

Risk of hip fracture in patients on dialysis or kidney transplant: a meta-analysis of 14 cohort studies

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Purpose: We aimed to conduct a meta-analysis of published cohort studies to evaluate the risk of hip fracture in patients undergoing dialysis or kidney transplantation (KT).

Methods: We identified relevant studies by searching PubMed, EMBASE and Google Scholar databases from their inception to December 31, 2017. Cohort studies evaluating risk of hip fractures in patients undergoing dialysis or KT were considered included. The methodological quality of the cohort studies was assessed using the modified Newcastle-Ottawa scale.

Results: In our meta-analysis of 14 retrospective cohort studies, a total of more than 1.5 million patients undergoing dialysis or KT were included, of whom more than 30,000 had hip fractures. After the merger, the proportion of hip fractures was 1.92% (95% CI, 1.38%–2.46%) with significant heterogeneity ($I^2=99.9\%$, $P=0.000$) in all patients, and the incidence rate of hip fractures (per 1,000 person-years) was 8.95 (95% CI, 4.05–13.85) with significant heterogeneity ($I^2=99.9\%$, $P=0.000$). The pooled relative risks (RR) value for dialysis patients compared with the general population were 6.35 (95% CI, 4.53–8.88) for male and 5.57 (95% CI, 4.44–6.99) for female. The pooled RR value for hemodialysis (HD) patients compared with peritoneal dialysis (PD) patients was 1.39 (95% CI, 1.13–1.70) with no heterogeneity ($I^2=0.0\%$, $P=0.763$).

Conclusion: In conclusion, the present meta-analysis reveals that about 2% of dialysis or KT patients go on to sustain a hip fracture during follow-up, with the overall hip fracture incidence rates being 8.95 per 1,000 person-years. The overall risk of hip fracture was more than 5-fold higher in dialysis patients than in the general population. Among patients on PD, HD, and KT, HD and KT patients had the highest and the lowest risk of hip fractures, respectively.

Keywords: risk, hip fracture, dialysis or kidney transplant, meta-analysis

Introduction

Hip fracture is a major concern among the general population. Such fractures result in extensive morbidity and mortality, and they impose a severe economic burden.^{1,2} One study has predicted that the number of hip fractures in the world will increase from 1.66 million in 1990 to 6.26 million by 2050.³

Recently, some studies have shown that patients undergoing dialysis or kidney transplant (KT) have a higher risk of hip fracture as compared to the general population.^{4–6} The incidence of hip fracture in dialysis or KT patients is between 1.9 and 29.3 events per 1,000 person-years.^{4–16} A population-based cohort study has found that the total mortality rate in dialysis patients with hip fractures is more than twice that of dialysis patients without such fractures.⁸ Dialysis patients with hip fractures have been shown to have a standardized mortality rate 2.4 times greater than that of those in the general population with hip fractures.⁵ Therefore, greater attention is needed when treating patients undergoing dialysis or KT, such as the use of osteoporosis

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drugs or other formulated measures aimed at reducing the risk of hip fracture in these at-risk individuals.

However, some studies have reported inconsistent findings with regard to the risk of hip fracture in patients with dialysis or KT. To address such inconsistencies, we therefore performed a meta-analysis using data from cohort studies to assess the risk of hip fracture in dialysis or KT patients.

Materials and methods

Search strategy

The present meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹⁷ Two reviewers (JT and YL) independently searched PubMed, EMBASE, and Google Scholar from their inception to December 31, 2017 using a combination of Medical Subject Heading (MeSH), free terms, and relevant keywords. The PubMed search strategy was as follows: (Transplantation [MeSH] OR “Kidney Transplantation” [MeSH] OR “Transplantation, Heterotopic” [MeSH] OR “Renal Dialysis” [MeSH]) AND (“Hip Fractures” [MeSH]). And the search strategy for free terms was as follows: (Transplantation OR Transplantations OR Transplant OR Transplants OR Dialysis OR Dialyses) AND (Hip OR Hips) AND (Fractures OR Fracture). The reference lists of all the selected articles were hand searched for further studies.

Selection criteria

The inclusion criteria for this meta-analysis were as follows: 1) studies were cohort (both prospective and retrospective) studies; 2) hip fractures were the fracture type; 3) incidence of hip fracture in patients undergoing dialysis or KT was reported; 4) data were not repeated in other articles. If studies did not meet these criteria, they were excluded. The selection of studies was conducted independently by two reviewers. Inconsistencies in selection were resolved by a third reviewer.

