

Sex Differences in the Survival of Patients Undergoing Maintenance Hemodialysis: A 10-year Outcome of the Q-Cohort Study

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Abstract

Background: A survival advantage of women is observed in the general population. However, inconsistent findings have been reported regarding this advantage in patients undergoing maintenance hemodialysis. The aim of this study was to compare the risk of mortality, especially infection-related mortality, between male and female hemodialysis patients.

Methods: A total of 3065 Japanese hemodialysis patients aged ≥ 18 years old were followed up for 10 years. Primary outcome was all-cause and infection-related mortality. The association between the sex and these outcomes were examined using Cox proportional hazards models.

Results: During the median follow-up of 8.8 years, 1498 patients died of any cause, and 387 died of infection. Compared with men, the multivariable-adjusted HRs (95% CIs) for all-cause and infection-related mortality in women were 0.51 (0.45–0.58) and 0.36 (0.27–0.47), respectively. This association remained significant even when the propensity score-matching or inverse probability of treatment weighting adjustment methods were employed. Furthermore, even when the non-infection-related mortality was considered a competing risk, the infection-related mortality rate in women was still significantly lower than that in men.

Conclusions: A female survival advantage over men is observed in Japanese patients undergoing maintenance hemodialysis.

Key Learning Points

What is already known about this subject:

1. In the general population, women live longer than men.
2. In patients undergoing maintenance hemodialysis, there has been controversy on the survival advantage of women over men.

What this study adds:

1. Women have a clearly survival advantage over men for all-cause mortality and infection-related mortality in patients undergoing hemodialysis.

What impact this may have on practice or policy:

1. This study may correct the perception that women have a poorer prognosis than men in patients undergoing HD. As a result, women undergoing HD might be treated aggressively like men if they become a severely ill condition.
2. Females undergoing HD may become less selected catheter use as vascular access.

Introduction

Women have a longer life expectancy than men in the general population¹. The World Health Organization's analysis of global health statistics according to sex clearly show that women have better longevity prospects than those of men². The biological differences between men and women are, amongst others, related to genetic and physiological factors such as the progressive skewing of X chromosome inactivation³, telomere attrition⁴, mitochondrial inheritance⁵, hormonal and cellular responses to stress⁶, and immune function^{7,8}. These factors may partly explain the longer life expectancy for women.

Regarding patients undergoing maintenance hemodialysis (HD), there has been conflicting data on the survival advantage of women over men. Some studies reported that men tend to be more susceptible than women to uremia and inflammation-induced anorexia⁹. Furthermore, inflammatory and nutritional variables may deteriorate over time in men¹⁰. Women with inflammation undergoing HD have lower mortalities than those of men with inflammation undergoing HD¹¹. Conversely, other studies have indicated similar mortalities between women and men undergoing HD^{15,16}. Additionally, several studies showed that infection-related mortality was higher in women than that in men undergoing HD^{12,13,14}. Hecking et al. hypothesized that the general survival advantage for women over men may be nullified because of the high prevalence of HD catheter use and resulting high infection-related mortality in women¹⁵. Considering that the prevalence of HD catheter use in Japan is relatively lower than that in other countries, it would be reasonable to examine the female survival advantage in Japanese HD patients by focusing on infection-related mortality¹⁷.

The current study aimed to investigate whether there is a sex difference in the risk of mortality, especially infection-related mortality, among HD patients. For this, we analyzed the dataset of the Q-Cohort Study, a multicenter, observational cohort study of Japanese patients undergoing maintenance HD¹⁸, by using conventional Cox proportional hazards models and propensity score (PS)-based statistical analysis.

Results

Baseline characteristics of the patients stratified by sex

The baseline characteristics of the patients stratified by sex are shown in Table 1. Women were significantly ($P < 0.05$) older and had a longer dialysis vintage, higher frequency of diabetic nephropathy, and lower frequency of CVD history. The cardiothoracic ratio, nPCR, single-pool Kt/V for urea, serum concentrations of total cholesterol, albumin-corrected Ca, and alkaline phosphatase were significantly ($P < 0.05$) higher in women than those in men. Conversely, the body weight, blood hemoglobin level, serum concentrations of urea nitrogen, creatinine, and albumin, and frequency of antihypertensive agent and VDRA use were lower in women than those in men.

Table 1
Baseline characteristics according to sex.

