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The influence of renal dialysis and hip fracture sites on the 10-year mortality of elderly hip fracture patients

A nationwide population-based observational study

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Abstract

Hip fractures in older people requiring dialysis are associated with high mortality. Our study primarily aimed to evaluate the specific burden of dialysis on the mortality rate following hip fracture. The secondary aim was to clarify the effect of the fracture site on mortality. A retrospective cohort study was conducted using Taiwan's National Health Insurance Research Database to analyze nationwide health data regarding dialysis and non-dialysis patients ≥65 years who sustained a first fragility-related hip fracture during the period from 2001 to 2005. Each dialysis hip fracture patient was age- and sex-matched to 5 non-dialysis hip fracture patients to construct the matched cohort. Survival status of patients was followed-up until death or the end of 2011. Survival analyses using multivariate Cox proportional hazards models and the Kaplan-Meier estimator were performed to compare between-group survival and impact of hip fracture sites on mortality. A total of 61,346 hip fracture patients were included nationwide. Among them, 997 dialysis hip fracture patients were identified and matched to 4985 non-dialysis hip fracture patients. Mortality events were 155, 188, 464, and 103 in the dialysis group, and 314, 382, 1505, and 284 in the non-dialysis group, with adjusted hazard ratios (associated 95% confidence intervals) of 2.58 (2.13–3.13), 2.95 (2.48–3.51), 2.84 (2.55–3.15), and 2.39 (1.94–2.93) at 0 to 3 months, 3 months to 1 year, 1 to 6 years, and 6 to 10 years after the fracture, respectively. In the non-dialysis group, survival was consistently better for patients who sustained femoral neck fractures compared to trochanteric fractures (0–10 years' log-rank test, $P < .001$). In the dialysis group, survival of patients with femoral neck fractures was better than that of patients with trochanteric fractures only within the first 6 years post-fracture (0–6 years' log-rank, $P < .001$). Dialysis was a significant risk factor of mortality in geriatric hip fracture patients. Survival outcome was better for non-dialysis patients with femoral neck fractures compared to those with trochanteric fractures throughout 10 years. However, the survival advantage of femoral neck fractures was limited to the first 6 years postinjury among dialysis patients.

Abbreviations: CCI = Charlson comorbidity index, CI = confidence interval, ESRD = end-stage renal disease, FRAX = WHO Fracture Risk Assessment Tool, HR = hazard ratio, ICD-9-CM = International Classification of Disease Clinical Modification, 9th revision, mCCI = modified Charlson comorbidity index, NHIRD = National Health Insurance Research Database.

Keywords: dialysis, end-stage renal disease, femoral neck fracture, fragility fracture, hip fracture, osteoporosis, trochanteric fracture

1. Introduction

Hip fractures in the geriatric population (people older than 65 years) are the subject of significant medical and public health concern due to their frequent adverse outcomes and high mortality rates.[1–4] It is estimated that 10% of women and 5% of men will sustain a hip fracture during their lifetime.[5] Hip fractures in elderly patients are associated with high mortality rates up to 20% and 2-fold excess mortality during the first year after injury.[4,6] Because the population is aging, the prevention and management of hip fractures have become some of the most important public health issues worldwide. In addition, end-stage renal disease (ESRD) is another growing public health issue among the aging population. In Europe, it is estimated that 48% of patients beginning maintenance dialysis are elderly patients.[7] Whereas in the United States, incidence rates of dialysis was 3-fold among geriatric population than those aged between 45 and 64 years (1500 per million and 500 per million, respectively).[8] Although maintenance dialysis prevents death

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from uremia, the mortality rate associated with ESRD remains high, including a higher mortality rate after hip fracture among patients on dialysis.[9–12] However, the effect of dialysis on the mortality rate of geriatric patients after hip fracture was not reported.

Based on the anatomic location of the fracture, hip fractures can be classified into 2 major types, namely femoral neck fractures and trochanteric fractures. The prevalence of these 2 types of fractures is similar in the general population, with a better survival rate reported for femoral neck fractures.[13–17] When specifically considering patients on dialysis, there is a trend toward a higher prevalence of femoral neck fractures compared to trochanteric fractures.[18–21] However, a clear distribution of hip fracture sites among patients receiving dialysis is yet to be determined using a large population-based cohort. Furthermore, how the hip fracture site influences the mortality rate of patients on dialysis has not been specifically evaluated.

Therefore, the aim of our study was to use nationwide population-based data from Taiwan's National Health Insurance Research Database (NHIRD) to compare mortality rates after fragility-related hip fractures among geriatric patients on dialysis with a comparable patient population not on dialysis. The secondary aim was to determine the distribution of hip fracture sites between these 2 patient groups and to evaluate the prognosis for trochanteric and femoral neck fractures in both groups.

2. Materials and methods

2.1. Data source

Data were extracted from the NHIRD database in Taiwan, which includes health information collected since 1995, when the Taiwan National Health Insurance, a single-payer health insurance system, was launched by the government. Ninety-nine percent of Taiwan's population is enrolled in this insurance system. The NHIRD is a large database derived from this system and includes a number of datasets, such as the Inpatients Expenditures Dataset, the Catastrophic Illness Dataset, and the Accident Dataset. The system uses International Classification of Disease Clinical Modification, 9th revision (ICD-9-CM) codes to classify diseases.

