Original Article

Female patients with end-stage renal failure treated by hemodialysis had a low mortality rate and small patient number compared to male patients: 5-year follow-up study in Japan

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(Received 22 August, 2024; Accepted 30 August, 2024; Released online in J-STAGE as advance publication 6 September, 2024)

This study aimed to evaluate gender differences of hemodialysis patients in adverse events, gastrointestinal bleeding, and bone fractures during 5 year longitudinal follow-up period in the regional core hospital in Japan. This study included 151 patients with maintenance hemodialysis for end-stage renal failure at Takagi Hospital in December 2017. All the patients, divided into females-group of 61 and males-group of 90. Data were evaluated in the electronic medical record. Multivariate analysis indicated a decrease in diabetes mellitus (odd ratio: 2.3, 95% confidence interval: 1.1–4.8, $p = 0.03$) and less mortality in those younger than 75 years old (odd ratio: 0.2, 95% confidence interval: 0.1–0.8, $p = 0.02$) were characterized factors in females. Gastrointestinal bleeding were not different between genders. Bone fractures were high in females (females: 34.4% vs males: 18.9%; $p<0.03$), whereas the mortality rate of bone fractured patients was markedly high in males (females: 28.6% vs males: 76.5%; $p = 0.003$) with lower body bone fractures. In conclusion, diabetes mellitus-induced end-stage renal failure was less common in females. The mortality rate during hemodialysis was higher in males less than 75 years old with increased mortality with lower bone fractures.

***Key Words*:** **bone fracture, cardiovascular disease, infection, diabetes mellitus, aging**

End-stage renal failure is a critical condition that necessitates proper medical intervention. Maintenance hemodialysis is commonly utilized in patients with end-stage renal failure to ensure survival.[1–3] In Japan, hemodialysis is commonly administered to patients with end-stage renal failure, regardless of comorbidities, underlying diseases causing renal failure, and age,[1–4] and is covered by the universal insurance system.[5,6] According to the Renal Data Registry of the Japanese Society for Dialysis Therapy, the prevalence of hemodialysis patients in Japan has shown a time-dependent increase, reaching 15 patients per 10,000 population.[3] Additionally, it is estimated that the number of female hemodialysis patients is approximately half that of male patients.[3]

Patients undergoing hemodialysis commonly present with various underlying diseases and comorbidities, such as diabetes mellitus,[3,7] cardiovascular and cerebrovascular diseases,[2,8,9] and malignant diseases.[3] Moreover, the therapeutic management of chronic hemodialysis is associated with various adverse events, including gastrointestinal bleeding,[10–13] bone fractures,[14–16] infection,[3,17] and cardiovascular and cerebrovascular diseases.[2,8,9] The occurrence of adverse events may vary between females and males, and there is limited research focusing on gender differences in this area.

This observational study sought to investigate gender disparities in the real-world patient characteristics of individuals undergoing maintenance hemodialysis at Takagi Hospital, a regional core hospital in Japan. Significantly, this study examined gender disparities in adverse events, gastrointestinal bleeding, and bone fractures over a 5-year follow-up period.

Materials and Methods

Patients. This longitudinal study included 151 patients in December 2017 undergoing maintenance hemodialysis for end-stage renal failure at the Human Dialysis Center of Nephrology in Takagi Hospital, a regional core hospital in Japan.[13,18,19] All patients who received maintenance hemodialysis for end-stage renal failure at Kouhou-kai Takagi Hospital were included, and the number of patients on December 1, 2017, was 151, who were followed up for 5 years or until mortality.[13,15] Monitoring of patients in outpatient care with blood sampling was performed every month. All patients were divided into two groups: a female, 61, and a male group, 90. Patient characteristics and events, including mortality and various clinical indicators, were detected in the electronic medical record for 5 years until December 2022. Age, duration of hemodialysis in December 2017, the origin of renal failure, and mortality were evaluated. A patient's blood test in December 2017 was detected, including hemoglobin, total protein, albumin, parathyroid hormone, iron, potassium, sodium, and calcium.

Serious complications. During the 5-year observation period, complications of gastrointestinal bleeding and bone fractures were detected. Gastrointestinal bleeding was determined by gastrointestinal endoscopy. All patients with signs of gastrointestinal bleeding, including melena, hematemesis, and reduction of serum hemoglobin, underwent gastrointestinal endoscopy at Takagi

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doi: 10.3164/jcbn.24-141

Table 1. The characteristics of male and female patients treated with the chronic hemodialysis for end-stage renal failure: 5 year-follow up during December 2017 and November 2022

	Females (n = 61)	Males (n = 90)	p value
Age (years old)	70.2 ± 13.4	67.8 ± 12.8	0.26
<75	35	59	0.31
≥75	26	31	
Duration of hemodialysis (months)	99.3 ± 93.6	110.0 ± 110.6	0.54
Origin of renal failure			0.02*
Diabetes mellitus	15	39	
Nephrogenic diseases	46	51	
Mortality Total	16/61	39/90	0.03*
<75 years old	3/35	18/59	0.01*
≥75 years old	13/26	21/31	0.17

Nephrogenic diseases, including chronic nephritis and nephrosclerosis. *p<0.05. Data are mean ± SD.