Variables	males (n = 1816)	females (n = 1249)	<i>P</i>-value
Age (years)	63.9 (55.8–71.7)	64.7 (55.9–74.0)	0.011
Diabetic nephropathy, n (%)	593 (32.7)	296 (23.7)	< 0.001
History of CVD, n (%)	619 (34.1)	342 (27.4)	< 0.001
Dialysis vintage (years)	5.0 (2.0–10.5)	5.4 (2.1–12.3)	0.020
Dialysis time (hours)	5 (4–5)	5 (4.5–5)	0.005
Body weight (kg)	57.5 (51.4–64.3)	46.4 (41.0–52.5)	< 0.001
Systolic blood pressure (mmHg)	156 (142–169)	150 (134–168)	< 0.001
Cardiothoracic ratio (%)	49.1 (46.0–52.4)	51.9 (48.1–55.2)	< 0.001
nPCR (g/kg/day)	0.94 (0.82–1.03)	0.97 (0.87–1.10)	< 0.001
Single-pool Kt/V for urea for urea	1.48 (1.32–1.58)	1.74 (1.56–1.96)	< 0.001
Blood hemoglobin (g/dL)	10.6 (9.9–11.4)	10.4 (9.7–11.1)	< 0.001
Serum urea nitrogen (mg/dL)	66 (56–76)	67 (57–77)	0.278
Serum creatinine (mg/dL)	11.1 (9.1–12.9)	9.2 (7.7–10.7)	< 0.001
Serum total cholesterol (mg/dL)	144 (125–166)	166 (145–191)	< 0.001
Serum albumin (g/dL)	3.8 (3.6–4.1)	3.8 (3.6–4.0)	0.006
Serum CRP (mg/dL)	0.13 (0.07–0.32)	0.12 (0.04–0.27)	< 0.001
Albumin-corrected serum Ca (mg/dL)	9.3 (8.8–9.9)	9.5 (9.0–10.0)	< 0.001
Serum phosphate (mg/dL)	4.9 (4.2–5.6)	4.9 (4.2–5.7)	0.693
Serum alkaline phosphatase (U/L)	224 (174–292)	253 (194–343)	< 0.001
Serum PTH (pg/mL)	107 (50–207)	103 (45–220)	0.808
Use of antihypertensive agents, n (%)	1220 (67.2)	717 (57.4)	< 0.001
Dose of ESAs, unit/week	3000 (1500–4500)	3000 (1500–4500)	0.007
Use of phosphate binders, n (%)	1512 (83.3)	1017 (81.4)	0.192
Use of VDRAs, n (%)	1338 (73.7)	838 (67.1)	< 0.001

Values are presented as median (interquartile range) for continuous variables and number (percentage) for categorical variables. Abbreviations: Ca, calcium; CRP, C-reactive protein; CVD, cardiovascular disease; ESAs, erythropoiesis-stimulating agents; nPCR, normalized protein catabolic rate; PTH, parathyroid hormone; VDRAs, vitamin D receptor activators.

The risk of all-cause and infection-related mortality stratified by sex

During the 10-year follow up, 1498 patients (48.9%) died of any cause, among which 387 patients (12.6%) died of infection-related death, 542 patients (17.7%) died of cardiovascular disease, and 204 patients (6.7%) died of malignancy. Regarding all-cause death, the unadjusted 10-year incidence rate of all-cause mortality was significantly associated with a decrease in women ($P < 0.001$) (Fig. 1A). Women had a lower risk of all-cause death than that of men after adjustment for full variables: the HR (95% CI) was 0.51 (0.45–0.58), $P < 0.001$ (Table 2).

Table 2
Hazard ratios and 95% CIs for all-cause mortality.

	Hazard ratio (95% CI) (versus males)	<i>P</i> -value
Age-adjusted Cox model	0.74 (0.66–0.82)	< 0.001
Fully adjusted Cox model	0.51 (0.45–0.58)	< 0.001
PS-matching model (1 : 1, n = 1322)	0.49 (0.42–0.58)	< 0.001
IPTW model (n = 3065)	0.61 (0.53–0.69)	< 0.001
The fully adjusted model included the following covariates: age, presence of diabetic nephropathy, history of CVD, dialysis vintage, systolic blood pressure, body weight, cardiothoracic ratio, nPCR, single-pool Kt/V for urea, blood hemoglobin, serum concentration of urea, creatinine, total cholesterol, albumin, CRP, albumin-corrected serum Ca, phosphate, alkaline phosphatase, and PTH, dose of ESAs, and use of antihypertensive drugs, phosphate binders, and VDRAs. The PS-matching model was adjusted for body weight and serum creatinine. The IPTW model weighted patients by PS and adjusted for body weight and serum creatinine.		
Abbreviations: Ca, calcium; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; ESAs, erythropoiesis-stimulating agents; IPTW, inverse probability of treatment weighting; nPCR, normalized protein catabolic rate; PS, propensity score; PTH, parathyroid hormone; VDRAs, vitamin D receptor activators.		