Data extraction

Two reviewers (JT and YL) independently read the selected studies and extracted the appropriate data. The data extracted included first author’s name, study year, country or region, study period, number of dialysis or KT patients, type of patients (HD, PD, and KT), patients’ age, proportion of males, follow-up durations, follow-up (person-years), number of hip fractures, proportion of hip fractures (%), and incident rate of hip fractures (per 1,000 person-years).

Quality assessment

The methodological quality of included cohort studies was assessed using the modified Newcastle-Ottawa scale, which consists of three factors: patient selection, comparability of the study groups, and assessment of outcome.¹⁸ A score of 0–9 (given as stars) was allocated to each study. Studies scoring 0–3, 4–6, and 7–9 were considered low-, medium-, and high-quality studies, respectively.

Statistical analysis

The incidence rate of hip fracture (per 1,000 person-years) in patients undergoing dialysis or KT were extracted from the original data, and the proportions of hip fracture (%) were the result of dividing the total number of hip fractures by the total number of patients undergoing dialysis or KT. To evaluate the relative risk (RR) and corresponding 95% CI of hip fracture among those on dialysis as compared to the general population and in HD as compared to PD, we combined the adjusted RRs and 95% CIs reported in the original studies. A sensitivity analysis was also carried out to eliminate each study, one at a time, from the meta-analysis. Results from a random-effects model were reported in the present meta-analysis. A heterogeneity assessment between the included studies was based on I^2 statistics. The I^2 values were 25%, 50% and 75% respectively, indicating low, medium and high degree of heterogeneity. The Begg’s test and Egger’s test were used to assess the publication bias. All statistical analyses were conducted using STATA version 11.0. P -values were two-sided, and $P < 0.05$ was defined as being statistically significant.

Results

Search results

The specific literature selection steps employed in this study are shown in Figure 1. From the three reviewed databases (PubMed, EMBASE, and Google Scholar) and other sources, a total of 2,534 studies were retrieved. After removing duplicates, a total of 752 studies remained. Then 595 studies were excluded after reviewing titles and abstracts. After a full text review of the remaining 157 studies, 143 articles were excluded, including 24 reviews, 26 case studies, and 58 studies that did not have specific data on hip fractures, and 35 studies that lacked available data. Finally, a total of 14 retrospective cohort studies^{4–7,9–14,19–22} were included in the present meta-analysis.

Study characteristics and quality

The characteristics of the 14 included studies are shown in Table 1. In this meta-analysis, a total of more than 1.5 million

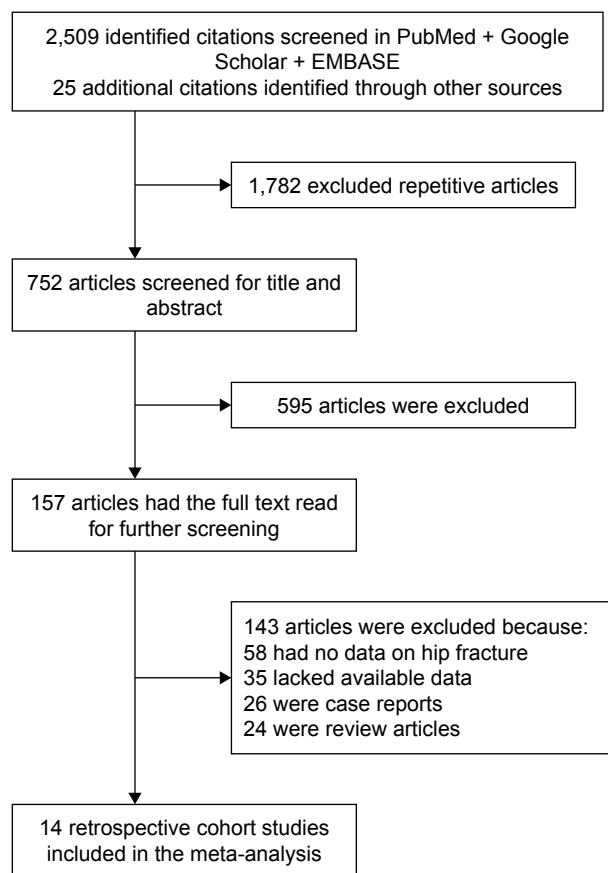


Figure 1 The steps of the literature selection.