Table 2. Blood test of the patients with the hemodialysis on December 2017: comparison between females and males

	Females (n = 61)	Males (n = 90)	p value
Hemoglobin (g/dl)	11.0 ± 1.3	10.9 ± 1.6	0.71
Total protein (g/dl)	6.4 ± 0.5	6.3 ± 0.7	0.39
Albumin (g/dl)	3.0 ± 0.8	2.9 ± 0.9	0.45
Intact parathyroid hormone (pg/ml)	133 ± 99	158 ± 137	0.24
Serum iron (mg/dl)	59 ± 24	62 ± 29	0.48
Potassium (mEq/L)	4.5 ± 0.1	4.5 ± 0.1	0.68
Sodium (mEq/L)	138.0 ± 0.5	139.0 ± 0.4	0.11
Corrected calcium (mg/dl)	9.2 ± 0.9	8.8 ± 0.9	0.11

Data are mean ± SD.

Hospital. Of 151 patients, 32 (21.2%: 4.2% per year) were endoscopically diagnosed with gastrointestinal bleeding. All hemodialysis patients with gastrointestinal bleeding were treated in the emergency and gastroenterology departments of Takagi Hospital. Bone fractures were diagnosed in orthopedic surgery at Takagi Hospital. Upper bone fractures included humeral fractures, radius fractures, and others. The lower bone fractures were femoral neck fractures, femoral inter- and sub-trochanteric fractures, and vertebral compression fractures. All hemodialysis patients with bone fractures were treated at the orthopedic surgery of Takagi Hospital.

Ethical approval. This study was conducted by the Declaration of Helsinki with ethical review and approval from the Takagi Hospital's Kouhou-kai Ethical Committee (#495) and the International University of Health and Welfare Ethical Committee (21-Ifh-027). Written informed consent was obtained from all patients with hemodialysis.

Statistical analysis. Baseline characteristics of female and male patients were compared using the Chi-squared test for categorical variables and the Student's t test for continuous variables. We applied the multiple logistic regression model with explanatory variables with significance levels (univariate p<0.05 on statistical tests) except for closely gender-related factors of height and body weight. Odds ratios and 95% confidence interval were shown in the tables. JMP Pro 16 (SAS Institute Inc., Cary, NC) was used for all analyses, and statistical significance was defined as p<0.05.

Results

Characteristics of female patients compared with male patients. Patient characteristics between female and male patients who received hemodialysis for end-stage renal failure were compared, as indicated in Table 1. The number of patients was small in females compared to males, and this difference was due to the origin of renal failure. Namely, patients of diabetes mellitus-induced renal failure were significantly less in females compared to males (p<0.02). The mortality rate was significantly lower in female patients compared to male patients (p<0.03), and low mortality in females was mainly due to the younger generation less than 75 years old (p<0.014), and the mortality rate in patients older than 75 years old was equivalent in females and males.

Blood test at entry on December 2017. Table 2 shows the blood test results when the patients entered the study in December 2017. Blood samples, including hemoglobin, total protein, albumin, parathyroid hormone, iron, potassium, sodium, and calcium, were not different between females and males.

Multivariate analysis of characterized factors of female patients with hemodialysis. As indicated in Table 3, multivariate analysis indicated that decreased number of diabetes mellitus patients for the origin of renal failure (odd ratio: 2.3, 95% confidence interval: 1.1–4.8, p = 0.03) and less mortality in younger than 75 years old (odd ratio: 0.2, 95% confidence interval: 0.1–0.8, p = 0.02) were independent characterized factors in female hemodialysis patients.

Gastrointestinal bleeding and bone fractures during hemodialysis. Table 4 shows the incidence of complications of gastrointestinal bleeding and bone fractures during a 5-year

doi: 10.3164/jcbn.24-141

Table 3. Multivariate analysis compared between female and male patients

Females vs Males	Odds ratio	95% CI	*p* value
Origin of renal failure	2.3	(1.1–4.8)	0.03*
Mortality <75 year-old (vs survival)	0.2	(0.1–0.8)	0.02*
Mortality ≥75 year-old (vs survival)	0.6	(0.3–1.4)	0.2

*p<0.05. 95% CI, 95% confidence interval.