Next, we determined the association between sex and infection-related death. The unadjusted 10-year incidence rate of infection-related death in women significantly decreased compared with that in men ($P < 0.001$) (Fig. 1B). Women had a lower risk of infection-related death than men after adjustment for full variables: the HR (95% CIs) was 0.36 (0.27–0.47) (Table 3). Furthermore, even when the competing events of non-infection-related deaths were considered, the infection-related mortality rate in women was significantly lower than that in men: the HR (95% CI) was 0.46 (0.35–0.60).

Table 3
Hazard ratios and 95% CIs for infection-related mortality.

	Hazard ratio (95% CI) (versus males)	<i>P</i> -value
Age-adjusted model	0.57 (0.49–0.70)	< 0.001
Fully adjusted model	0.36 (0.27–0.47)	< 0.001
Fine & Gray model	0.46 (0.35–0.60)	< 0.001
PS-matching model (1 : 1, n = 1416)	0.31 (0.23–0.43)	< 0.001
IPTW model (n = 3065)	0.51 (0.44–0.58)	< 0.001
<p>The fully adjusted model included the following covariates: age, diabetic nephropathy, history of CVD, dialysis vintage, systolic blood pressure, body weight, nPCR, single-pool Kt/V for urea, blood hemoglobin, serum concentration of urea, creatinine, total cholesterol, albumin, CRP, albumin-corrected serum Ca, phosphate, alkaline phosphatase, and PTH, dose of ESAs, use of antihypertensive drugs, phosphate binders, and VDRAs. The Fine & Gray model with non-infection-related deaths as a competing risk was used to consider the competing risk. The PS-matching model was adjusted for body weight and serum creatinine. The IPTW model weighted patients by PS and adjusted for body weight and serum creatinine.</p>		
<p>Abbreviations: Ca, calcium; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; ESAs, erythropoiesis-stimulating agents; IPTW, inverse probability of treatment weighting; nPCR, normalized protein catabolic rate; PS, propensity score; PTH, parathyroid hormone; VDRAs, vitamin D receptor activators.</p>		

The risk of all-cause and infection-related deaths analyzed by the PS-matching method and IPTW adjustment method

The logistic regression model used in the PS analysis for all-cause and infection-related deaths showed a high discriminatory power with area under the receiver operating characteristics curve values of 0.86 and 0.84, respectively. The imbalances of baseline covariates in the pre-matching cohort were well balanced after adjusting with the PS-matching method (Supplementary data, Table S1 and S2). Serum creatinine and body weight were not included in the creation of the PS; however, these two covariates are regarded as inherent characteristics of gender differences and were thus balanced across sex after using the PS methodology. Importantly, the survival advantage of women remained statistically significant even when the PS-matching and IPTW methods were employed (Tables 2 and 3).

Subgroup IPTW analyses stratified by baseline clinical characteristics

To assess whether the survival benefit of women is consistent across a variety of baseline clinical backgrounds, the effects of modification by subgroups stratified by potential confounders at baseline

were examined using the IPTW method (Fig. 2 and Fig. 3). The association between women and a lower rate of all-cause death was enhanced in patients with diabetic nephropathy or higher serum creatinine or albumin concentrations. Also, the protective effect of being female in reducing infection-related death tended to be attenuated in older patients, patients with shorter dialysis vintage, patients with diabetic nephropathy or a history of CVD, or lower levels of blood hemoglobin, serum creatinine or albumin, or with higher levels of serum total cholesterol.

Discussion

In the present study, by employing various statistical approaches, we clearly demonstrated a survival advantage of women over men independent of all-cause and infection-related deaths in patients undergoing HD. Regarding all-cause mortality, the effect of being female was smaller in patients with diabetic nephropathy or higher serum levels of creatinine or albumin. Moreover, in the subgroup analysis of infection-related mortality, the impact of being female was smaller in younger patients or patients with diabetic nephropathy, history of CVD, higher blood hemoglobin, and higher serum levels of creatinine, total cholesterol, or albumin. Taken together, our results suggest a potential survival benefit for female patients undergoing maintenance HD.

The present study has provided evidence that women have a survival advantage during HD. To the best of our knowledge, our study is the first to demonstrate that the female survival advantage is consistent regarding infection-related mortality in HD patients. This relationship remains statistically significant even after adjustment for potential confounding factors, PS-matching, or IPTW adjustment. Furthermore, when non-infection-related death was considered a competing risk, the infection-related mortality rate in women was significantly lower than that in men. As for all-cause death, a report from the Dialysis Outcomes Practice Patterns Study (DOPPS) demonstrated that the HR (95% CI) of all-cause mortality in men (versus women) was 1.09 (1.04–1.14) after adjusting for age and time on dialysis¹⁶, consistent with our current observations. Taken together, our data and previous reports strongly suggest that women have a survival advantage over men during maintenance HD.

