

# The Association of Visual Impairment With Clinical Outcomes in Hemodialysis Patients

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**Abstract:** Visual impairment limits people's ability to perform daily tasks and affects their quality of life. We evaluated the impact of visual impairment on clinical outcomes in hemodialysis (HD) patients.

HD patients were selected from the Clinical Research Center registry a prospective cohort study on dialysis patients in Korea. Visual impairment was defined as difficulty in daily life due to decreased visual acuity or blindness. The primary outcome was all-cause mortality and the secondary outcomes were cardiovascular and infection-related hospitalization.

A total of 3250 patients were included. Seven hundred thirty (22.5%) of the enrolled patients had visual impairment. The median follow-up period was 30 months. The Kaplan–Meier curve and log-rank test showed that all-cause mortality rates ( $P < 0.001$ ) as well as cardiovascular and infection-related hospitalization rates ( $P < 0.001$  and  $P < 0.001$ ) were significantly higher in patients with visual impairment than in patients without visual impairment. In the multivariable analysis, visual impairment had significant predictive power for all-cause mortality (Hazard ratio [HR], 1.77, 95% confidence interval [CI], 1.21–2.61,  $P = 0.004$ ) and cardiovascular hospitalization (HR 1.45 [1.00–1.90],  $P = 0.008$ ) after adjusting for confounding variables. Of these 3250 patients, 634 patients from each group were matched by propensity scores. In the propensity score matched analysis, patients

with visual impairment had independently significant associations with increased all-cause mortality (HR 1.69 [1.12–2.54],  $P = 0.01$ ) and cardiovascular hospitalization (HR 1.48 [1.08–2.02],  $P = 0.01$ ) compared with patients without visual impairment after adjustment for confounding variables.

Our data demonstrated that visual impairment was an independent risk factor for clinical adverse outcomes in HD patients.

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**Abbreviations:** ACEi = angiotensin-converting enzyme inhibitor, AMD = age-related macular degeneration, ARB = angiotensin receptor blocker, BMI = body mass index, BP = blood pressure, CI = confidence interval, CKD = chronic kidney disease, CRC = Clinical Research Center, DM = diabetes mellitus, DR = diabetic retinopathy, ESRD = end-stage renal disease, GN = glomerulonephritis, HD = hemodialysis, HR = hazard ratio, hs-CRP = high-sensitivity C-reactive protein, iPTH = intact parathyroid hormone, K = dialyzer clearance, LDL = low-density lipoprotein, SD = standard deviation,  $spKt/V$  = single-pool  $Kt/V$ ,  $t$  = time,  $V$  = volume of water a patient's body contains, VI = visual impairment.

## INTRODUCTION

Visual impairment has long been recognized as an important factor in the aging process, and there is growing awareness of its influence on health and functional status.<sup>1</sup> Visual impairment often limits people's ability to perform daily tasks and affects their quality of life.<sup>2–4</sup> In addition to causing morbidity, recent studies have shown that visual impairment has a prognostic value as an independent predictor of cardiovascular disease and all-cause mortality in the elderly as well as the general population.<sup>5–7</sup>

Chronic kidney disease (CKD) patients receiving dialysis have higher mortality and morbidity compared to the general population: cardiovascular mortality rates are 10- to 20-fold higher,<sup>8</sup> and mortality rates from infection are up to 30-fold higher.<sup>9</sup> CKD is strongly associated with various major ocular diseases such as age-related macular degeneration (AMD), glaucoma, cataract, and diabetic retinopathy (DR).<sup>10</sup> This close association between CKD and major ocular diseases is attributed to the share of common risk factors such as age, and metabolic and vascular risk factors, for example diabetes mellitus (DM), hypertension, and smoking. The major mechanisms of the development and progression of CKD are atherosclerosis, vascular remodeling, endothelial dysfunction, inflammation, and oxidative stress; these mechanisms are also applied to various ocular diseases.<sup>10</sup>

We hypothesized that the prevalence of visual impairment would be relatively high and visual impairment would be associated with increased mortality and hospitalization in hemodialysis (HD) patients. However, the available data on this issue was limited. The present study investigated the

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association of visual impairment and clinical outcomes in HD patients using data from the Clinical Research Center (CRC) registry for end-stage renal disease (ESRD) cohort in Korea.

## PATIENTS AND METHODS

### Study Population

All patients in this study participated in the CRC registry for ESRD. The CRC registry for ESRD is an observational prospective cohort performed in patients with ESRD from 31 medical centers in Korea (Supplement 1, <http://links.lww.com/MD/A951>). This cohort study started in April 2009 and was followed up to July 2014. The enrolled criteria were patients >18 years of age undergoing HD. A total of 3329 patients undergoing HD were enrolled from April 2009 to May 2014. We excluded patients for who did not answer the questionnaire about visual impairment ( $n=79$ ). Demographic and clinical data were collected at the time of study enrollment. The research protocol was approved by the institutional review board at each center and performed in accordance to the Declaration of Helsinki, and all participants provided informed consent.

### Baseline Assessment

Baseline demographic and clinical data were collected from the clinical chart and patient medical history. Age, sex, body mass index (BMI), smoking, systolic and diastolic blood pressures (BP), left ventricular hypertrophy on electrocardiogram, comorbidities, causes of ESRD, duration of dialysis, health insurance, education, HD adequacy, laboratory investigations, and therapeutic characteristics were recorded. Cardiovascular disease was defined as one or more of presence of coronary heart disease, congestive heart failure, peripheral vascular disease, and cerebrovascular disease. HD adequacy was defined as single-pool  $Kt/V$  ( $spKt/V$ ). The single-pool  $Kt/V$  was determined by a 2-point urea modeling based on the intradialytic reduction in blood urea and intradialytic weight loss. Detailed data on antihypertensive medication such as angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), and  $\beta$ -blockers were recorded in the clinical chart. Serum levels of hemoglobin, creatinine, albumin, corrected calcium, phosphorus, lipid profiles, intact parathyroid hormone (iPTH), HbA1c, and high-sensitivity C-reactive protein (hs-CRP) were determined from blood samples.

### Assessment of Visual impairment

Patients' vision was assessed by a question "Is your vision good enough to see objects and read regular print (with or without glasses)." Participants were asked a questionnaire for visual impairment. Their answers were divided into a 3-category visual impairment status variable: category 1, no difficulty seeing; 2, some difficulty seeing, can read and write regular print; can recognize objects to drive; 3, Blind, unable to read/write/drive. Because only 74 patients and 2.3% of all participants belonged to the "Blind" group, category 3 "Blind" was pooled together with "some difficulty seeing" to form the group "visual impairment," resulting in a 2-category determined visual impairment measure: no visual impairment versus visual impairment.

### Clinical Outcomes

The primary outcome measure was all-cause mortality, and the secondary outcomes were cardiovascular and infection-related hospitalization. All participants were followed until

death or until the research terminated. Deaths and hospitalization events during the study were reported to study investigators, who identified the causes of death and hospitalization according to the research classification system at the each clinical center.