Table 4. BGastrointestinal (GI) bleeding and bone fracture during 5 year-follow period: comparison between females and males

	Females (n = 61)	Males (n = 90)	*p* value
GI bleeding	10/61	22/90	0.23
Mortality	3/10	12/22	0.36
Upper GI bleeding	6/61	18/90	0.14
Mortality	1/6	9/18	0.15
Lower GI bleeding	4/61	3/90	0.36
Mortality	2/4	3/3	0.14
Bone fracture	21/61	17/90	0.03*
Mortality	6/21	13/17	0.003**
Upper body bone fracture	8/61	4/90	0.05
Mortality	2/8	2/4	0.39
Lower body bone fracture	13/61	13/90	0.28
Mortality	4/13	11/13	0.006**

*p<0.05, **p<0.01.

follow-up period compared between female and male patients. Regarding upper gastrointestinal bleeding, incidence and mortality due to bleeding were not different between females and males. The incidence of lower gastrointestinal bleeding was less than that of upper gastrointestinal bleeding, and incidence and mortality were not different between females and males. The complication rate of bone fracture was high in females compared to males (females: 34.4% vs males: 18.9%; p<0.03), whereas the mortality rate of bone fractured patients was markedly high in males compared to females (females: 28.6% vs males: 76.5%; p = 0.003). The increase in mortality rate in males was definitely in patients with lower body bone fractures (p = 0.006).

Discussion

The current 5-year follow-up study conducted at a regional core hospital in Japan has revealed the clinical characteristics of female and male patients undergoing chronic hemodialysis for end-stage renal failure. Specifically, i) The incidence of end stage renal failure attributed to diabetes mellitus was lower in females than in males. ii) Mortality rates during hemodialysis were lower in females, particularly among patients younger than 75 years old. iii) The incidence of upper and lower major gastrointestinal bleeding was similar between females and males. iv) While bone fractures were more common in female patients undergoing hemodialysis, mortality was higher in male patients with lower bone fractures during hemodialysis.

Lower prevalence of chronic hemodialysis was observed in females compared males in the study, which can be attributed due the incidence number of end-stage renal caused by diabetes mellitus in females. Nevertheless, the incidence of hemodialysis in patients with nephrogenic diseases was similar in both genders. This finding was corroborated by the 2022 annual survey of the Japanese Society for Dialysis Therapy Renal Data Registry.[3] In 2016, the number of diabetes mellitus patients in Japan was approximately 10 million, with female patients accounting for half of the male patients due to lifestyle-related diseases.[20,21] This gender discrepancy may be a contributing factor to the lower number of female patients undergoing chronic hemodialysis.

The mortality among individuals under than 75 of age old, was higher in males than in females, while the mortality among those aged 75 and the old was similar between in genders. In numerous studies, cardiovascular and cerebrovascular diseases, as well as infectious diseases, have been identified as the primary comorbidities associated with mortality in hemodialysis patients.[2–4,8,9,22–24] Additionally, it has been observed that vascular diseases are more prevalent among male patients in Japan.[25] The current study did not precisely assess the specific causes of mortality for each patient, indicating a need for further investigation. As demonstrated in the current study, bone fractures resulted in higher mortality rates among male patients compared to female patients, potentially contributing to gender disparities in mortality among hemodialysis patients.

Lower body bone fractures including vertebral compression and femoral fractures, along with concomitant fragility elderly populations, generations, emerged as significant societal concerns problems in Japan and nations countries.[16,26–28] As previously shown,[29] bone fractures pose a complex issue for hemodialysis patients and were found to be frequent in the current study, occurring at a rate of 27.2% over 5 years (5.4% per year). The incidence of complications from bone fractures was found to be higher in female hemodialysis patients compared to male patients, with rates of 34.4% and 18.9% respectively. The mortality rate among hemodialysis patients with complicated lower body bone fractures was notably higher in male patients (30.8% for females vs 84.6% for males). The findings indicate that lower body bone fractures may lead to significant harm, such as fragility, in hemodialysis patients, with a lesser impact observed in females compared to males.

The current retrospective follow-up study has several limita-

tions. The sample size was limited in the single-institution study conducted at the regional core hospital in Japan. The therapeutic approach and the number of end-stage renal failure patients may vary from one country to another. The duration of hemodialysis treatment for the patient, spanning 5 years, was deemed insufficient. It is important to emphasize that all 151 patients were closely monitored at Takagi Hospital and received comprehensive medical attention.

In conclusion, end-stage renal failure induced by diabetes mellitus was prevalent frequent in males than in females, whereas disease-induced renal failure induced by nephrogenic disease equally distributed between in females and males. Mortality rates were lower among female hemodialysis patients, particularly those under 75 years of age and those with lower body bone fracture complications.

Acknowledgments

We would like to appreciate Professor Tsutomu Yamazaki, the International University of Health and Welfare Graduate School of Medicine, for invaluable advice and direction.

Conflict of Interest

No potential conflicts of interest were disclosed.

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doi: 10.3164/jcbn.24-141