Several potential mechanisms might explain the survival advantage of women over men undergoing HD. Previous studies reported that, in comparison to female patients undergoing HD, men might be more susceptible to inflammation-induced anorexia and can exhibit more severe symptoms (e.g., handgrip strength decline⁹) and deterioration over time, as evidenced by nutritional and inflammatory variables such as albumin, body weight, CRP, and interleukin-6¹⁰. It has also been demonstrated in regards to inflammation that women have better outcomes than men¹¹. These results suggest that men are more vulnerable than women in the HD population. In the general population, mounting evidence has also shown a survival advantage of women that is related to genetic and physiological factors. Inactivation of the disadvantageous X chromosome³, longer telomeres⁴, a lower resting metabolic rate²⁰, estrogen²¹, and mitogenome-nuclear genome interactions⁶ might play a role in the longer longevity of women. These factors could partly explain the underlying mechanism of our observations. Furthermore, the heightened

immune response in women is generally considered to make them more resistant to infections^{7,8,22}. Our study confirmed a similar relationship in patients undergoing maintenance HD.

The subgroup analysis of all-cause mortality revealed that the effect of being female was enhanced in patients with diabetic nephropathy or higher serum levels of creatinine or albumin. Additionally, the subgroup analysis of infection-related mortality revealed that the effect of being female was attenuated in older patients, or patients with diabetic nephropathy, a history of CVD, lower blood hemoglobin, serum levels of creatinine, or albumin or higher levels of total cholesterol. In our analysis, the protective effect of being female in diabetic nephropathy was different in each outcome. Previous studies have shown that the age-related decline of immune cells and inflammatory mediators were slower in women than in men^{7,8}. Furthermore, sex hormones might reduce antioxidants²⁰, and women are more resistant to anorexia and lower malnutrition^{9,10}. However, recent observational studies demonstrated an inverse association between sex and a high death rate in younger patients undergoing HD^{14,23}. Hence, further studies are necessary to elucidate whether the effects of the baseline factors observed in the current study are present across a variety of HD populations and whether their underlying mechanisms are related to sex hormones.

Despite the accumulation of these findings to date, the advantage of being female regarding human life expectancy of patients undergoing HD is still controversial. Sex-dependent differences in the proportion of types of vascular access might partially explain the inconsistency. The results from the DOPPS have revealed that the selection of vascular access showed sex-dependent differences, with less frequent catheter use in male HD patients (12.2%) than that in female HD patients (18.4%); subgroup analyses indicated that HD catheter use was associated with a higher risk of all-cause mortality in female patients undergoing HD¹⁶. As catheter users are likely to develop catheter-related infections and resulting persistent inflammation followed by malnutrition, it is possible that they are at increased risks of infection-related and all-cause death. In this regard, sex differences in the proportion of types of vascular access may be important confounders that might have nullified the natural specific advantage of women. Importantly, a national survey conducted in 2008 in Japan reported that more than 90% of the patients undergoing maintenance HD used arteriovenous fistula while only 0.5% used a catheter¹⁷. Additionally, there was no sex discrepancy in the proportion of types of vascular access in Japanese patients in the DOPPS¹⁶. This result suggests that catheter users were presumed to be minor in our study and that there is no sex discrepancy in the proportion of types of vascular access. In the present study, even when PS-matching or IPTW adjustment was employed, the survival advantage of women was statistically significant, particularly regarding all-cause and infection-related death. This indicates that catheter use during HD might diminish the natural specific advantage of women. However, it is impossible to assess this in the present study, because we had no direct data regarding the type of vascular access. Therefore, further studies with data regarding the type of vascular access are necessary to determine whether women undergoing HD have a survival advantage regardless of the type of vascular access.

The strength of our study was its large-scale and wide-ranging inclusion criteria. As such, our results are generalizable to real-world HD patients. However, some limitations in our study should be noted. First, the measurements of baseline parameters might have been insufficient. For instance, data regarding the use of steroid or immunosuppressive agents and the acceptance rate of renal replacement therapy were missing. Recent studies indicate that elderly women are more likely to choose conservative care than renal replacement therapy, and the female survival advantage diminished among HD patients²⁴. However, our results obtained with PS-based methodologies for adjusting this selection bias revealed a female survival advantage. Second, we had no data on the serum levels of sex hormones. A previous study showed that women undergoing HD had lower serum estradiol levels than those in the general population²⁵. Thus, the activity of sex hormones might hardly explain the discrepancy in mortality. The length of exposure to female hormones before HD initiation may determine the impact of the female advantage on survival. Third, the participating patients in this study were all Japanese, and thus our results might not be applicable to other ethnic groups. Despite these limitations, we believe that this study provides further evidence that women have a survival advantage over men during HD.