2.2. Nationwide hip fracture cohort

The study protocol was approved by the Institutional Review Board of the National Taiwan University Hospital (application and agreement number 201306043W). Because hip fracture has not been found to pose an additional risk for mortality in younger populations, the present study focused on the mortality of geriatric patients sustaining a hip fracture.[22] The Inpatients Expenditures Dataset from 1998 to 2005 was used to identify the geriatric patients who sustained a first fragility-related hip fracture. The following inclusion criteria were used to screen for prospective patients during the index years from 2001 to 2005: first incidence of hip fracture (ICD-9-CM diagnosis code 820.X); age ≥65 years at the time of fracture; and fracture management by closed reduction with percutaneous osteosynthesis (ICD-9-CM procedure code 79.1), open reduction with internal fixation (ICD-9-CM procedure code 79.3), or prosthetic arthroplasty (ICD-9-CM procedure code 81.5) at the time of hospitalization for the fracture. Patients were excluded based on the following criteria: history of hip fractures; malignancy-associated fractures (ICD-9-CM diagnosis codes 733.14 and 733.15); open fractures (ICD-9-CM diagnosis codes 820.10, 820.11, 820.12, 820.13, 820.19, 820.30, 820.31, 820.32, and 820.9); and hip fractures not associated with low-energy trauma. In the present study, low-energy trauma was defined as the energy resulting in hip fracture that was less than or equal to that of a fall from a standing height. The Accident Dataset was used to exclude patients with non-fragility hip fractures, including those fractures associated with traffic accidents, falls from a high place, and others. The list of patients with a first fragility-related hip fractures was cross-linked to the Catastrophic Illness Dataset to identify patients who had undergone regular maintenance dialysis on the day of admission for their hip fractures (Catastrophic Illness Dataset disease category code 4; ICD-9-CM diagnosis codes 585.05, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, and 404.93). To exclude patients with acute renal failure who required emergency dialysis for resuscitation during the acute stage of fracture treatment, only patients who had been undergoing regular maintenance dialysis for 1 year or longer were included in the study.

A total of 61,346 first fragility hip fracture patients were identified and included in the nationwide hip fracture cohort. Among them, 997 undergoing dialysis treatment formed the dialysis hip fracture group and the remaining 60,349 formed the non-dialysis hip fracture group.

2.3. Matched cohort

To improve study efficiency and precision, we performed a matching procedure for survival analysis.[23] Each dialysis hip fracture patient was age- and sex-matched to 5 randomly selected non-dialysis patients who had sustained a hip fracture during the same year. Complete matching was not possible for 27 patients because we could not find 5 patients of the same age in the non-dialysis population; therefore, these patients were matched to non-dialysis peers with an age difference of up to 3 years. After the matching procedure, a total of 5982 patients were included in the matched cohort for survival analysis that comprised 997 dialysis hip fracture patients and 4985 non-dialysis hip fracture patients. The flowchart of patient selection is shown in Figure 1. The Registry of Deaths, which includes annually updated dates of birth and death for the entire population of Taiwan, was used to study survival time, with death defined as the outcome event. Survival time was defined as the period from the date of admission for hip fracture until the date of death. The follow-up time was defined as the period from the date of admission until the end of the study. Survival of the matched cohort was followed-up through 2011. The last patient's admission date was December 31, 2005; therefore, the shortest follow-up period was 6 years.

2.4. Risk factors

Risk factors potentially confounding the relationship between hip fracture and mortality were recorded, including age, sex, fracture site, and pre-existing comorbidities. Fracture sites were identified based on the ICD-9-CM diagnosis and procedure codes. Patients with a diagnosis of trochanteric fractures (ICD-9-CM diagnosis codes 820.20, 820.21, and 820.22) and treated with implant fixation (ICD-9-CM procedure codes 79.1 and 79.3) were classified as the trochanteric fracture group. Patients with a diagnosis of femoral neck fractures (ICD-9-CM diagnosis codes 820.00–820.09) were classified as the femoral neck fracture