### Statistical Analysis

Continuous variables were presented as the mean  $\pm$  standard deviation (SD) or the median with interquartile ranges, as appropriate. Categorical variables were presented as numbers with percentages. Differences between 2 groups were analyzed by Student's  $t$  test for continuous nonparametric variables and by Pearson's chi-square test for categorical variables. The univariable and multivariable logistic regression analyses were used to assess clinical factors associated with visual impairment in HD patients.

As patients in this study were not randomly assigned according to visual impairment, we used the propensity score to reduce potential confounding and selection biases. Propensity scores were calculated using the multivariable logistic regression to estimated probability of using no visual impairment versus visual impairment. The covariates of age, DM, and cardiovascular disease were included in the propensity score model. Propensity scores were then used to match patients without visual impairment to patients with visual impairment using a greedy nearest-neighbor matching algorithm. A one-to-one propensity score matching analysis with preset caliper width was performed. Patients without a corresponding match were excluded. We analyzed all available data without imputation of missing values. The area under the receiver operating characteristic curve was 0.67, and the Hosmer Lemeshow goodness for this model was 9.72 ( $P=0.28$ ). Propensity score matching was performed with SAS (version 9.2, SAS Inc., Cary, NC). After matching, demographic data were compared using the Wilcoxon signed rank test for continuous variables and the McNemar test for categorical variables.

The absolute mortality rate was presented per 100 person-years of follow up. Survival curve for visual impairment was estimated by the Kaplan–Meier method and test of significance for survival curve was assessed by the log-rank test. The hazard ratio (HR) with 95% confidence intervals (CI) for all-cause mortality and cardiovascular or infection-related hospitalization according to visual impairment were calculated by the Cox proportional hazard regression analysis before and after propensity score matching. Before propensity score matching, model 1 was adjusted for age and sex, and model 2 was adjusted for age, sex, BMI, systolic and diastolic BP, smoking, DM, cardiovascular disease, education, health insurance, duration of dialysis, the use of ACEi or ARB, the use of  $\beta$ -blocker, left ventricular hypertrophy on electrocardiogram, serum creatinine, serum albumin, total cholesterol, iPTH, HbA1c and  $spKt/V$ . After propensity score matching, model 1 was adjusted for age and sex, and model 2 was adjusted for age, sex, DM, cardiovascular disease, education, health insurance, duration of dialysis, the use of ACEi or ARB, left ventricular hypertrophy on electrocardiogram, serum creatinine, serum albumin, and HbA1c. All statistical analyses were performed using SPSS 20.0 software (IBM Corp., Armonk, NY). A value of  $P < 0.05$  was considered as statistical significance.

## RESULTS

### Patient Characteristics

A total of 3250 HD patients were enrolled into this study. The baseline characteristics of the study population segregated

by visual acuity before and after propensity score matching are shown in Table 1. Seven hundred thirty patients (22.5%) had visual impairment. Patients with visual impairment were significantly older than patients without visual impairment. Among causes of ESRD, diabetic renal disease was more common in patients with visual impairment than in those without visual impairment. "Others/unknown" was composed of unknown cause (88.2%, 1028/1173), graft failure (6.0%, 69/1173), and others. "Others" was composed of renovascular disease, interstitial nephritis, acquired obstructive uropathy, chronic pyelonephritis, gouty nephropathy, urolithiasis, hereditary disease including Alport's syndrome, and cast nephropathy. Patients with visual impairment had a higher prevalence of DM and cardiovascular disease than patients without visual impairment. Sex, BMI, smoking, duration of dialysis, left ventricular hypertrophy on electrocardiogram, hemoglobin, corrected calcium, phosphorus, triglyceride, low-density lipoprotein (LDL)-cholesterol, hs-CRP levels, and HD adequacy were not significantly different between patients without visual impairment and those with visual impairment. There was no difference in the use of  $\beta$ -blocker at the time of enrollment between the 2 groups. Patients with visual impairment had higher systolic BP and iPTH levels and lower diastolic BP, serum albumin, and total cholesterol than patients without visual impairment. The use of ACEi or ARB and the proportion of Medicaid were significantly higher in patients with visual impairment than patients without visual impairment. The proportion of higher education was significantly higher in patients without visual impairment than patients with visual impairment. Following propensity score matching, standardized mean difference were calculated within 0.2, except BMI and health insurance, between 2 groups.

### Clinical Factors Influencing Visual Impairment in Hemodialysis Patients

Table 2 shows the clinical and laboratory risk factors influencing visual impairment in HD patients. In the univariable analysis, age, systolic and diastolic BP, DM, cardiovascular disease, serum creatinine, serum albumin, serum phosphorus, total cholesterol and iPTH, health insurance, and education status significantly influenced visual impairment in HD patients. In the multivariable logistic analysis, the comorbid condition of DM was the most significant risk factor for visual impairment (odds ratio [OR] 2.777, 95% confidence interval [CI] 2.170–3.553,  $P < 0.001$ ). Age, cardiovascular disease, and health insurance were also significant clinical factors affecting visual impairment (OR 1.215; 95% CI 1.099–1.344,  $P < 0.001$ , OR 1.289; 95% CI 1.015–1.637,  $P = 0.04$ , OR 0.628; 95% CI 0.496–0.795,  $P < 0.001$ , respectively). Lower education levels were independently associated with visual impairment ( $P < 0.001$ ).

### Effect of Visual impairment on All-cause mortality

The median follow-up period was 30 months (interquartile range: 12–47 months). Two hundred ninety-three deaths were recorded during the study period and the absolute mortality rate was 3.7 deaths per 100 person-years. During follow-up, 956 patients withdrew from the study for reasons other than death (32.3% of all patients). The reasons for censoring data included kidney transplantation (196, 20.5% of all withdrawals), transfer to a nonparticipating hospital (423, 44.2% of all withdrawals), refusal to participate further (150, 15.6% of all withdrawal), and

other causes (187, 19.6% of all withdrawals). The leading causes of death were cardiovascular (36.7% of all deaths) and infection-related disease (26.6% of all deaths). There were no significant differences in the distribution of causes of death between 2 groups (Table 3,  $P = 0.708$ ). Figure 1 depicts the Kaplan–Meier curve for all-cause mortality as visual impairment. As shown, all-cause mortality was significantly increased in patients with visual impairment compared with in patients without visual impairment ( $P < 0.001$ , by the log-rank test).

Table 4 shows the univariable and multivariable Cox regression analyses for all-cause mortality according to visual impairment. In the crude model, the HR for all-cause mortality of patients with visual impairment was 1.96 (95% CI, 1.54–2.48,  $P < 0.001$ ) when patients without visual impairment were used as the reference category. In the multivariable analysis, patients with visual impairment had an independently significant association with increased all-cause mortality compared with patients without visual impairment in model 1 (HR 1.67, 95% CI, 1.31–2.12,  $P < 0.001$ ) and model 2 (HR 1.77, 95% CI, 1.21–2.61,  $P = 0.004$ ) after adjustment for age and sex, BMI, systolic and diastolic BP, DM, cardiovascular disease, smoking, health insurance, education, duration of dialysis, the use of ACEi or ARB, the use of  $\beta$ -blocker, left ventricular hypertrophy on electrocardiogram, serum creatinine, serum albumin, total cholesterol, serum iPTH, HbA1c, and  $\text{spKt/V}$ .