In conclusion, our findings on patients undergoing maintenance HD suggest that women have a survival advantage over men. Further studies are required to confirm this female survival advantage and its underlying mechanisms during HD.

Methods

Study design and population

The details regarding the design of the Q-Cohort Study were described previously¹⁸. We recruited 3598 outpatients aged 18 years or older that were receiving maintenance HD in 39 HD facilities between 31 December 2006 and 31 December 2007. Participants were followed up until 31 December 2016. The participants' health status was checked annually by local physicians at each dialysis facility. When patients moved to other HD facilities in which collaborators of this study were not present, we conducted follow-up surveys by mail or telephone. We excluded 533 participants with missing data on one or more baseline characteristics and whose outcome information could not be obtained. We enrolled the remaining 3065 patients in the final study population. The study protocol was approved by the Clinical Research Ethics Committee of the Institutional Review Board of Kyushu University (Approval Number 20–31) and all participating institutions. First, we followed the patients from 2006 until 2010. Written informed consent was obtained from all participants at the start of the study. The present study was performed according to the Ethics of Clinical Research (Declaration of Helsinki). Next, we surveyed the patients' further follow-up from 2011 to 2016. The ethics committees of all participating institutions granted approval to waive requirement for written informed consent for the additional follow-up surveys from 2011–2016 because of the retrospective nature of the study, which is registered in the University Hospital Medical Information Network (UMIN) clinical trial registry (UMIN ID: 000000556).

Covariates

The main factor assessed was sex, and the potential confounders were as follows: age, presence of diabetic nephropathy, history of cardiovascular disease (CVD), dialysis vintage, pre-dialysis systolic blood pressure, body weight, cardiothoracic ratio, normalized protein catabolic rate (nPCR), single-pool Kt/V for urea, blood hemoglobin levels, serum concentrations of urea nitrogen, creatinine, total cholesterol, albumin, C-reactive protein (CRP), calcium (Ca), phosphate, alkaline phosphatase, and parathyroid hormone (PTH), dose of erythropoiesis-stimulating agents (ESAs), and the use of antihypertensive agents, phosphate binders, and vitamin D receptor activators (VDRAs). The ESA dosage for darbepoetin alfa administration was calculated by multiplying the dosage (μg) of darbepoetin alfa by 200. These data were collected by reviewing medical records. Blood samples were collected before starting each HD session. The serum albumin-corrected serum Ca concentration was calculated with Payne's formula: $\text{corrected Ca (mg/dL)} = \text{observed total Ca (mg/dL)} + (4.0 - \text{serum albumin concentration [g/dL]})$, only if the serum albumin concentration was < 4.0 g/dL. Serum PTH levels were measured using whole or intact PTH assays and expressed as intact PTH assay levels¹⁹.

Definition of outcomes

The primary outcomes were all-cause and infection-related deaths. The events were determined based on the patients' medical records.

Statistical analysis

Group differences in continuous variables were determined using the t-test; categorical variables were compared using the chi-square test. The incidence rates and 95% confidence intervals (95% CIs) for all-cause and infection-related mortality were calculated using the person-year method. The unadjusted, age-adjusted, and fully adjusted hazard ratios (HRs) with 95% CIs of all-cause and infection-related mortality according to sex were calculated using a Cox proportional hazards model. The fully adjusted model for all-cause mortality was adjusted for the above-mentioned potential confounders. The fully adjusted model for infection-related mortality was adjusted for the same factors except the cardiothoracic ratio and use of antihypertensive agents. To adjust the selection bias by sex, we used the PS methodology¹⁹. The PS was calculated for each patient using a multivariable-adjusted logistic regression model with sex as the dependent variable. To analyze all-cause and infection-related mortality and calculate the PS, the same covariates as the above-mentioned potential confounders were selected. The discriminatory power of the PS was evaluated by calculating the area under the receiver operating characteristics curve. A PS-matching model with adjustment for body weight and serum creatinine was employed to compare the impact of sex on mortality independently of potential confounders. The inverse probability of treatment weighting (IPTW) model was applied to weigh patients by the PS and was adjusted for body weight and

serum creatinine. Statistical analyses were performed using R version 3.6.1 (<http://www.r-project.org>). A two-tailed P-value of <0.05 was considered statistically significant.