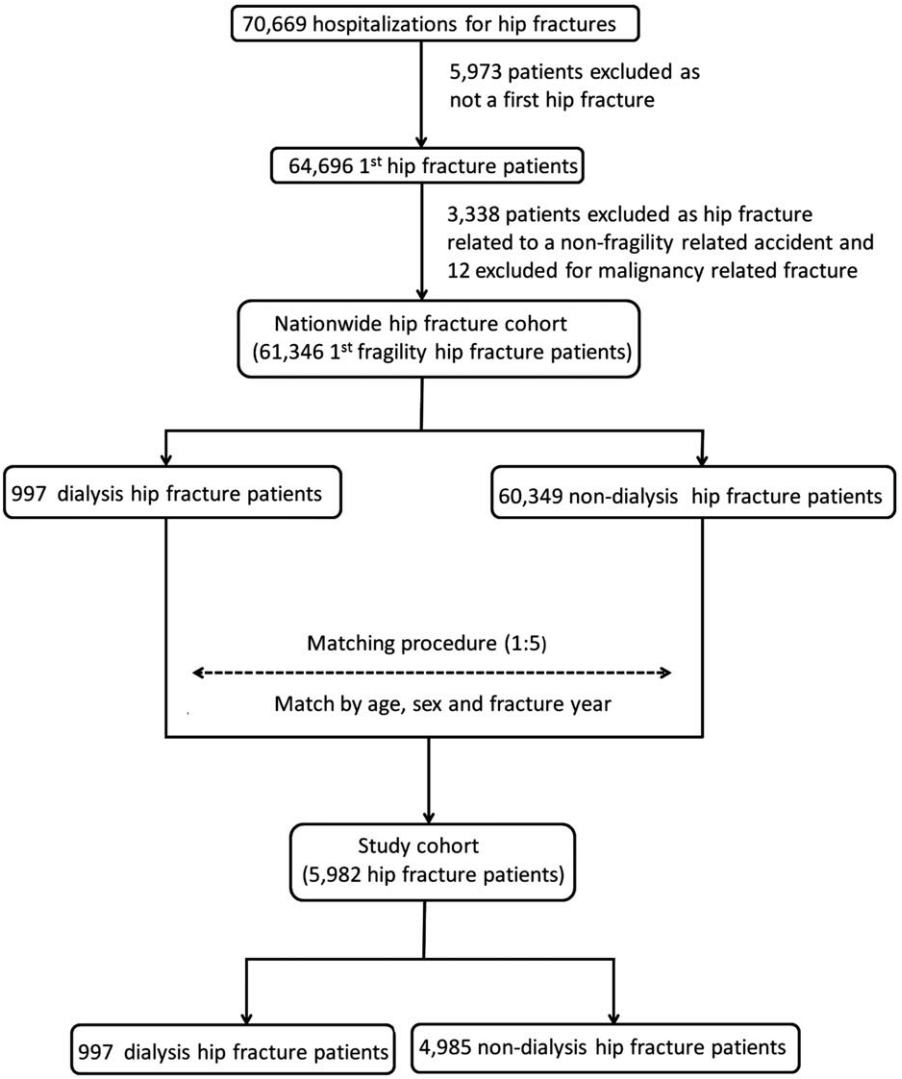

Figure 1. Flowchart for the identification of participants.

group. Because the only indication for prosthetic arthroplasty for hip fractures in the Taiwan National Insurance plan is displaced femoral neck fractures, patients with a diagnosis of nonspecified fracture sites (ICD-9-CM diagnosis code 820.8) treated with prosthetic arthroplasty (ICD-9-CM procedure code 81.5) were also classified as the femoral neck fracture group. Patients with a diagnosis of trochanteric fractures treated by arthroplasty and all other patients with a fracture site that could not be identified by ICD-9-CM codes were classified as having an "unknown fracture site."

Comorbidities were identified based on the ICD-9-CM diagnosis codes and disease category codes included in the Inpatients Expenditures Dataset and Catastrophic Illness Dataset. The Charlson comorbidity index (CCI), which identifies 19 categories of comorbidities defined by ICD-9-CM diagnosis codes, was used to quantify the burden of coexisting health conditions. Each category of the CCI is associated with a weight score based on the adjusted risk for mortality. For example, the category with a diagnosis of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, rheumatoid arthritis, or diabetes mellitus was assigned a score of 1; the category with paraplegia or moderate to severe renal disease was assigned a score of 2; and moderate or severe liver disease was assigned a score of 3. The sum of all scores of each indicated diagnosis provided a single CCI score for each patient.[24]

2.5. Statistical analysis

Between-group differences were evaluated by 2 independent sample t tests for continuous variables and the χ^2 test for categorical variables. Survival analysis including the Cox proportional hazards model and the Kaplan-Meier estimator was performed for the matched cohort. The Cox proportional hazards model was constructed to calculate the hazard ratio (HR) and the associated 95% confidence interval (CI) to evaluate the increased risk of mortality associated with dialysis. Unadjusted HRs of mortality for each risk factor, including dialysis status, age, sex, fracture site, and comorbidities, were computed. To identify the final set of risk factors, a forward stepwise procedure was performed with an entry criterion of $P < .05$ and a removal criterion of $P \geq .1$. Risk factors with $P = .05$ to .1 were retained in

the model. In particular, the CCI was utilized for between-group comparisons of baseline comorbidities, whereas the modified Charlson comorbidity index (mCCI), which is computed from the CCI without age and renal disease scores, was used for the multivariate model to avoid multicollinearity. The Kaplan-Meier estimator was used to compare the mortality risk for the dialysis and non-dialysis groups; the log-rank test was used to evaluate significant differences. All analyses were performed using the SAS statistical package (version 9.2 for windows, SAS Institute, Cary, NC). Statistical significance was defined as $P < .05$.

3. Results

3.1. Characteristics of the nationwide hip fracture cohort

Baseline characteristics and the 10-year crude survival rate of the nationwide hip fracture cohort are listed in Table 1. There was no significant difference in the sex distribution between the dialysis and non-dialysis hip fracture groups ($P = .05$). However, there was a significant between-group difference in age ($P < .001$). Participants in the dialysis hip fracture group were younger (75 ± 6 years) than those in the non-dialysis group (79 ± 7 years). There was also a significant between-group difference in the distribution of hip fracture sites, with a higher proportion of femoral neck fractures in the dialysis group compared to the non-dialysis group (51% and 42%, respectively; $P < .001$). Within the dialysis group specifically, there was a higher proportion of femoral neck fractures (51%) compared to trochanteric fractures (38%). The dialysis group also had higher CCI scores compared to the non-dialysis group (CCI scores: 8.6 ± 2.8 and 6.2 ± 2.7, $P < .001$; CCI scores without inclusion of the variable moderate-to-severe renal disease: 6.6 ± 2.8 and 6.1 ± 2.7, $P < .001$), as well as an overall higher proportion of specific comorbidities, including myocardial infarction (dialysis, 4.0%; non-dialysis, 2.2%; $P < .001$), congestive heart failure (dialysis, 18%; non-dialysis, 8.9%; $P < .001$), peripheral vascular disease (dialysis, 3.2%; non-dialysis, 1.4%; $P < .001$), and diabetes mellitus (dialysis, 66%; non-dialysis, 26%; $P < .001$). The proportion of fractures managed with prosthetic arthroplasty was also higher in the dialysis group. Arthroplasty was performed for 48% of cases in dialysis group and for 40% of cases in the non-dialysis group ($P < .001$). At the census point of the study, 43,781 (71%) patients had died. The mortality rate was significantly higher for patients in the dialysis group, with a mortality rate of 91% compared to 71% for those in the non-dialysis group ($P < .001$).

Table 1

Between-group comparison of baseline characteristics and 10-year crude survival rate of the nationwide hip fracture cohort.