Of the 3250 patients, 634 patients without visual impairment were matched with 634 patients with visual impairment. In the propensity score-matched analysis, patients with visual impairment had a significantly higher risk of all-cause mortality compared with patients without visual impairment in crude model (HR 1.72, 95% CI, 1.21–2.45,  $P = 0.003$ ), model 1 (HR 1.71, 95% CI, 1.21–2.44,  $P = 0.003$ ) and model 2 (HR 1.69, 95% CI, 1.12–2.54,  $P = 0.01$ ) even after adjusting for sex, DM, cardiovascular disease, health insurance, education, duration of dialysis, the use of ACEi or ARB, left ventricular hypertrophy on electrocardiogram, serum creatinine, serum albumin, and HbA1c.

### Subgroup Analysis of All-Cause Mortality by Risk Factors According to Visual Impairment

Subgroup analysis associations between visual impairment and all-cause mortality in various subgroups of patients are displayed in Figure 2. In subgroup analyses, there were no significant interactions between visual impairment and sex, BMI, serum albumin, total cholesterol, serum iPTH and the use of ACEi or ARB in all-cause mortality. However, there was a tendency for significant interactions to exist between visual impairment and age ( $< 65$  or  $\geq 65$  year,  $P$  for interaction  $< 0.001$ ), DM ( $P$  for interaction = 0.001), and cardiovascular disease (CVD,  $P$  for interaction  $< 0.001$ ). The HR of all-cause mortality was significantly higher in the non-DM and non-CVD group than in DM and CVD groups and was substantially lower in patients  $> 65$  years compared with those 65 years and younger.

### Effect of Visual impairment on Cardiovascular and Infection-related Hospitalization

During follow-up, a total of 1436 hospitalization events were recorded, and cardiovascular (325, 22.5% of all hospitalization) and infection-related hospitalization (331, 23.0% of all hospitalization) were the common causes of hospitalization. The mean durations of hospitalization were  $10.6 \pm 16.2$  days in cardiovascular disease and  $20.9 \pm 30.2$  days in infection-related

TABLE 1. Baseline Characteristics of the Study Population According to Visual Impairment Before and After Propensity Score Matching