Declarations

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Authors' contributions

H.T. contributed to the study design, statistical analysis, data interpretation, and drafting of the manuscript. S.Y. contributed to the statistical analysis, and data interpretation of the manuscript. H.H. contributed to data acquisition, and critical revision of the manuscript. Toshiaki Nakano, M.T., K.T. and K.T. contributed to the data acquisition and critical revision of the manuscript. T.K. contributed to critical revision of the manuscript and supervision of the study. All authors provided critical reviews of the draft and approved the final version.

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Conflict of interest statement

The authors declare that they have no relevant financial interests.

Data availability

The dataset used in this study is under the control of the Data Management Committee of Kyushu University Q-Cohort and cannot be shared publicly due to the data set containing patient data. However, when the researcher needs to use the data for the individual patient level meta-analysis or the validation study between another independent cohort, the data set will be available. The amended protocol will need to be approved by the Kyushu University ethical committee. Send a request to Toshiaki Nakano, MD, PhD, Kyushu University Hospital, toshink@med.kyushu-u.ac.jp.

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Figures

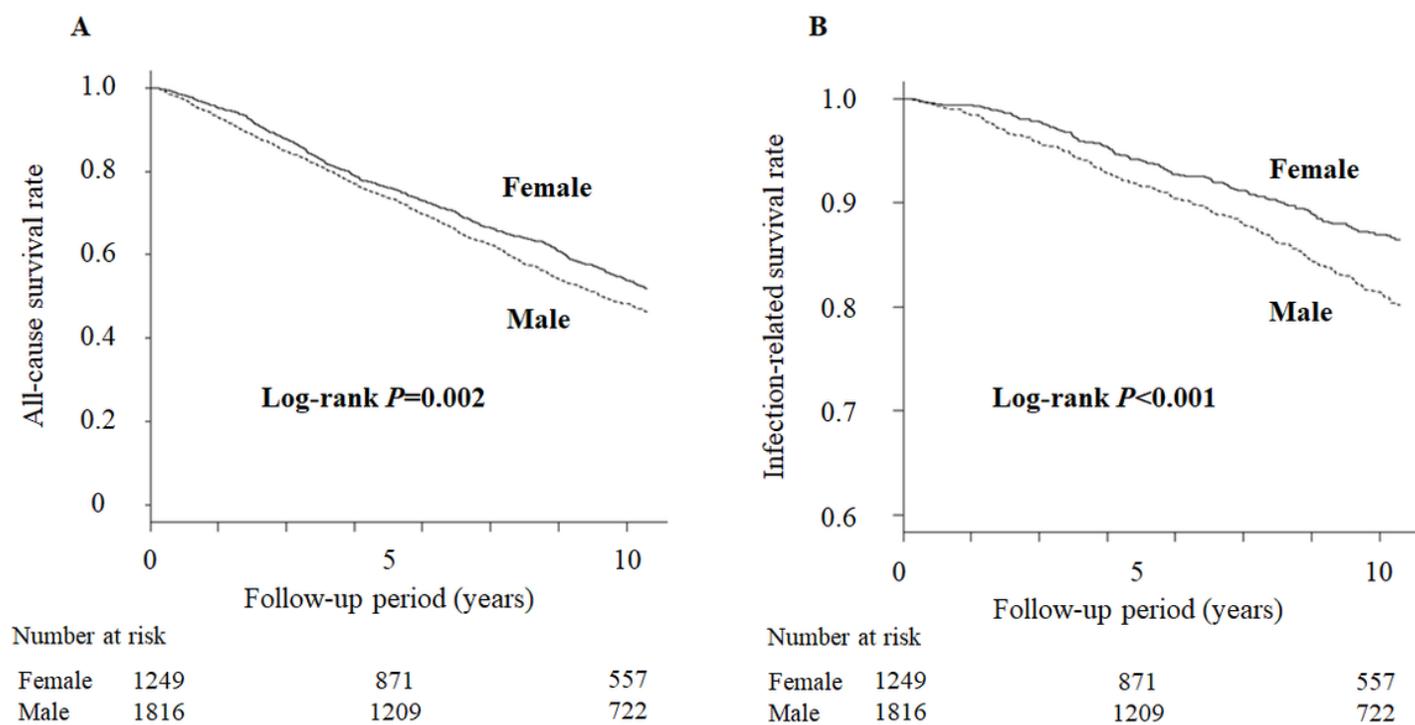


FIGURE 1

Figure 1

Kaplan-Meier curves for all-cause (A) and infection-related (B) mortality stratified by sex. The 10-year incidence rates of all-cause mortality and infection-related mortality in women were significantly lower

than that in males (P <0.05). A log-rank test was used to determine whether there was a significant difference between women and men. A P-value of less than 0.05 was considered statistically significant.