patients undergoing dialysis or KT were included, of whom more than 30,000 had hip fractures. Among these 14 retrospective cohort studies, the year of publication ranged from 2000^{4,5,19} to 2016.²² Eight studies were conducted in the United States,^{4,5,7,9–11,19,20} two in Japan,^{6,14} two in Taiwan,^{12,13} one in Canada²² and one in England.²¹ The age of dialysis or KT patients ranged from 47⁷ to 76¹¹ years, and sample sizes ranged from 1,272⁵ to 409,040¹¹ patients, and average follow-up durations were between 1^{6,10,14} and 10²² years. The proportions of hip fracture in dialysis or KT patients ranged from 0.84%^{12,19} to 4.40%,⁵ and the incidence rate was 1.54²¹ to 16.6 per 1,000 person-years.¹⁰ Twelve studies^{4–6,9–14,20–22} were considered to be of high methodologic quality, and only two studies^{7,19} were of moderate quality (Table 1).

Proportions and incidence rate of hip fractures in patients undergoing dialysis or KT

Of the 14 included studies, seven studies^{6,9,10,12–14,19} included a total of 645,418 patients on HD, of whom 10,791 had hip fractures; four studies^{4,12,13,19} included a total of 334,720 patients on PD, of whom 6,642 had hip fractures; three studies^{5,7,11}

included 451,407 HD and PD patients of whom 22,559 had hip fractures, and five studies^{7,19–22} included a total of 154,316 KT patients, of whom 1,362 had hip fractures. After pooling these data, the overall incidence of hip fractures (Figure 2) was 2.28% (95% CI, 1.63%–2.93%) with significant heterogeneity ($I^2=99.8\%$, $P=0.000$) in HD patients, 1.46% (95% CI, 0.70%–2.23%) with significant heterogeneity ($I^2=96.1\%$, $P=0.000$) in PD patients, 3.25% (95% CI, 0.56%–5.94%) with significant heterogeneity ($I^2=99.9\%$, $P=0.000$) in PD and HD patients, 0.89% (95% CI, 0.78%–1.00%) with moderate heterogeneity ($I^2=69.4\%$, $P=0.011$) in KT patients, and 1.92% (95% CI, 1.38%–2.46%) with significant heterogeneity ($I^2=99.9\%$, $P=0.000$) in all patients. The incidence rate of hip fractures (per 1,000 person-years, Figure 3) was 11.70 (95% CI, 9.44%–13.96%) with significant heterogeneity ($I^2=91.5\%$, $P=0.000$) in HD patients, 7.60 (95% CI, 3.54–11.65) with significant heterogeneity ($I^2=54.3\%$, $P=0.087$) in PD patients, 15.40 (95% CI, –5.66–36.46) with significant heterogeneity ($I^2=99.8\%$, $P=0.000$) in PD and HD patients, 2.98 (95% CI, 2.08–3.88) with no heterogeneity ($I^2=0.0\%$, $P=0.420$) in KT patients, and 8.95 (95% CI, 4.05–13.85) with significant heterogeneity ($I^2=99.9\%$, $P=0.000$) in all patients. The individual removal of specific studies one at a time did not significantly alter the overall results. No evidence of publication bias was found when evaluated using Begg's test ($P=0.26$), or Egger's test ($P=0.15$).

RR of hip fracture in patients on dialysis relative to the general population

The RR of hip fracture in patients on dialysis is greater than that of the general population. Three of the included studies^{4,5,16} reported this comparison. The pooled RR value was 6.35 (95% CI, 4.53–8.88) for males and 5.57 (95% CI, 4.44–6.99) for females (Figure 4).

RR of hip fractures in HD patients relative to PD patients

Three of the included studies^{12,13,19} reported the RR value for HD patients compared with PD patients. The pooled RR value was 1.39 (95% CI, 1.13–1.70) with no heterogeneity ($I^2=0.0\%$, $P=0.763$) (Figure 5).

Discussion

The present meta-analysis of 14 retrospective cohort studies including a total of more than 1.5 million patients undergoing dialysis or KT and more than 30,000 hip fracture patients reveals that about 2% of dialysis or KT patients had sustained a hip fracture during follow-up, with the overall hip fracture incidence rates being 8.95 per 1,000 person-years.