|                                 | Before Propensity Score Matching |                    |                    |        | After Propensity Score Matching |                    |                    |        |
|---------------------------------|----------------------------------|--------------------|--------------------|--------|---------------------------------|--------------------|--------------------|--------|
|                                 | Total (n = 3250)                 | No VI (n = 2520)   | VI (n = 730)       | P      | Total (n = 1268)                | No VI (n = 634)    | VI (n = 634)       | P      |
| Age                             | 58.3 ± 13.6                      | 57.2 ± 13.9        | 62.0 ± 12.0        | <0.001 | 61.9 ± 11.7                     | 61.8 ± 11.6        | 61.9 ± 11.9        | 0.70   |
| Sex (male), n (%)               | 1928 (59.3)                      | 1516 (60.2)        | 412 (56.4)         | 0.07   | 751 (59.2)                      | 393 (62.0)         | 358 (56.5)         | 0.04   |
| BMI                             | 22.7 ± 3.4                       | 22.7 ± 3.5         | 22.5 ± 3.2         | 0.22   | 23.0 ± 3.5                      | 23.4 ± 3.7         | 22.5 ± 3.2         | <0.001 |
| Smoking (nonsmoker), n (%)      | 1853 (57.0)                      | 1435 (57.4)        | 418 (57.3)         | 0.90   | 707 (55.8)                      | 350 (55.2)         | 357 (56.3)         | 0.68   |
| DM, n (%)                       | 1475 (53.1)                      | 1010 (47.3)        | 465 (72.5)         | <0.001 | 926 (73.0)                      | 464 (72.9)         | 462 (72.9)         | 0.007  |
| Cardiovascular disease, n (%)   | 789 (24.3)                       | 554 (26.6)         | 235 (36.8)         | <0.001 | 461 (36.4)                      | 229 (36.1)         | 232 (36.6)         | 0.69   |
| Insurance                       |                                  |                    |                    | <0.001 |                                 |                    |                    | <0.001 |
| Medicaid, n (%)                 | 1164 (35.8)                      | 855 (33.9)         | 309 (42.3)         |        | 426 (33.7)                      | 167 (26.4)         | 259 (40.9)         |        |
| NHI, n (%)                      | 2071 (63.7)                      | 1650 (65.5)        | 421 (57.7)         |        | 840 (66.4)                      | 465 (73.6)         | 375 (59.6)         |        |
| Education                       |                                  |                    |                    | <0.001 |                                 |                    |                    | 0.24   |
| Uneducated, n (%)               | 145 (4.7)                        | 98 (4.1)           | 47 (6.7)           |        | 69 (5.7)                        | 29 (4.8)           | 40 (6.6)           |        |
| Primary education, n (%)        | 528 (16.9)                       | 363 (15.0)         | 165 (23.6)         |        | 266 (22.0)                      | 126 (20.8)         | 140 (23.2)         |        |
| Secondary education, n (%)      | 1646 (52.8)                      | 1294 (53.5)        | 352 (50.4)         |        | 625 (51.7)                      | 316 (52.1)         | 309 (51.2)         |        |
| Tertiary education, n (%)       | 797 (25.6)                       | 663 (27.4)         | 134 (19.2)         |        | 250 (20.7)                      | 135 (22.3)         | 115 (19.0)         |        |
| Cause of ESRD, n (%)            |                                  |                    |                    | <0.001 |                                 |                    |                    | 0.002  |
| DM                              | 1588 (48.9)                      | 1066 (42.3)        | 522 (71.5)         |        | 861 (67.9)                      | 414 (65.3)         | 447 (70.5)         |        |
| GN                              | 404 (12.4)                       | 358 (14.2)         | 46 (6.3)           |        | 71 (5.6)                        | 33 (5.2)           | 38 (5.9)           |        |
| PCKD                            | 85 (2.6)                         | 74 (2.9)           | 11 (1.5)           |        | 21 (1.7)                        | 10 (1.6)           | 10 (1.6)           |        |
| Others/Unknown                  | 1173 (36.1)                      | 1022 (40.6)        | 151 (20.7)         |        | 315 (24.8)                      | 176 (27.8)         | 139 (21.9)         |        |
| Duration of dialysis (months)   | 25.6 ± 44.1                      | 25.8 ± 45.3        | 25.0 ± 39.8        | 0.67   | 19.0 ± 35.1                     | 15.6 ± 32.3        | 22.5 ± 37.3        | 0.001  |
| Systolic BP (mm Hg)             | 142.4 ± 22.2                     | 141.9 ± 21.8       | 144.0 ± 23.4       | 0.04   | 143.9 ± 22.9                    | 144.0 ± 22.0       | 143.8 ± 23.8       | 0.88   |
| Diastolic BP (mm Hg)            | 77.3 ± 13.4                      | 77.8 ± 13.3        | 75.4 ± 13.7        | <0.001 | 75.3 ± 13.6                     | 75.5 ± 13.4        | 75.1 ± 13.8        | 0.72   |
| LVH on ECG, n (%)               | 822 (30.9)                       | 611 (30.0)         | 211 (33.8)         | 0.08   | 305 (29.3)                      | 126 (25.1)         | 179 (33.2)         | 0.003  |
| Hemoglobin (g/dL)               | 10.0 ± 3.9                       | 9.9 ± 3.9          | 10.0 ± 4.3         | 0.52   | 9.8 ± 3.1                       | 9.6 ± 1.6          | 9.9 ± 4.1          | 0.10   |
| Serum creatinine (mg/dL)        | 9.1 ± 3.8                        | 6.8 ± 4.8          | 7.3 ± 4.4          | <0.001 | 8.6 ± 3.7                       | 8.6 ± 3.8          | 8.6 ± 3.6          | 0.92   |
| Serum albumin (g/dL)            | 3.6 ± 0.6                        | 3.7 ± 0.6          | 3.6 ± 0.6          | <0.001 | 3.6 ± 0.6                       | 3.6 ± 0.6          | 3.5 ± 0.6          | 0.13   |
| Serum corrected calcium (mg/dL) | 9.0 ± 6.1                        | 9.1 ± 8.2          | 8.8 ± 2.9          | 0.72   | 8.8 ± 3.5                       | 8.7 ± 3.8          | 8.8 ± 3.1          | 0.65   |
| Serum phosphorus (mg/dL)        | 5.4 ± 9.1                        | 5.2 ± 1.8          | 5.0 ± 2.5          | 0.23   | 5.1 ± 2.2                       | 5.1 ± 1.7          | 5.1 ± 2.6          | 0.75   |
| Total cholesterol (mg/dL)       | 154.3 ± 42.1                     | 155.3 ± 41.9       | 151.1 ± 42.5       | 0.02   | 150.6 ± 42.1                    | 152.3 ± 43.0       | 149.1 ± 41.2       | 0.17   |
| Triglyceride (mg/dL)            | 122.8 ± 78.8                     | 122.6 ± 79.7       | 123.4 ± 75.6       | 0.81   | 127.6 ± 81.7                    | 131.2 ± 86.7       | 124.3 ± 76.7       | 0.16   |
| LDL-cholesterol (mg/dL)         | 86.0 ± 37.5                      | 86.7 ± 38.8        | 83.9 ± 33.1        | 0.11   | 82.8 ± 32.9                     | 83.0 ± 33.5        | 82.6 ± 32.5        | 0.85   |
| Serum iPTH (pg/mL)              | 164.6 (76.3–298.1)               | 175.8 (82.0–322.0) | 197.2 (53.8–238.5) | <0.001 | 157.6 (73.4–262.6)              | 174.3 (87.6–286.5) | 139.3 (56.7–241.0) | 0.05   |
| HbA1c (%)                       | 6.4 ± 1.6                        | 6.2 ± 1.5          | 6.7 ± 1.7          | <0.001 | 6.6 ± 1.7                       | 6.4 ± 1.7          | 6.7 ± 1.7          | 0.02   |
| hs-CRP (mg/dL)                  | 0.26 (0.04–1.43)                 | 0.26 (0.04–1.40)   | 0.31 (0.04–1.53)   | 0.83   | 0.40 (0.08–2.07)                | 0.44 (0.08–2.29)   | 0.39 (0.07–1.77)   | 0.11   |
| Medications                     |                                  |                    |                    |        |                                 |                    |                    |        |
| ACEi or ARB, n (%)              | 1630 (52.8)                      | 1233 (51.7)        | 397 (56.6)         | 0.03   | 661 (54.5)                      | 311 (51.2)         | 350 (57.5)         | 0.03   |
| β-blocker, n (%)                | 1489 (48.3)                      | 1138 (47.8)        | 351 (50.1)         | 0.28   | 626 (51.7)                      | 313 (51.8)         | 313 (51.5)         | 0.91   |
| HD adequacy                     |                                  |                    |                    |        |                                 |                    |                    |        |
| spKt/V                          | 1.4 ± 0.5                        | 1.4 ± 0.5          | 1.4 ± 0.3          | 0.14   | 1.4 ± 0.4                       | 1.4 ± 0.5          | 1.4 ± 0.3          | 0.14   |

Note: Values for continuous variables are given as mean ± standard deviation and variables without a normal distribution are given as median and interquartile range; values for categorical variables are given as number (percentage).

ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, BP = blood pressure, DM = diabetes mellitus, ECG = electrocardiogram, ESRD = end-stage renal disease, GN = glomerulonephritis, HD = hemodialysis, hs-CRP = high-sensitivity C-reactive protein, iPTH = intact parathyroid hormone, K = dialyzer clearance, LDL = low-density lipoprotein, LVH = left ventricular hypertrophy, NHI = national health insurance, PCKD = polycystic kidney disease, SMD = standardized mean difference, spKt/V = single pool Kt/V, t = time, V = volume of water a patient's body contains, VI = visual impairment.