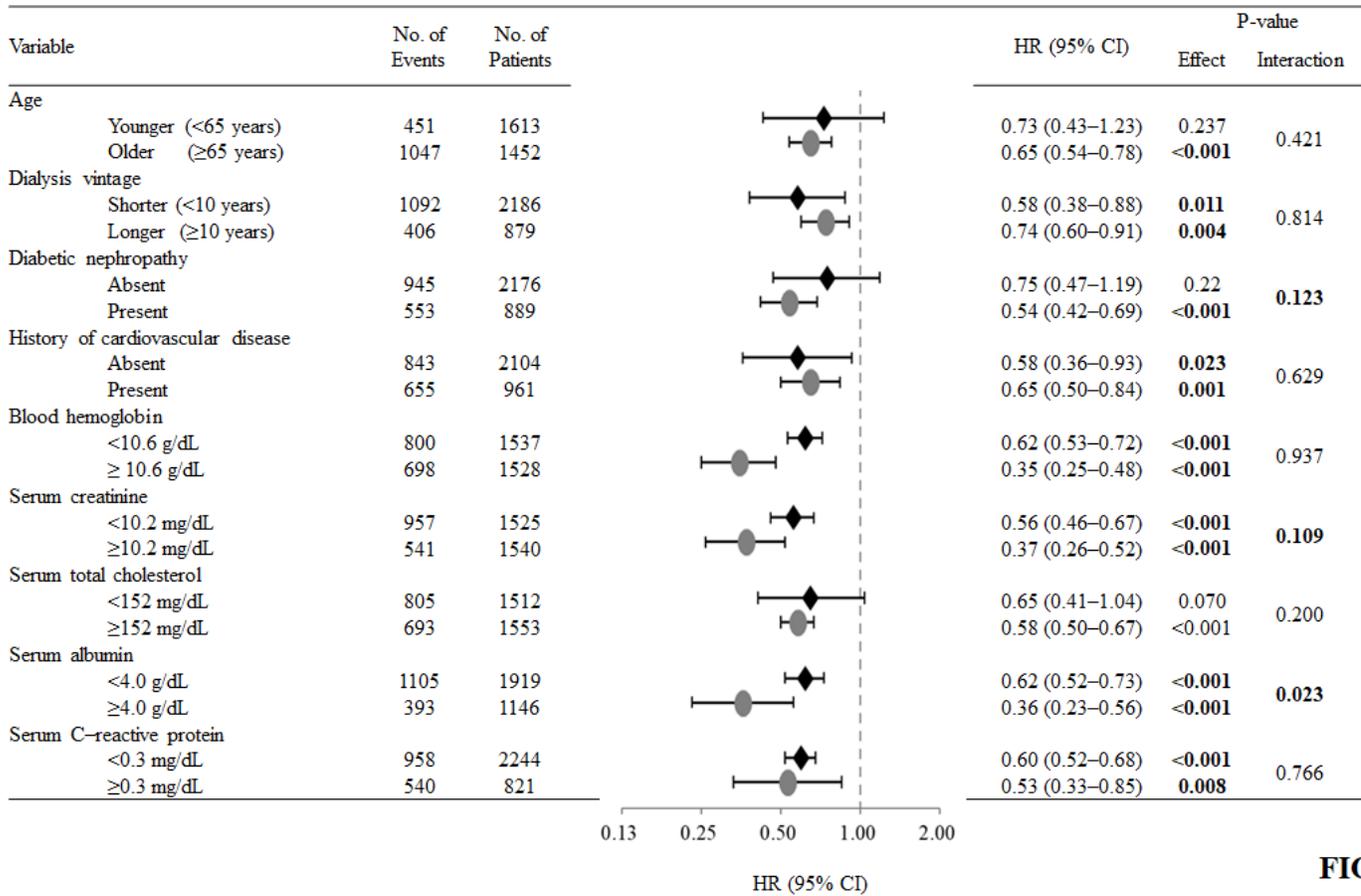


FIGURE 2

Figure 2

The propensity-weighted HRs and 95% CIs for all-cause mortality in women compared with that in men according to the subgroups of baseline characteristics adjusted using Cox regression analysis in propensity score-weighted samples. Adjustment was performed for baseline characteristics (age, diabetic nephropathy, history of cardiovascular disease, dialysis vintage, blood hemoglobin, serum levels of creatinine, total cholesterol, albumin, and C-reactive protein). A P-value of less than 0.05 was considered statistically significant. Abbreviations: CI, confidence interval; HR, hazard ratio.