Table 1 Characteristics of 14 retrospective studies included in present meta-analysis

First author's name	Year	Country/region	Study period	Number of dialysis or KT (n)	Type	Age (years)	Male (%)	Follow-up (years)	Follow-up (person-years)	Number of hip fractures (n)	Proportion of hip fracture (%)	Incident rate of hip fracture ^a	Study quality
Alem et al ⁴	2000	USA	1989–1996	326,464	PD	59.5	55.9	1.97	643,831	6,542	2.00	10.16	7
Arneson et al ¹⁰	2013	USA	2010	203,857	HD	67	54.4	1	175,422	2,912	1.43	16.6	7
Ball et al ⁷	2002	USA	1990–1999	41,095	HD+PD	47	57.4	2.98	147,989	424	1.03	2.9	6
Chen et al ¹²	2014	Taiwan	1998–2009	59,944	KT	47	57.4	2.98	166,778	547	0.91	3.3	8
Coco and Rush ⁵	2000	USA	1988–1998	1,272	HD	62	46.54	3	187,353	2,548	4.29	13.6	8
Ferro et al ²¹	2015	England	2001–2013	21,769	PD	58	49	3.17	6,240	39	0.84	6.25	8
Lin et al ¹³	2014	Taiwan	1999–2006	47,986	HD+PD	54.5	48.3	4.14	4,039	56	4.40	13.9	8
Maruyama et al ¹⁴	2014	Japan	2009–2010	185,277	KT	NA	NA	4.71	112,512	173	0.79	1.54	8
Nair et al ¹¹	2013	USA	1996–2009	409,040	HD	54.5	41.6	4.14	198,172	1,843	3.84	9.3	8
Naylor et al ²²	2016	Canada	2003–2013	2,385	PD	66	61.9	1	14,634	60	1.72	4.1	7
Rudser et al ⁹	2007	USA	1990–2003	16,328	HD	76	51.9	3	NA	1,586	0.86	11.7	8
Stehman-Breen et al ¹⁹	2000	USA	1993–1996	4,372	HD+PD	50	63.1	10	610,478	17,887	4.37	29.3	8
Sukumaran et al ²⁰	2014	USA	1997–2010	69,740	KT	50	45.4	2.44	21,579	41	1.70	1.9	8
Wakasugi et al ¹⁶	2013	Japan	2007–2008	128,141	HD	59.7	51.7	2.86	39,785	370	2.27	9.3	7
					HD	NA	NA	2.86	12,014	95	2.17	7.91	6
					PD	NA	NA	2.86	288	1	0.98	3.47	7
					KT	NA	NA	2.86	1,351	4	0.84	2.96	7
					KT	51	61	2.2	155,341	597	0.86	3.8	7
					HD	64.3	61.9	1	126,912	1,437	1.12	11.32	7

Note: ^aper 1,000 person-years.
Abbreviations: HD, hemodialysis; KT, kidney transplantation; PD, peritoneal dialysis; NA, not available.