	Dialysis	Non-dialysis	*P* value
Age	74.9 (± 6.1)	78.8 (± 7.1)	<.001
65–74 y	512 (51.4%)	17470 (28.9%)	<.001
75–84 y	406 (40.7%)	29448 (48.8%)	
≥85 y	79 (7.9%)	13431 (22.3%)	
Sex			.05
Male	351 (35.2%)	23065 (38.2%)	
Female	646 (64.8%)	37284 (61.8%)	
Fracture site			<.001
Femoral neck	512 (51.4%)	25649 (42.5%)	
Trochanteric	381 (38.2%)	30019 (49.7%)	
Unknown sites	104 (10.4%)	4681 (7.8%)	
Operation type			<.001
Arthroplasty	479 (48.0%)	24047 (39.8%)	
CRIF/ORIF	518 (52.0%)	36302 (60.2%)	
CCI	8.6 (± 2.8)	6.2 (± 2.7)	<.001
CCI*	6.6 (± 2.8)	6.1 (± 2.7)	<.001
MI	40 (4.0%)	1331 (2.2%)	<.001
CHF	175 (17.6%)	5370 (8.9%)	<.001
PVD	32 (3.2%)	863 (1.4%)	<.001
CVA	176 (17.7%)	11041 (18.3%)	.60
RA	7 (0.7%)	364 (0.6%)	.69
DM	659 (66.1%)	15782 (26.1%)	<.001
Paraplegia	10 (1.0%)	1848 (3.1%)	<.001
Survived	87 (8.7%)	17478 (29.0%)	<.001
Total	997	60349	

Values are reported as the mean (± standard deviation) for continuous variables and number (%) for categorical variables. CCI = Charlson comorbidity index, CCI* = Charlson comorbidity index without the inclusion of the variable moderate-to-severe renal disease, CHF = congestive heart failure, CRIF/ORIF = close or open reduction and internal fixation, CVA = cerebrovascular disease, DM = diabetic mellitus, MI = myocardial infarction, PVD = peripheral vascular disease, RA = rheumatoid arthritis, y = years.

Table 2

Between-group comparison of baseline characteristics and 10-year crude survival rate of the matched cohort.

	Dialysis	Non-dialysis	*P* value
Age	74.9 (± 6.1)	74.9 (± 6.1)	1
65–74 y	512 (51.4%)	2583 (51.8%)	.976
75–84 y	406 (40.7%)	2004 (40.2%)	
≥85 y	79 (7.9%)	398 (8.0%)	
Sex			1
Male	351 (35.2%)	1755 (35.2%)	
Female	646 (64.8%)	3230 (64.8%)	
Fracture site			<.001
Femoral neck	512 (51.4%)	2191 (44.0%)	
Trochanteric	381 (38.2%)	2348 (47.1%)	
Unknown sites	104 (10.4%)	446 (8.9%)	
Operation type			<.001
Arthroplasty	479 (48.0%)	2047 (41.1%)	
CRIF/ORIF	518 (52.0%)	2938 (58.9%)	
CCI	8.6 (± 2.8)	5.8 (± 2.8)	<.001
CCI*	6.6 (± 2.8)	5.7 (± 2.8)	<.001
MI	40 (4.0%)	112 (2.2%)	.001
CHF	175 (17.6%)	388 (7.8%)	<.001
PVD	32 (3.2%)	70 (1.4%)	<.001
CVA	176 (17.7%)	933 (18.7%)	.43
RA	7 (0.7%)	49 (1.0%)	.40
DM	659 (66.1%)	1902 (32.6%)	<.001
Paraplegia	10 (1.0%)	172 (3.5%)	<.001
Survived	87 (8.7%)	1960 (39.3%)	<.001
Total	997	4985	

Values are reported as the mean (± standard deviation) for continuous variables and number (%) for categorical variables. CCI = Charlson comorbidity index, CCI* = Charlson comorbidity index without the inclusion of the variable moderate-to-severe renal disease, CHF = congestive heart failure, CRIF/ORIF = close or open reduction and internal fixation, CVA = cerebrovascular disease, DM = diabetic mellitus, MI = myocardial infarction, PVD = peripheral vascular disease, RA = rheumatoid arthritis, y = years.

3.2. Characteristics of the matched cohort

Baseline characteristics and the 10-year crude survival rate of the matched cohort are listed in Table 2. In the matched cohort, the dialysis and non-dialysis groups were comparable with respect to age, sex, and fracture year, as defined by the matching scheme. Similar to the results of the nationwide hip fracture cohort, patients in the dialysis group were more likely to have sustained a femoral neck fracture compared to the non-dialysis group (51% and 44%, respectively; $P < .001$), to have been treated with arthroplasty (48% and 41%, respectively; $P < .001$), and to have

Table 3

Results of unadjusted Cox proportional model stratified by age and sex for the matched cohort analysis.

	0–3 mo		3–12 mo		1–6 y		6–10 y	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Male								
65–74 y	2.70 (1.70–4.29)	<.001	3.37 (2.23–5.10)	<.001	2.80 (2.17–3.61)	<.001	2.63 (1.67–4.16)	<.001
75–84 y	2.51 (1.70–3.72)	<.001	2.19 (1.45–3.32)	<.001	2.54 (1.94–3.31)	<.001	2.17 (1.10–4.28)	.026
≥85 y	1.40 (0.61–3.23)	.43	3.31 (1.64–6.66)	<.001	2.02 (1.04–3.93)	.04	3.54 (0.76–16.46)	.11
Female								
65–74 y	2.93 (1.95–4.42)	<.001	2.88 (2.05–4.06)	<.001	3.50 (2.91–4.22)	<.001	3.08 (2.25–4.21)	<.001
75–84 y	3.22 (2.20–4.71)	<.001	3.46 (2.43–4.92)	<.001	3.03 (2.48–3.72)	<.001	1.91 (1.24–2.96)	.004
≥85 y	1.05 (0.40–2.75)	.92	3.06 (1.57–5.99)	.001	2.38 (1.55–3.67)	<.001	1.67 (0.40–6.98)	.49
Overall	2.58 (2.13–3.13)	<.001	2.95 (2.48–3.51)	<.001	2.84 (2.55–3.15)	<.001	2.39 (1.94–2.93)	<.001

