.320 | 1.46 | 1.04–2.06 | 0.031 | 1.91 | 1.23–2.95 | 0.004 |
| Total cholesterol (mg/dL) | | | | | | |
| <139.0 | Ref. | | | Ref. | | |
| ≥139.0 and <170.0 | 1.00 | 0.75–1.34 | 0.984 | 0.89 | 0.63–1.26 | 0.508 |
| ≥170.0 | 0.83 | 0.62–1.11 | 0.206 | 0.78 | 0.53–1.16 | 0.221 |
| Ferritin (ng/mL) | | | | | | |
| <69.6 | Ref. | | | Ref. | | |
| ≥69.4 and <259.5 | 1.02 | 0.73–1.43 | 0.910 | 0.95 | 0.65–1.39 | 0.805 |
| ≥259.5 | 1.12 | 0.74–1.70 | 0.577 | 1.29 | 0.87–1.90 | 0.203 |
| Epoetin ≥3000 IU/week (versus <3000 IU/week) | 1.09 | 0.85–1.38 | 0.503 | 1.18 | 0.87–1.59 | 0.291 |

CVD, cardiovascular diseases; DMN, diabetic nephropathy; Ref, reference group. HRs for all covariates were demonstrated. Several factors related to survival either positively or negatively within each age stratum. We should be cautious to interpret the data, because we did not investigate the interaction between each variable and age groups. CI, confidence interval; ESRD, end-stage renal disease; DMN, diabetic nephropathy; CVD, cardiovascular diseases; Ref., reference group.
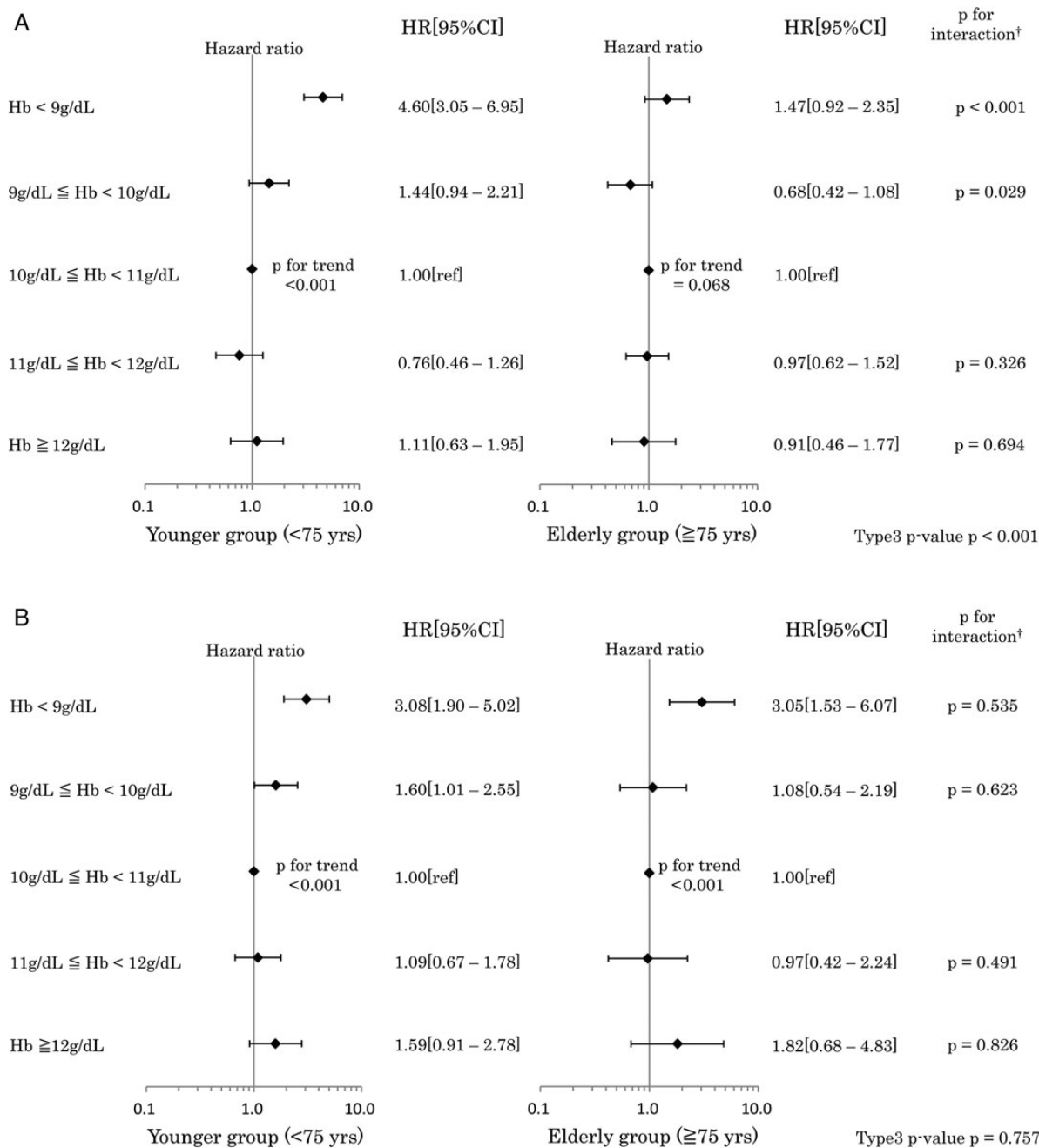
**FIGURE 3:** Analyses stratified by the primary diagnosis of diabetic nephropathy were performed for the groups where the cutoff age was 75 years. (**A**) Analyses for patients without diabetic nephropathy; (**B**) analyses for patients with diabetic nephropathy. The HR of mortality for patients in each Hb group versus reference was assessed using Cox models adjusted for sex, years on dialysis, smoking, 13 comorbidities (coronary artery disease, cancer, other cardiovascular disease, cerebrovascular disease, congestive heart failure, diabetes, gastrointestinal bleeding, hypertension, lung disease, neurological disorder, psychological disorder, peripheral vascular disease and recurrent cellulitis), body mass index, single-pool Kt/V, albumin, C-reactive protein, adjusted Ca, serum P, total cholesterol, ferritin and epoetin dose of ≥4500 IU/week with inverse propensity treatment weighting. P for trend indicates the significance across Hb strata within each age group, whereas P for interaction indicates the significance between both age groups in each Hb strata. Hb, hemoglobin; HR, hazard ratio; 95% CI, 95% confidence interval.