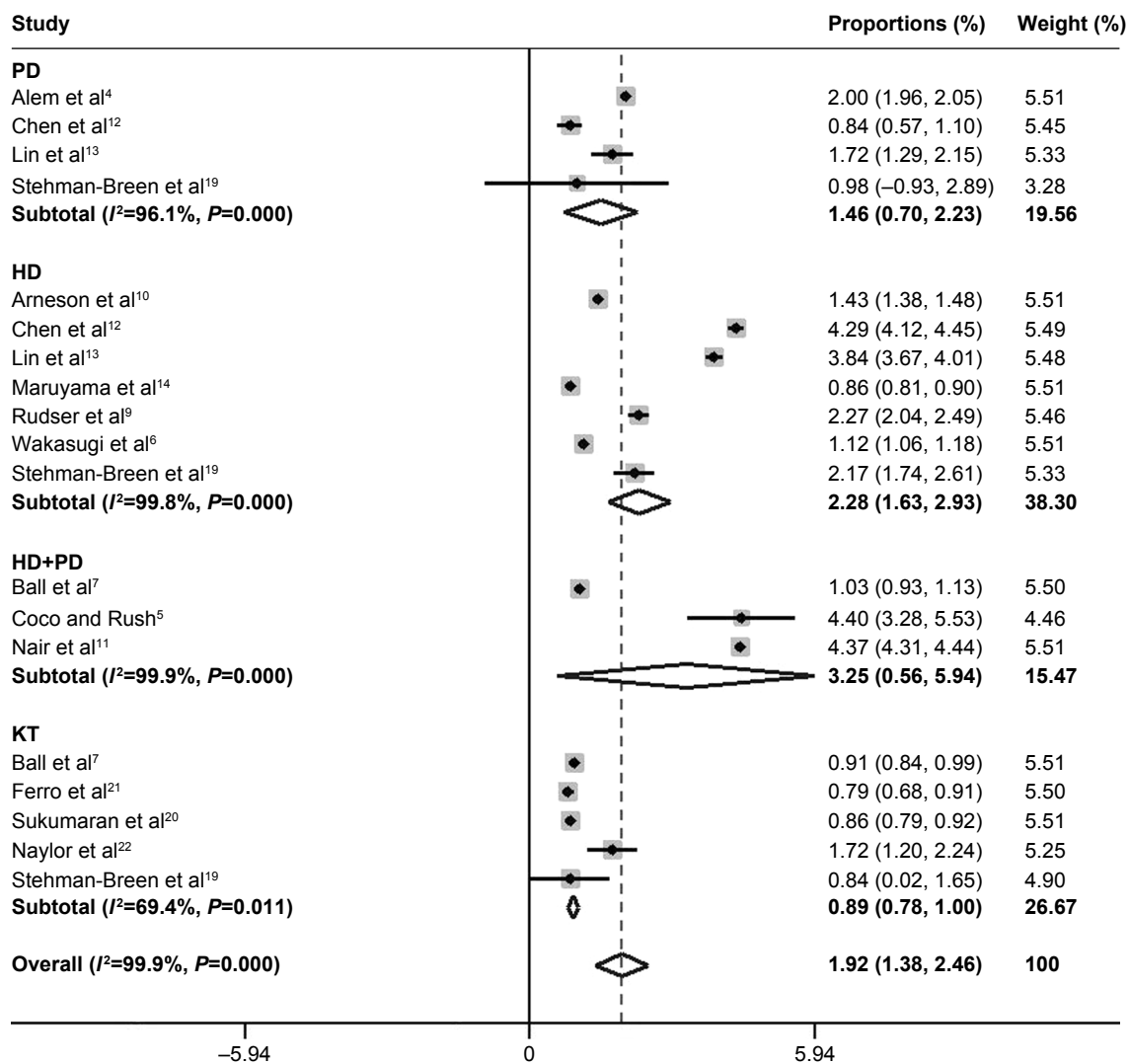


Figure 2 Proportions (%) of hip fracture in patients on dialysis or KT.

Note: Weights are from random effects analysis.

Abbreviations: HD, hemodialysis; KT, kidney transplantation; PD, peritoneal dialysis.

The overall RR of hip fracture was more than 5-fold higher in dialysis patients than in the general population. Furthermore, the RR of hip fracture was higher in patients on HD, who had a 1.39-fold increase in their risk of suffering a hip fracture as compared to patients on PD.

The high incidence of hip fracture in patients on dialysis or KT has the potential to substantially impact patient health and standards of living. Dialysis patients with hip fractures had a 2.4-fold greater standardized mortality rate than those in the general population with hip fractures.⁵ The mechanisms governing this high risk of hip fracture among patients undergoing dialysis or KT are not well understood, and are likely related to multiple comorbidities in such patients, including secondary hyperparathyroidism, abnormal vitamin D metabolism, hypogonadism, chronic acidosis, and related disorders.^{23,24} A major driver of this elevated fracture

rate is likely the lower bone mineral density (BMD) in these patients.²⁵ Low BMD is itself an independent risk factor for hip fracture in the general population²⁶ and has been associated with fractures in patients undergoing dialysis²⁷ and KT.²⁸

Among patients undergoing PD, HD, and KT, those undergoing HD and KT had the highest and the lowest risk of hip fractures in our meta-analysis, respectively. Different dialysis methods are associated with different risk rates for hip fracture. The risk of hip fracture in patients on HD was 1.39-fold higher than that in patients on PD in our meta-analysis. One possible explanation for this finding may be that patients on PD were on average younger than those on HD, whereas patients on HD had a higher incidence rate of diabetes than did those patients on PD.²⁹ Although we found no data directly comparing the incidence of hip fractures