**TABLE 2.** Clinical Factors Influencing Visual Impairment in End-Stage Renal Disease Patients Receiving Hemodialysis

|                                   | Univariate          |        | Multivariate        |        |
|-----------------------------------|---------------------|--------|---------------------|--------|
|                                   | Odds Ratio (95% CI) | P      | Odds Ratio (95% CI) | P      |
| Age (per 10 years)                | 1.337 (1.252–1.427) | <0.001 | 1.215 (1.099–1.344) | <0.001 |
| Sex (male)                        | 1.165 (0.987–1.377) | 0.07   |                     |        |
| SBP (per 10 mm Hg)                | 1.043 (1.004–1.083) | 0.03   |                     |        |
| DBP (per 10 mm Hg)                | 0.876 (0.823–0.933) | <0.001 |                     |        |
| DM                                | 2.943 (2.426–3.570) | <0.001 | 2.777 (2.170–3.553) | <0.001 |
| Cardiovascular diseases           | 1.652 (1.369–1.993) | <0.001 | 1.289 (1.015–1.637) | 0.04   |
| Duration of dialysis (per 1 year) | 1.000 (0.998–1.001) | 0.67   |                     |        |
| Serum creatinine (per 1 mg/dL)    | 0.941 (0.917–0.965) | <0.001 |                     |        |
| Serum albumin (every 1 mg/dL)     | 0.719 (0.625–0.827) | <0.001 |                     |        |
| Serum phosphorus (per 1 mg/dL)    | 0.933 (0.889–0.978) | <0.001 |                     |        |
| Total cholesterol (per 1 mg/dL)   | 0.998 (0.996–1.000) | 0.02   | 0.997 (0.994–1.000) | 0.021  |
| HbA1c (per 1 %)                   | 1.000 (0.995–1.004) | 0.88   |                     |        |
| Serum iPTH (per 100 pg/mL)        | 0.875 (0.833–0.919) | <0.001 | 0.999 (0.998–1.000) | 0.003  |
| LVH on ECG                        | 1.189 (0.983–1.440) | 0.08   |                     |        |
| Insurance                         |                     |        |                     |        |
| National health insurance         | 0.706 (0.569–0.836) | <0.001 | 0.628 (0.496–0.795) | <0.001 |
| Education                         |                     |        |                     | <0.001 |
| Primary education                 | 0.948 (0.639–1.405) | 0.79   | 0.979 (0.582–1.646) | 0.94   |
| Secondary education               | 0.567 (0.393–0.819) | 0.002  | 0.617 (0.375–1.014) | 0.06   |
| Higher education                  | 0.421 (0.284–0.625) | <0.001 | 0.463 (0.271–0.792) | 0.005  |
| The use of ARB or ACEi            | 1.157 (0.977–1.369) | 0.09   |                     |        |
| The use of $\beta$ -blocker       | 1.098 (0.927–1.299) | 0.30   |                     |        |
| spKt/V (per 1)                    | 1.129 (0.923–1.380) | 0.24   |                     |        |

ARB = angiotensin receptor blocker, ACEi = angiotensin converting enzyme inhibitor, CI = confidence interval, DBP = diastolic blood pressure, DM = diabetes mellitus, ECG = electrocardiogram, LVH = left ventricular hypertrophy, iPTH = intact parathyroid hormone, SBP = systolic blood pressure, spKt/V = single-pool Kt/V, K = dialyzer clearance, t = time, V = volume of water a patient's body contains.

disease. The distribution of detailed causes for cardiovascular and infection-related hospitalization is shown in Table 5. Ischemic heart disease had the highest rate among cardiovascular causes of hospitalization, and respiratory infection had the highest rate among infection-related causes of hospitalization. Cardiovascular hospitalization due to ischemic heart disease had a higher incidence in patients with visual impairment than in patients without visual impairment, accounting for 41/105 (39.0%) and 58/220 (26.4%) patients with or without visual impairment, respectively. Higher rates of nonaccess-related infections (e.g., pulmonary, musculoskeletal and soft tissue, and genitourinary) were observed among patients with visual impairment than among patients without visual impairment. Musculoskeletal and soft tissue infections in particular showed the biggest differences between patients with or without visual impairment. Figure 3A and B shows the Kaplan–Meier curve of

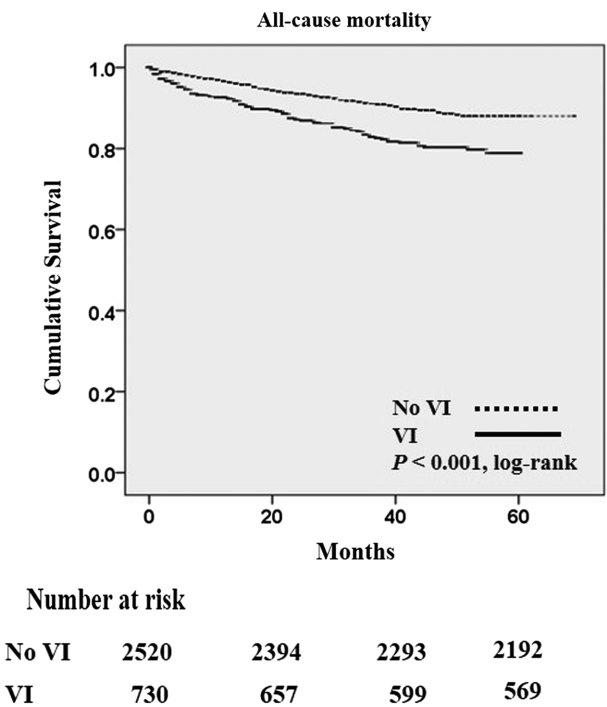
cause-specific hospitalization as visual impairment. Patients with visual impairment significantly increased in both cardiovascular and infection-related hospitalization rates compared with patients without visual impairment ( $P < 0.001$  and  $P < 0.001$ , by the log-rank test).

The univariable and multivariable Cox regression analyses for cardiovascular and infection-related hospitalization before and after propensity score matching are shown in Table 6. In the crude model of unmatched data, the HR for cardiovascular hospitalization of patients with visual impairment was 1.70 (95% CI, 1.35–2.15,  $P < 0.001$ ) using patients without visual impairment as the reference category. In the multivariable analysis, patients with visual impairment had an independently significant association with increased cardiovascular hospitalization compared with patients without visual impairment in model 1 (HR 1.57, 95% CI, 1.29–1.91,  $P < 0.001$ ) and model 2

**TABLE 3.** Causes of Deaths of the Study Population According to Visual Impairment

|                                                                 | No VI (n = 2520) | VI (n = 730) | Total (n = 3250) | P      |
|-----------------------------------------------------------------|------------------|--------------|------------------|--------|
| All cause of death (n, %)                                       | 188 (7.5)        | 105 (14.4)   | 293 (9.0)        | <0.001 |
| Cardiovascular disease including cerebrovascular disease (n, %) | 68 (36.6)        | 38 (36.9)    | 106 (36.7)       | 0.708  |
| Infection-related disease (n, %)                                | 47 (25.3)        | 30 (29.1)    | 77 (26.6)        |        |
| Others (n, %)                                                   | 71 (38.2)        | 35 (34.0)    | 106 (36.7)       |        |

VI = visual impairment.



**FIGURE 1.** Kaplan–Meier survival curve for all-cause mortality according to visual impairment.

(HR 1.45, 95% CI, 1.00–1.90,  $P < 0.001$ ) even after adjustment for confounding clinical and laboratory variables. In the propensity score-matched analysis, patients with visual impairment had a significantly higher risk of cardiovascular hospitalization compared with patients without visual impairment in crude model (HR 1.63, 95% CI, 1.24–2.14,  $P < 0.001$ ), model 1 (HR 1.62, 95% CI, 1.24–2.14,  $P = 0.001$ ) and model 2 (HR 1.48,

95% CI, 1.08–2.02,  $P = 0.001$ ) even after adjustment for confounding clinical and laboratory variables including age and sex, DM, cardiovascular disease, health insurance, education, duration of dialysis, the use of ACEi or ARB, left ventricular hypertrophy on electrocardiogram, serum creatinine, serum albumin and HbA1c.