Unadjusted HR of dialysis-related mortality among hip fracture patients, stratified for age and sex. 95% CI = 95% confidence interval, HR = hazard ratio, y = years.

more comorbidities (CCI scores: 8.6 ± 2.8 and 5.8 ± 2.8, $P < .001$; CCI scores without inclusion of the variable moderate-to-severe renal disease: 6.6 ± 2.8 and 5.7 ± 2.8, $P < .001$). The median follow-up duration was 8.02 years (interquartile range, 2.27 years) for dialysis hip fracture patients and 8.04 years (interquartile range, 2.23 years) for the matched non-dialysis hip fracture patients. At the end of 2011, a total of 3935 mortality events were identified, which accounted for 66% of the matched cohort participants. The mortality rate of the patients in the dialysis group was significantly higher than that of the patients in the non-dialysis group (91% and 61%, respectively; $P < .001$). Among these mortality events, 38% of deaths in the dialysis group occurred during the first year after the fracture incident; 23% of deaths occurred during the first year after hip fracture in the non-dialysis group ($P < .001$).

3.3. Dialysis and mortality

The results of the unadjusted Cox model are reported in Table 3. HRs for mortality among patients with hip fractures and undergoing dialysis remained high during all time periods: 2.58 (95% CI, 2.13–3.13) at 0 to 3 months; 2.95 (95% CI, 2.48–3.51) at 3 months to 1 year; 2.84 (95% CI, 2.55–3.15) at 1 to 6 years; and 2.39 (95% CI, 1.94–2.93) at 6 to 10 years. The HRs for dialysis were significant for all ages for both men and women except for patients older than 85 years during the time periods of 0 to 3 months and 6 to 10 years. Results of the multivariate Cox proportional hazards model are reported in Table 4. After adjusting the model for potential risk factors, including age, sex, fracture site, and comorbidities, dialysis remained a significant risk factor for mortality during all time periods ($P < .001$). Other significant risk factors during all time periods included mCCI ≥ 2 ($P < .001$) and male sex ($P < .001$).

3.4. Fracture sites and mortality

The Kaplan-Meier estimator for all-cause mortality in the dialysis and non-dialysis groups of the matched cohort is presented in Figure 2. The survival curve for patients in the dialysis hip fracture group declined and significantly diverged from that of patients in the non-dialysis hip fracture group from the first month after fracture (log-rank $P < .001$). This between-group difference remained significant (log-rank $P < .001$) when estimated survival curves were stratified by age and sex (Figs. 3 and 4, respectively). The estimated survival curves for the non-dialysis group stratified by fracture sites are shown in Figure 5. The survival curve for patients with femoral neck fractures was significantly higher than that for patients with trochanteric fractures during the 10-year period of the study (log-rank $P < .001$). The survival trend was different for patients on dialysis, as evident from the survival curves stratified by fracture sites (Fig. 6). In the dialysis group, the survival curve was significantly higher for patients with femoral neck fractures within the first 6 years after injury (log-rank, $P < .001$). However, the survival curves of both types of

Table 4

Result of adjusted Cox proportional model for the matched cohort analysis.

	0–3 mo		3–12 mo		1–6 y		6–10 y	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (reference: patients 65–74 y)								
75–85 y	1.26 (1.03–1.54)	.03	1.02 (0.85–1.22)	.82	1.24 (1.12–1.36)	<.001	1.34 (1.16–1.54)	<.001
≥85 y	1.45 (1.08–1.95)	.01	1.27 (0.97–1.65)	.08	1.79 (1.53–2.09)	<.001	2.25 (1.71–2.96)	<.001
Sex (reference: female patients)								
Male	1.68 (1.40–2.01)	<.001	1.56 (1.32–1.84)	<.001	1.49 (1.36–1.63)	<.001	1.30 (1.13–1.49)	<.001
Dialysis status (reference: non-dialysis patients)								
Dialysis	2.36 (1.94–2.87)	<.001	2.49 (2.09–2.98)	<.001	2.70 (2.43–3.00)	<.001	2.32 (1.89–2.86)	<.001
Fracture site (reference: femoral neck fractures)								
Trochanter	1.32 (1.09–1.59)	.005	0.96 (0.81–1.15)	.67	1.02 (0.93–1.11)	.74	1.09 (0.95–1.25)	.23
mCCI (reference: patients with mCCI = 0)								
1	1.64 (0.80–3.34)	.17	2.23 (0.95–5.25)	.07	1.58 (1.23–2.04)	<.001	1.86 (1.40–2.46)	<.001
≥2	4.19 (2.14–8.22)	<.001	10.83 (4.81–24.36)	<.001	3.26 (2.56–4.15)	<.001	2.86 (2.17–3.77)	<.001

95% CI = 95% confidence interval, HR = hazard ratio, mCCI = modified Charlson comorbidity index, weight of age, and renal disease was removed from CCI for multivariate model adjustment, y = years.