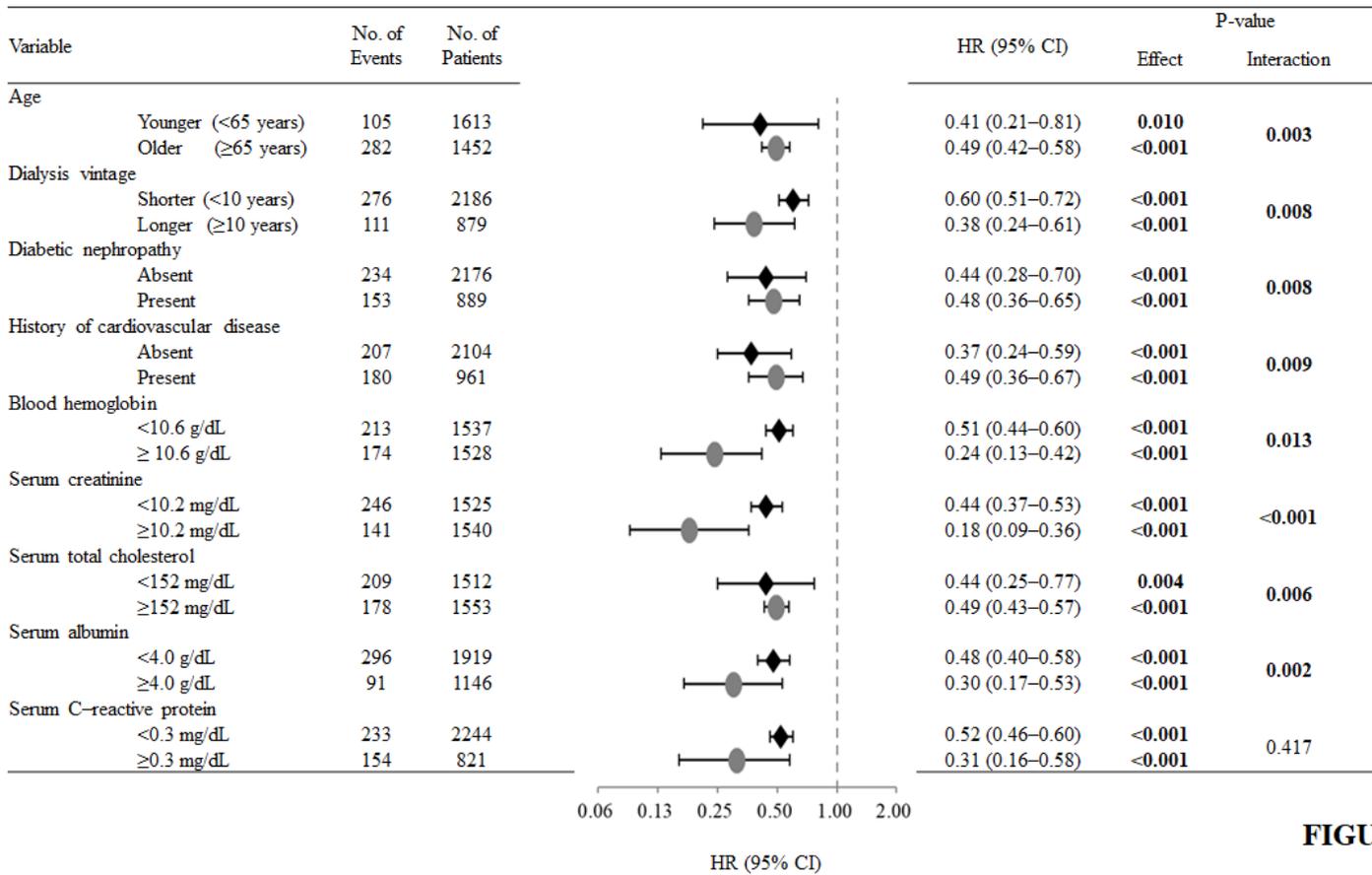


FIGURE 3

Figure 3

Propensity-weighted HRs and 95% CIs for infection-related mortality in women compared with that in men according to subgroups of baseline characteristics adjusted using Cox regression analysis in propensity score-weighted samples. Adjustment was performed for baseline characteristics (age, diabetic nephropathy, history of cardiovascular disease, dialysis vintage, blood hemoglobin, serum levels of creatinine, total cholesterol, albumin, and C-reactive protein). A P-value less than 0.05 was considered statistically significant. Abbreviations: CI, confidence interval; HR, hazard ratio.

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