Patients with visual impairment had also a higher risk for infection-related hospitalization compared with patients without visual impairment in crude model (HR 1.85, 95% CI, 1.48–2.33,  $P < 0.001$ ) and model 1 (HR 1.77, 95% CI, 1.40–2.22,  $P < 0.001$ ) before propensity score matching. However, patients with visual impairment did not have a higher risk for infection-related hospitalization than patients without visual impairment in the multivariable analysis of unmatched data and the univariable and multivariable analysis of matched data.

DISCUSSION

In this multicenter prospective observational study, we demonstrated that visual impairment was significantly associated with an increased risk of all-cause mortality even after adjusting for confounding variables in HD patients in unmatched cohort as well as propensity score-matched cohort. Furthermore, visual impairment had a significant increased risk of cardiovascular hospitalization, whereas visual impairment was not independently associated with a risk factor of infection-related hospitalization in HD patients. These findings of visual impairment as an independent risk factor for mortality are compatible with previous studies in the general population.<sup>7,11–13</sup> To the best of our knowledge, there has been no multicenter prospective cohort study for visual impairment in HD patients. The strength of our study is the first study investigating the association of visual impairment and clinical outcomes in ESRD patients undergoing HD treatment.

We found a significant association between visual impairment and age, co-morbidities such as DM and cardiovascular disease and sociodemographic status such as health insurance and education in HD patients. In general, the association with increasing age and the risk of visual impairment has been

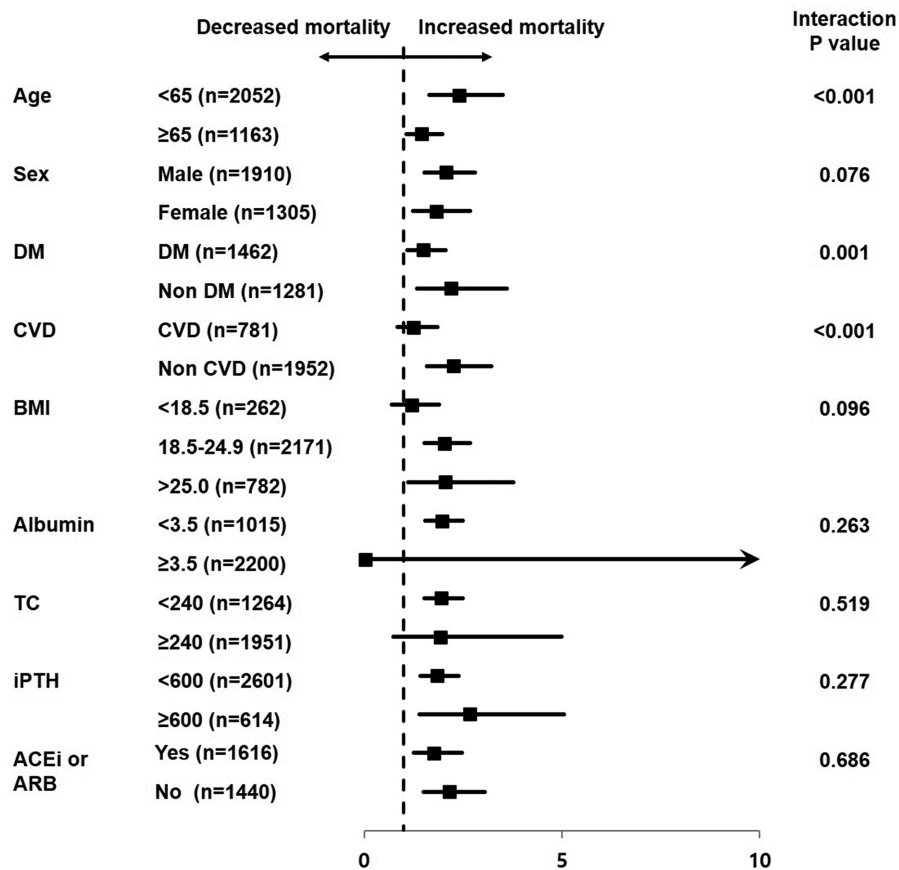
**TABLE 4.** Univariable and Multivariable Cox Regression Analyses for All-Cause Mortality According to Visual Impairment

|                     | Crude Model |               |        | Model 1 |               |        | Model 2 |               |       |
|---------------------|-------------|---------------|--------|---------|---------------|--------|---------|---------------|-------|
|                     | HR          | 95% CI        | P      | HR      | 95% CI        | P      | HR      | 95% CI        | P     |
| Unmatched cohort    |             |               |        |         |               |        |         |               |       |
| All-cause mortality |             |               |        |         |               |        |         |               |       |
| No VI               |             | 1 (reference) |        |         | 1 (reference) |        |         | 1 (reference) |       |
| VI                  | 1.96        | 1.54–2.48     | <0.001 | 1.67    | 1.31–2.12     | <0.001 | 1.77    | 1.21–2.61     | 0.004 |
| Matched cohort      |             |               |        |         |               |        |         |               |       |
| All-cause mortality |             |               |        |         |               |        |         |               |       |
| No VI               |             | 1 (reference) |        |         | 1 (reference) |        |         | 1 (reference) |       |
| VI                  | 1.72        | 1.21–2.45     | 0.003  | 1.71    | 1.21–2.44     | 0.003  | 1.69    | 1.12–2.54     | 0.01  |

*Notes: Unmatched Cohort:* Model 1: multivariable model including age and sex, Model 2: multivariable model including model 1 + BMI, systolic BP, diastolic BP, DM, cardiovascular disease, smoking, health insurance, education, duration of dialysis, the use of ACEi or ARB, the use of  $\beta$ -blocker, LVH on ECG, serum creatinine, serum albumin, total cholesterol, serum iPTH, HbA1c, spKt/V.

*Matched Cohort:* Model 1: multivariable model including age and sex, Model 2: multivariable model including model 1 + DM, cardiovascular disease, health insurance, education, duration of dialysis, the use of ACEi or ARB, LVH on ECG, serum creatinine, serum albumin, HbA1c.

ACEi=angiotensin-converting enzyme inhibitor, ARB=angiotensin receptor blocker, BMI=body mass index, BP=blood pressure, CI=confidence interval, DM=diabetes mellitus, ECG=electrocardiogram, HR=hazard ratio, iPTH=intact parathyroid hormone, K=dialyzer clearance, LVH=left ventricular hypertrophy, SGA=subjective global assessment, spKt/V=single pool Kt/V, t=time, V=volume of water a patient's body contains, VI=visual impairment.