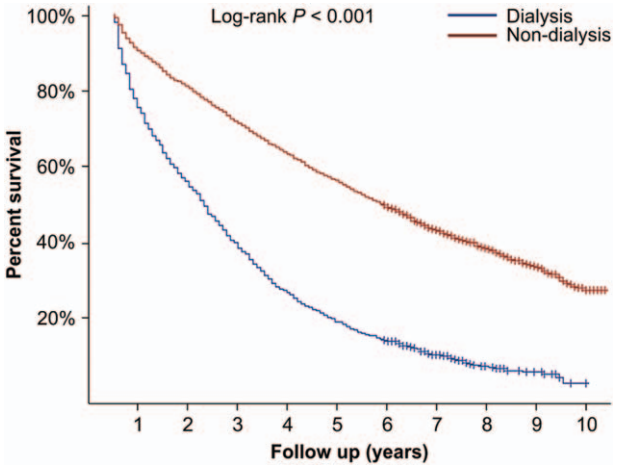

Figure 2. Results of the Kaplan-Meier estimation of cumulative mortality of patients in the dialysis and non-dialysis hip fracture groups. Ten-year Kaplan-Meier estimates of the cumulative probability of survival after hospital admission for hip fracture. Each vertical tick mark indicates a follow-up month during which patient censoring occurred.

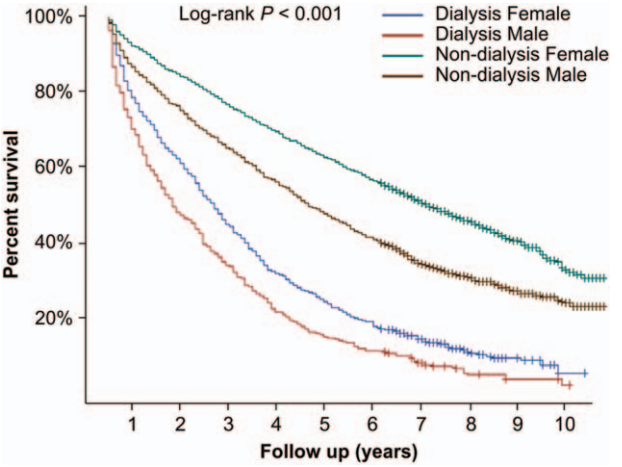

Figure 4. Results of the Kaplan-Meier estimator of cumulative mortality of patients in the dialysis and non-dialysis hip fracture groups stratified by sex. Ten-year Kaplan-Meier estimates of the cumulative probability of survival after hospital admission for hip fracture stratified by sex. Each vertical tick mark indicates a follow-up month during which patient censoring occurred.

fractures were comparable 6 years after fracture (log-rank, $P = .18$).

4. Discussion

In this nationwide longitudinal cohort study, survival data of 70,669 elderly patients who had sustained a hip fracture were evaluated for up to 10 years. Overall, the mortality rate was significantly higher among patients in the dialysis group compared to age- and sex-matched controls in the non-dialysis group. Even after adjusting for other potential risk factors, the average mortality rate was still more than 2-fold higher for patients in the dialysis group compared to the non-dialysis group (Table 4). The proportion of femoral neck fractures was significantly higher for patients in the dialysis group compared to the non-dialysis group. Furthermore, the survival rate of patients who sustained femoral neck fractures was higher than that for those who sustained trochanteric fractures. However, the higher survival rate among femoral neck fracture patients was limited to the first 6 years after injury among the dialysis group, whereas it lasted throughout the 10 years among the non-dialysis group.

To date, the additional burden of dialysis on the mortality rate after hip fracture has been evaluated by direct comparison of these rates between patients on dialysis with and without hip fracture.[9–12] In their single-site dialysis study, Coco et al reported a 1-year mortality rate of 64% for dialysis patients who sustained a hip fracture.[10] Using data from the US Renal Data System, Mittalhenkle et al[12] reported a 1-year mortality rate of

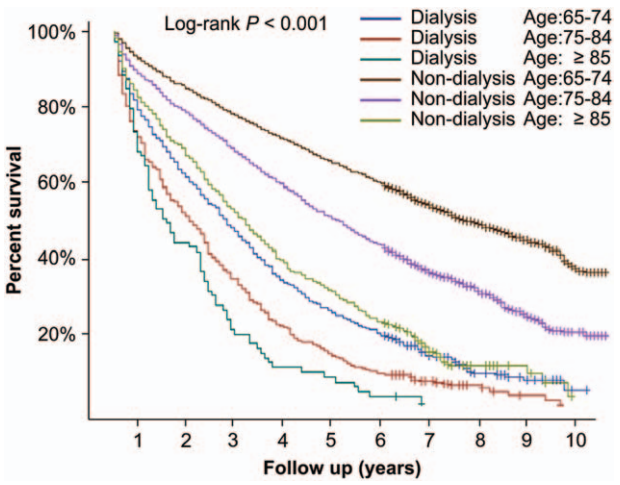

Figure 3. Results of the Kaplan-Meier estimator of cumulative mortality of patients in the dialysis and non-dialysis hip fracture groups stratified by age. Ten-year Kaplan-Meier estimates of the cumulative probability of survival after hospital admission for hip fracture stratified by age. Each vertical tick mark indicates a follow-up month during which patient censoring occurred.

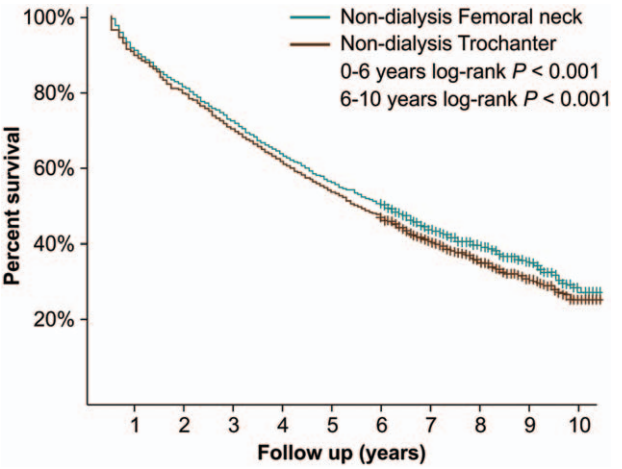

Figure 5. Results of the Kaplan-Meier estimator of cumulative mortality of patients in the non-dialysis hip fracture group stratified by fracture site. Ten-year Kaplan-Meier estimates of the cumulative probability of survival after hospital admission for hip fracture in patients in the non-dialysis group stratified by fracture site. Survival outcome was consistently higher over the course of 10 years for patients with femoral neck fractures compared with patients with trochanteric fractures. Each vertical tick mark indicates a follow-up month during which patient censoring occurred.