consider that there are two reasons for this. The first is the increased statistical power; the numbers of exposure increased markedly in a time-dependent model. The second is, more importantly, that trend of Hb but not single measurement is more predicable for prognosis. A *post hoc* analysis of NHCT study indicated that the changes in Hb levels are greater (especially, Hb fall) before the cardiovascular events occurred [40].

Therefore, the time-dependent models can more precisely capture even a subtle change of Hb levels that might affect prognosis.

In this study, we employed the IPTW method to adjust the factor that the prescribed ESA doses were appropriate or not with characteristics of each patient taken into account. Therefore, we can partly adjust practice pattern about ESA prescription as

well as the background of each patient including ESA dose itself by the IPTW method. The fact that the result did not change even after such adjustment reinforce the robustness of the results of this study.

We also investigated the effect of other anemia therapies. Of these, iron use can relate to the mortality in patients with higher Hb levels [41]. However, both ESA use and iron prescription status did not change the results. Therefore, we can deduce that anemia treatment itself did not affect the interaction of age and Hb levels on mortality, with the results of IPTW taken together.

The interaction between age and Hb levels was lost in the diabetic nephropathy population. This might indicate that diabetic nephropathy patients uniformly experience poorer prognosis irrespective of age or Hb levels. Inaba et al. [42] demonstrated that high hematocrit (Ht) values related to better survival only among nondiabetic nephropathy patients but not among diabetic nephropathy patients although another study reported that such interaction was not observed [43]. The current report shares the evidence with the study reported by Inaba et al.

Naturally occurring higher Hb was reported not to increase mortality [44]. In this study, patients with high Hb values had lower ESA dose as well as ESA responsiveness index values. This might partly be accounted for by the fact that the mortality risks were not significantly higher among the Hb group larger than 12 g/dL except for the results for the younger group by IPTW adjustment.

This study has several limitations. The first is its observational nature. Therefore, the results do not add information on the cause-and-effect relationship between Hb values themselves and prognosis.

The second limitation is the residual effect of unmeasured or measured but excluded confounders. The degree to which the actual delivered doses of ESA could be predicted from clinical values was only 15% (data not shown) in this population. This indicated the existence of uncollected or misclassified clinical conditions, especially differences in the practice pattern of each facility. However, DOPPS collected extremely detailed clinical data. We also attempted to adjust for confounders as extensively as possible, including by means of IPTW methods. In fact, we obtained a significant relationship instead of a null result. Therefore, we believe in the statistical power of this study.

The third limitation was the low mortality rate even in the elderly group. We obviated the reduced power of the present study in two ways. One was the target population, which comprised a combined J-DOPPS phase 3 and 4 population. The other was our use of time-dependent analyses, which increased the sample number of Hb values in the investigated population.

The fourth limitation was the fact that the statistical power might not be sufficient among the patients older than 75 years, which accounted for one-fifth of the entire population. This could be one of the reasons why the relationship between several Hb groups and mortality among the elderly group was not significant. However, the numbers of death were moderately balanced across the groups (Table 3), which could maximize the statistical power of this study.

The fifth limitation was that the target population was limited to the Japanese HD population. Further studies might be required for different countries.

The last limitation is the heterogeneity of the elderly population. The present study treated the elderly and nonelderly populations as a whole. However, clinical common sense suggests that there is a wide variety of patient characteristics in terms of nutrition, physical activity and frailty [45]. Although some of these factors have been adjusted by covariates, some remained unadjusted or were even not investigated. Therefore, the heterogeneities should be considered when applying the present data to the actual population.

## CONCLUSIONS

The relationship between Hb levels and survival might differ according to age. Lower Hb levels did not relate to poor prognosis among the elderly population. This reinforces the need for individualizations of anemia management.

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