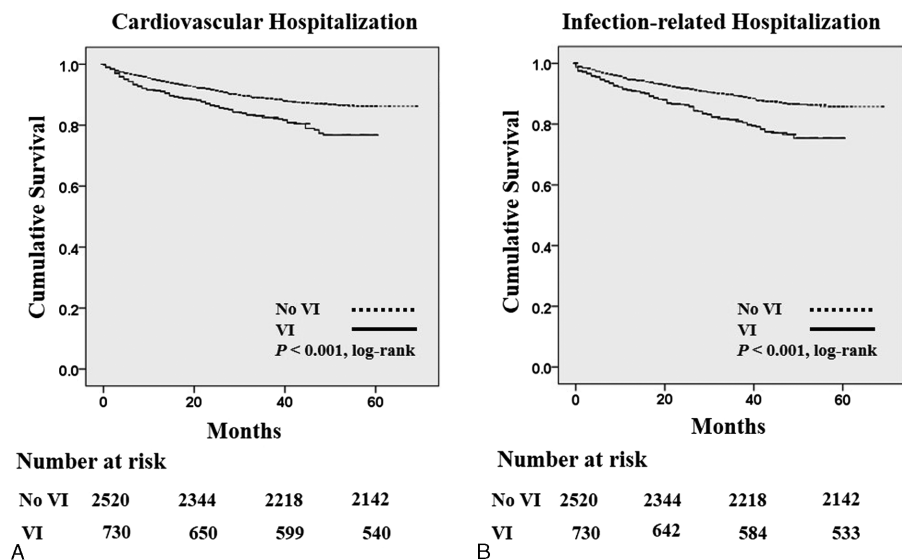


**FIGURE 2.** Hazard ratio (95% CI) for all-cause mortality associated with visual impairment in subgroups of hemodialysis patients. ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, CI = confidence interval, CVD = cardiovascular disease, DM = diabetes mellitus, TC = total cholesterol.

**TABLE 5.** Distribution of Causative Diseases in Patients With Cardiovascular and Infection-Related Hospitalization During the Follow-Up Period

|                                                  | No VI (n = 2520) | VI (n = 730) | P     |
|--------------------------------------------------|------------------|--------------|-------|
| Cardiovascular hospitalization                   |                  |              | 0.04  |
| Ischemic heart diseases, n (%)                   | 58 (26.4)        | 41 (39.0)    |       |
| Congestive heart failure, n (%)                  | 51 (23.2)        | 20 (19.0)    |       |
| Arrhythmia, n (%)                                | 18 (8.2)         | 13 (12.4)    |       |
| Cerebral vascular diseases, n (%)                | 51 (23.2)        | 21 (20.0)    |       |
| Peripheral vascular diseases, n (%)              | 11 (5.0)         | 5 (4.8)      |       |
| Other cardiovascular diseases, n (%)             | 31 (14.1)        | 5 (4.8)      |       |
| Total, n (%)                                     | 220 (100)        | 105 (100)    |       |
| Infection-related hospitalization                |                  |              | 0.008 |
| Respiratory infection, n (%)                     | 98 (45.0)        | 54 (47.8)    |       |
| Gastrointestinal infection, n (%)                | 23 (10.6)        | 8 (7.1)      |       |
| Urinary tract infection, n (%)                   | 7 (3.2)          | 9 (8.0)      |       |
| Musculoskeletal and soft tissue infection, n (%) | 27 (12.4)        | 25 (22.1)    |       |
| Bacteremia, n (%)                                | 11 (5.0)         | 2 (1.8)      |       |
| Vascular access related infection, n (%)         | 22 (10.1)        | 10 (8.8)     |       |
| Other infections, n (%)                          | 30 (13.8)        | 5 (4.4)      |       |
| Total, n (%)                                     | 218 (100)        | 113 (100)    |       |

VI = visual impairment.



**FIGURE 3.** Kaplan–Meier survival curve for cardiovascular (A) and infection-related hospitalization (B) according to visual impairment.

consistently reported in other previous studies of the general population.<sup>14,15</sup> Recent study based on a national health survey in Korea demonstrated that risk indicators of visual impairment were increasing age, low education status, and the absence of private health insurance.<sup>16</sup> In this study, both univariable and multivariable analyses indicated DM to be a major risk factor for visual impairment in HD patients. Previous large cross-sectional studies also showed that DM was independently associated with visual impairment in Southeast Asian or American population.<sup>14,17</sup> The risk factors of visual impairment in HD patients seems to be not different from those in the general population.

The mechanism underlying the association between visual impairment and mortality in HD patients is unclear and

**TABLE 6.** Univariable and Multivariable Cox Regression Analyses for Cardiovascular and Infection-Related Hospitalization According to Visual Impairment

| Crude model                       |               |           |        | Model 1       |           |          | Model 2       |           |          |
|-----------------------------------|---------------|-----------|--------|---------------|-----------|----------|---------------|-----------|----------|
| HR                                | 95% CI        | <i>P</i>  |        | HR            | 95% CI    | <i>P</i> | HR            | 95% CI    | <i>P</i> |
| Unmatched cohort                  |               |           |        |               |           |          |               |           |          |
| Cardiovascular hospitalization    |               |           |        |               |           |          |               |           |          |
| No VI                             | 1 (reference) |           |        | 1 (reference) |           |          | 1 (reference) |           |          |
| VI                                | 1.70          | 1.35–2.15 | <0.001 | 1.57          | 1.29–1.91 | <0.001   | 1.45          | 1.00–1.90 | 0.008    |
| Infection-related hospitalization |               |           |        |               |           |          |               |           |          |
| No VI                             | 1 (reference) |           |        | 1 (reference) |           |          | 1 (reference) |           |          |
| VI                                | 1.85          | 1.48–2.33 | <0.001 | 1.77          | 1.40–2.22 | <0.001   | 1.06          | 0.75–1.49 | 0.75     |
| Matched cohort                    |               |           |        |               |           |          |               |           |          |
| Cardiovascular hospitalization    |               |           |        |               |           |          |               |           |          |
| No VI                             | 1 (reference) |           |        | 1 (reference) |           |          | 1 (reference) |           |          |
| VI                                | 1.63          | 1.24–2.14 | <0.001 | 1.62          | 1.24–2.14 | 0.001    | 1.48          | 1.08–2.02 | 0.01     |
| Infection-related hospitalization |               |           |        |               |           |          |               |           |          |
| No VI                             | 1 (reference) |           |        | 1 (reference) |           |          | 1 (reference) |           |          |
| VI                                | 1.33          | 0.98–1.80 | 0.07   | 1.38          | 1.01–1.88 | 0.04     | 1.04          | 0.73–1.48 | 0.84     |

*Notes:* **Unmatched Cohort:** Model 1: multivariable model including age and sex, Model 2: multivariable model including model 1 + BMI, systolic BP, diastolic BP, DM, cardiovascular disease, smoking, health insurance, education, duration of dialysis, the use of ACEi or ARB, the use of  $\beta$ -blocker, LVH on ECG, serum creatinine, serum albumin, total cholesterol, serum iPTH, HbA1c, spKt/V.

**Matched Cohort:** Model 1: multivariable model including age and sex, Model 2: multivariable model including model 1 + DM, cardiovascular disease, health insurance, education, duration of dialysis, the use of ACEi or ARB, LVH c ECG, serum creatinine, serum albumin, HbA1c.