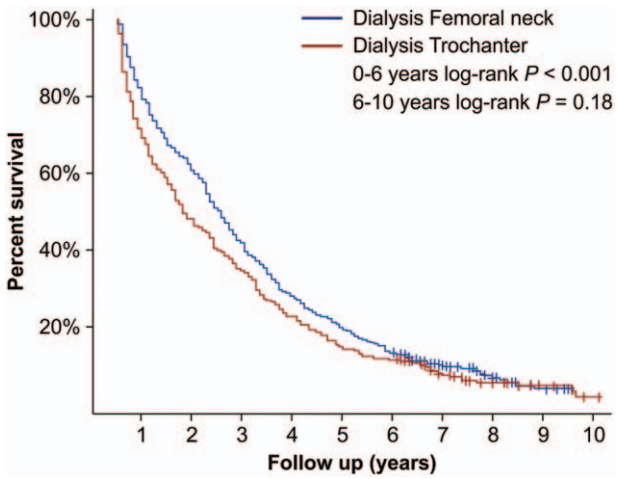

Figure 6. Results of the Kaplan-Meier estimator for cumulative mortality of patients in the dialysis hip fracture group stratified by fracture site. Ten-year Kaplan-Meier estimates of the cumulative probability of survival after hospital admission for hip fracture in patients in the dialysis group stratified by fracture site. Survival outcome was better for patients with femoral neck fractures compared to patients with trochanteric fractures during the first 6 years. Both estimation curves were comparable during the past 4 years. Each vertical tick mark indicates a follow-up month during which patient censoring occurred.

50%. In our matched cohort, the 1-year mortality rate for dialysis hip fracture patients was 38% and the 10-year mortality rate of dialysis hip fracture patients was 92%; however, these were reported to be 12% and 66% among dialysis patient without hip fractures.[25] The variation in the reported mortality rates of patients on dialysis after a hip fracture between studies could reflect the differences in care and health care expense reimbursement of dialysis patients between countries.

Another finding from our study was evidence of a significant risk of death during the acute stage after hip fractures for patients on dialysis, with mortality rates of 17% at 3 months and 38% at 1 year compared to rates of 10% and 23% at 3 months and 1 year, respectively, for non-dialysis patients. This higher risk of mortality within the first post-fracture year in the dialysis population could be explained by frailty syndrome. Frailty syndrome can be defined as a lack of physiological reserve seen across multiple-organ systems.[26] Fried et al proposed phenotype criteria of the frailty syndrome, including unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity.[27] They further validated the association between frailty syndrome and adverse outcomes, including mortality. A 73% prevalence of frailty syndrome was reported among dialysis patients; in the general population, this prevalence was 4.0% to 17%.[28,29] Even through hip fracture patients might have a high incidence of frailty syndrome,[30] when they were superimposed with dialysis, frailty syndrome-related conditions may further lead to loss of homeostatic capability and make it more difficult for dialysis patients to withstand the acute phase of hip fracture and its related surgeries.

Patients in the dialysis group had a more than 2-fold increase in mortality rates during all time intervals compared to patients in the non-dialysis group, with the exception of patients older than 85 years, who had mortality rates at 0 to 3 months and 6 to 10 years that were similar for both patient groups. This is because patients older than 85 years were too old to survive the acute phase of hip fractures or to survive longer than 6 years after surgery. The most common cause of death among patients in the dialysis group after hip fracture was reported to be cardiovascular complications, including myocardial infarction, peripheral vascular disease, congestive heart failure, and cerebrovascular accident.[31] However, after adjusting for these known confounding factors in our model, dialysis remained an independent risk factor for mortality across all time periods. It was postulated that the dialysis-related pathologies, such as bleeding tendency, immobilization, malnutrition, frailty syndrome, and high rate of subsequent hip fractures, are associated with increased mortality.

In the present study, we focused specifically on hip fractures of geriatric patients. In this geriatric population, dialysis patients sustained a hip fracture at a younger age than non-dialysis patients (dialysis, 75 ± 6.1 years; non-dialysis, 79 ± 7.1 years; $P < .001$). This could be attributed to poor renal function, which decreases overall physical capabilities and increases the risk of falls in relatively younger patients.[32] Additionally, dialysis-related osteodystrophies, such as secondary hyperparathyroidism and amyloid deposition, may lead to low bone strength in addition to osteoporosis. These reasons may explain why bone mineral density studies using dual-energy x-ray absorptiometry, which is commonly used to detect osteoporosis, cannot provide a reliable assessment of fracture risk in patients on dialysis.[33,34] This also explains why the WHO Fracture Risk Assessment Tool (FRAX), another commonly used tool to predict fracture in non-dialysis patients, has been found to be less effective for estimating the fracture risk of dialysis patients.[35,36] Furthermore, it is very difficult to improve the bone strength of patients on dialysis because the use of bisphosphonates, which are widely used antiosteoporotic agents, is contraindicated in this clinical population. Therefore, with an increased risk of fall, absence of a reliable predictor of fracture risk, and undertreatment of fragile bones, patients on dialysis are at higher risk for fracture than non-dialysis patients of the same age.