ACEi=angiotensin-converting enzyme inhibitor, ARB=angiotensin receptor blocker, BMI=body mass index, BP=blood pressure, CI=confidence interval, DM=diabetic mellitus, ECG=electrocardiogram, HR=Hazard ratio, iPTH=intact parathyroid hormone, LVH=left ventricular hypertrophy, spKt/V=single pool Kt/V, K=dialyzer clearance, t=time, V=volume of water a patient’s body contains, VI=visual impairment.

multifactorial. Previous studies using structural equation modeling techniques demonstrated that visual impairment was a risk factor for increasing mortality both directly and indirectly.<sup>18,19</sup> Some possible explanations can be proposed based on literature review and on our study. First, visual impairment is an indicator of aging, which is directly related to mortality risk. Age-related eye diseases are markers of biological aging and those ocular conditions may share a common attribute with conditions associated with increased mortality in the general population.<sup>19</sup> In subgroup analysis of our study, there was a significant interaction between visual impairment and age subgroup in all-cause mortality. The HR of all-cause mortality was substantially higher in patients <65 years compared with those 65 years and older at baseline. These findings indicate that visual impairment is more detrimental to the younger age than it is to the older age. The explanation may be that the mortality rate is already high in elderly patients because of many risk factors for mortality so that there is a limit to the additional contribution from visual impairment to mortality.

Second, visual impairment itself is not only an indicator of age, but also an indicator of chronic illnesses. Risk factors for cardiovascular disease such as DM, hypertension, and smoking, have been thought to play a role in the development and aggravation of visual impairment. CKD shares common risk factors with ocular diseases and is also important risk factor of increased mortality, especially cardiovascular mortality. In the present study, a weak relation between visual impairment and mortality was found in subgroup with DM and cardiovascular disease compared with subgroup without DM and cardiovascular disease. However, visual impairment was an independent risk factor of increased mortality in the multivariable Cox regression analysis before and after propensity score matching including DM and cardiovascular disease. Therefore, we suggest that visual impairment may be a direct causal factor of increased mortality independent from comorbidities associated with chronic illness in HD patients.

Third, visual impairment may be associated with an increased likelihood of accidents, with falls being the most noticeable event. Vision is essential to a person's ability to plan and coordinate movement in response to environmental hazards as well as assisting with balance. Visual impairment may result in an increased likelihood of falls with potentially serious consequences such as hip fracture in the general population.<sup>20,21</sup> Fourth, visual impairment may cause a variety of psychological changes such as social isolation, cognitive impairment, and depression, and a reduction in daily functional status. These changes were previously shown to be indirectly associated with an increased risk of mortality in the general population.<sup>22,23</sup> In this study, visual impairment was an independent risk factor for all-cause mortality after adjusting sociodemographic risk factors associated indirect causes of mortality such as medical history, health insurance, and education status before and after propensity scoring matching in the multivariable regression analysis. Visual impairment was also an independent risk factor of increased mortality in the multivariable regression analysis including nutritional markers such as serum albumin, serum creatinine, and total cholesterol. However, we did not investigate the mortality or hospitalization rates caused by accidents, psychological problem, or malnutrition, and it is difficult to confirm the indirect effects of visual impairment for all-cause mortality in this cohort. More research is necessary to elucidate how visual impairment is associated with mortality or hospitalization rates caused by accidents, psychological problem, or malnutrition, and whether visual impairment act as an intervening risk factor in this relationship.

Another interesting finding of this study is that, in addition to being a risk factor of all-cause mortality, visual impairment was an independent risk factor for cardiovascular hospitalization in HD patients. Cardiovascular diseases are the leading cause of mortality in patients with ESRD. We demonstrated that patients with visual impairment had a significantly higher risk for cardiovascular hospitalization compared with patients without visual impairment even after adjustment for clinical variables in the multivariable Cox regression analysis before and after propensity score matching. To date, there have been no clinical studies that have demonstrated that visual impairment is associated with increased cardiovascular hospitalization in HD patients. Only 1 study reported a relationship between visual impairment and the prevalence of cardiovascular disease, especially ischemic heart disease, in patients with non-CKD type 2 DM, but not CKD. They suggested that the severity of visual impairment was associated with an increased prevalence of ischemic heart disease.<sup>24</sup> In line with the previous study, the present study also found that an incidence of cardiovascular hospitalization caused by ischemic heart disease was higher in patients with visual impairment than in patients without visual impairment.

On the other hand, infection-related hospitalization rates were significantly increased in patients with visual impairment compared with patients without visual impairment, but visual impairment was not an independent risk factor for infection-related hospitalization in HD patients. In this study, higher rates of respiratory, urinary tract, and musculoskeletal and soft tissue infection were observed in patients with visual impairment than patients without visual impairment. Our findings reinforce the importance of understanding that patients with visual impairment undergoing dialysis experience a high burden of infection-related complications and highlight the fact that dialysis patients with visual impairment are at high risk for acquiring a number of serious infections. Although we did not elucidate that visual impairment was an independent risk factor of infection-related hospitalization, these findings suggest that physicians should give attention to infection-related morbidity and mortality in HD patients with visual impairment.

Our study has several limitations. First, patient visual acuity was self-reported by questionnaire. It is easy to understand but is not an objective measurement for visual acuity. Self-reported assessment of visual function by questionnaire is independently associated with objective index of visual acuity.<sup>25</sup> Although self-reported assessment of visual function is inherent in the possibility of misclassification of visual impairment status, global validation studies have been reported that self-reported visual impairment measures correlated modestly with clinical indicators of visual acuity.<sup>26,27</sup> Therefore, the questionnaire for assessing visual acuity shows fairly consistent findings compared with an objective measurement for visual acuity. Second, we did not account for the type of eye disease such as AMD, DR, glaucoma, or cataract. We could not establish the association between mortality and certain eye diseases in HD patients. Third, the median follow-up period was relatively short. Fourth, despite the multicenter nature of the study, the participants were consisted of only Korean HD patients. Our results may not be generalized to other ethnic groups undergoing HD therapy. Last, the number of patients who withdrew from the study for the reasons other than death was relatively high. It may be due to the high percentage of patients with "transfer to a nonparticipating hospital." In Korea, the creation of vascular access and the initiation of HD are performed at the university hospitals or general

hospitals, but maintenance HD is usually performed at the private clinics. Unfortunately, some of the private clinics did not participate in this study, which may cause the high percentage of patients with “transfer to a nonparticipating hospital.”

However, despite these limitations, our observations are of importance as this is the first time that such data have been reported from HD patients in the Korean population. In addition, our study suggests that identifying and targeting visually impaired HD patients could be a potentially useful strategy for preventing a decline in their life expectancy. Specifically, regular assessment of HD patients for the presence of visual impairment could lead to earlier detection and treatment of eye disease which could reduce the negative impacts of visual impairment.

In conclusion, our study demonstrated that visual impairment was an independent risk factor for all-cause mortality and cardiovascular hospitalization in HD patients. Our findings underscore the need for careful attention of the visually impaired HD patients.

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