A tendency for a higher prevalence of femoral neck fractures compared to trochanteric fractures for patients on dialysis has been reported in several studies, with the incidence rate of femoral neck fractures ranging between 66% and 73% for all dialysis hip fracture patients.[18–21] However, these studies were limited in size; therefore, these differences were nonsignificant. In our nationwide cohort with 61,346 patients sustaining a first fragility hip fracture, femoral neck fractures accounted for 51% of hip fractures among patients in the dialysis group, which was significantly higher than the incidence of trochanteric fractures (38%). This higher proportion of femoral neck fractures compared to trochanteric fractures might indicate the selective effect of dialysis and chronic renal disease for reducing the bone strength of the femoral neck to a greater extent than in the trochanter.

For example, dialysis-related amyloidosis is associated with the formation of cystlike osteolytic lesions commonly located close to a synovial joint, which can cause more femoral neck fractures than trochanteric fractures.[19,37,38] Hyperparathyroidism may also predispose to hip fractures. This chronic kidney disease-related metabolic bone disease preferentially affects cortical bone, resulting in periosteal resorption, cortical bone porosity, and formation of osteitis fibrosa, which further decreases the cortical strength of the bone. Cortical bone-rich areas, such as the femoral neck, are therefore at higher risk for fracture.[39] These selective effects of chronic renal disease and dialysis on bone strength have been confirmed by peripheral quantitative computed tomography studies reporting a significant decrease in cortical bone

density in dialysis patients compared to non-dialysis controls, with no difference in trabecular bone density.[34,40]

In the general population, it was found that patients with femoral neck fractures might have better survival outcomes than patients with trochanteric fractures.[13,14] However, other studies have shown opposite results.[15,16] The present study showed that in the non-dialysis group, the survival rate was consistently higher among patients with femoral neck fractures compared to those with trochanteric fractures throughout the 10-year follow-up period. In contrast, in the dialysis group, the trend was different according to the survival curves (Fig. 6). The survival rate was significantly higher for patients with femoral neck fractures during the first 6 years, but it was comparable between the 2 fracture groups thereafter. Mortality rates of dialysis patients with femoral neck fractures have continued to increase and approach those of dialysis patients with trochanteric fractures. This could be explained by the higher long-term complication rate after femoral neck fracture surgeries. It was postulated that after long-term follow-up, the complication rate of trochanteric fractures might be stabilized if the fractures achieved union. In contrast, even after the acute stage of surgery, femoral neck fracture patients are at risk for complications that require revision surgery. Complications included non-union and avascular necrosis for osteosynthesis and infections, prosthesis loosening and failure for prosthetic arthroplasty.[41] It has been reported that dialysis patients are at even higher long-term risk for these complications after femoral neck fracture surgery.[42,43] One study reported 5-year rate of complications such as non-union or avascular necrosis of femoral neck fractures managed by osteosynthesis in patients with dialysis (83%) was higher than that in femoral neck fractures in the general population (20–36%).[42] Another 8-year follow-up study evaluating the outcomes of prosthetic arthroplasty after femoral neck fractures reported a prosthesis loosening rate of 35% and an infection rate of 4% among patients on dialysis compared to 12% and 0%, respectively, for the non-dialysis group.[43] Increased long-term complications after femoral neck fractures for dialysis patient are indications for readmissions and reoperations, which are associated with higher mortality rates.[44,45]

The strength of our study was our utilization of a large nationwide cohort, with the NHIRD capturing nearly 100% of the population in Taiwan. This is in contrast to other studies using hospital-based data or public insurance data such as Medicare and Medicaid that were limited to certain sectors of the population or service.[46,47] The NHIRD included health care data for the entire population of Taiwan and could be linked to other administrative datasets. Therefore, it provided the largest and most comprehensive databases for medical research, which reduce the chance variation to the minimal level. Besides, with stringent definition for clear differentiation, the study variables used in the present study like hip fracture, renal dialysis, mortality, and others could reduce the observation bias and ensure high consistency across the study subgroups.

The limitations of our study must be considered in the interpretation of outcomes. First, the identification of diseases based on the ICD-9-CM diagnosis codes alone might have caused substantial coding errors. The present study used the Catastrophic Illness Dataset to further confirm the diagnoses of catastrophic diseases. Treatment details for patients with catastrophic diseases were included in this dataset and patients did not need to pay extra for the treatments associated with their catastrophic diseases. This dataset is regulated by strict guidelines and is verified by an external review, thereby ensuring high reliability. The association between reimbursement and diagnosis datasets further increase the accuracy of coding. However, other non-catastrophic diseases, including those used as confounding factors in our analysis, were not coded with the same high level of accuracy. Second, it is important to note that the NHIRD as a secondary database did not include all the necessary data for adjusting the mortality rate of hip fracture patients, such as the severity of fractures, and the quality of dialysis. Third, there may be some misclassification of fracture sites, which may result in underestimation of their effects on mortality. Because almost all hip fracture patients in Taiwan are hospitalized for surgery, ICD-9-CM procedure codes, which are also associated with reimbursement, were introduced to minimize the misclassification. Fourth, NHIRD does not include the type or exact duration of dialysis. Therefore, the present study could not assess the dialysis type and its dose-response relationship with mortality. Fifth, the present study could not establish the cause-effect relationship between dialysis and mortality in hip fracture patients. It is difficult to demonstrate causality because of the complex long natural history of human disease and the ethical restraints on human experimentation. Furthermore, there are no standardized rules for determining whether a relationship is causal. In the present study, the evidences just demonstrate a valid association between an exposure and an outcome with well-controlled random error, bias, or confounding. Despite these limitations, this remains the first nationwide cohort study investigating the impact of fracture sites on the mortality of dialysis and non-dialysis hip fracture patients.

In conclusion, the additional negative impact of dialysis on the mortality of hip fracture patients was evident for at least 10 years. Patients with femoral neck fractures have better survival outcomes than those with trochanteric fractures. The better survival rate of femoral neck fracture patients lasted throughout 10 years in the non-dialysis group, whereas it only lasted the first 6 years in the dialysis group.

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