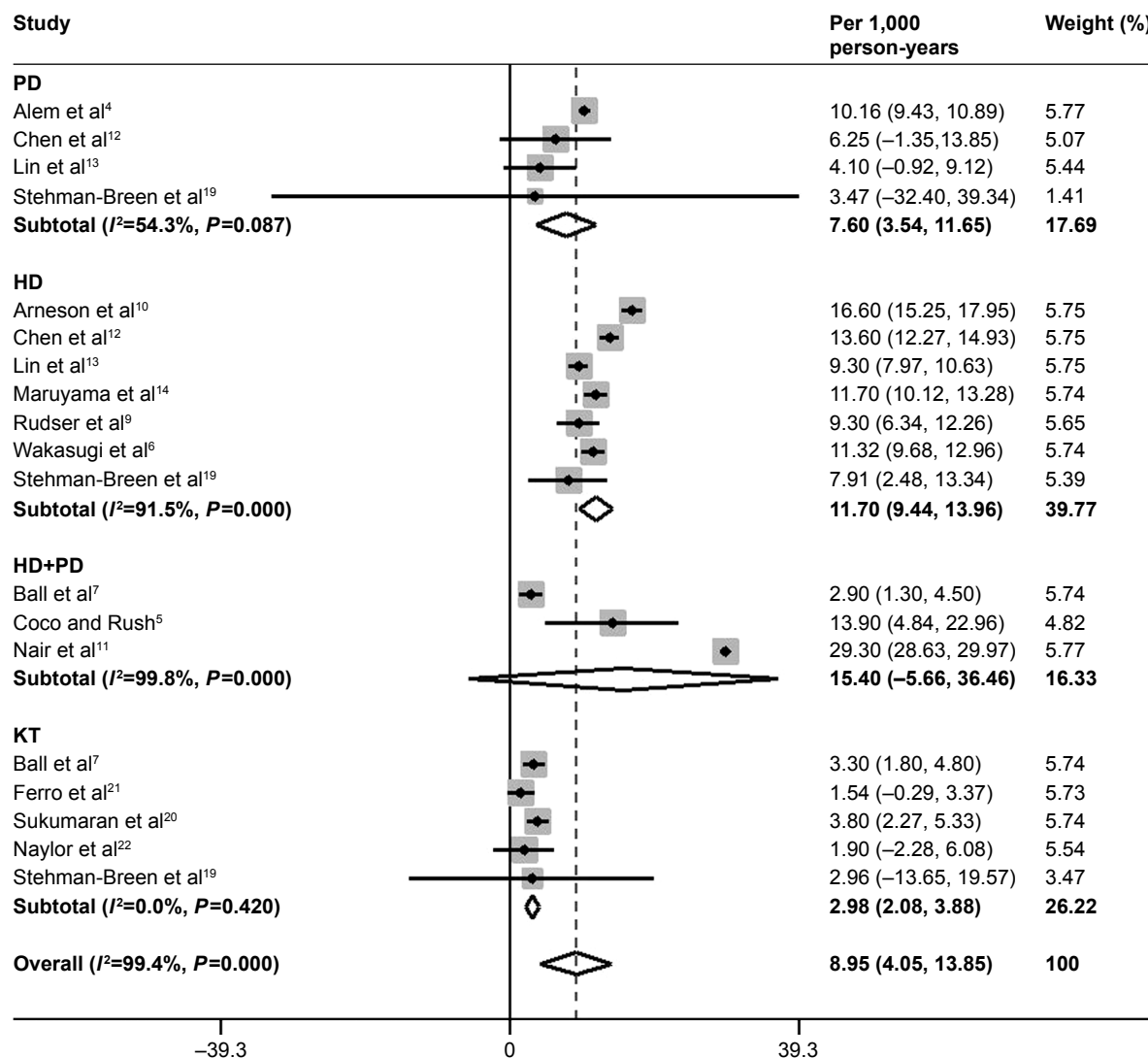


Figure 3 Incidence rate of hip fracture (per 1,000 person-years) in patients on dialysis or KT.
Note: Weights are from random effects analysis.
Abbreviations: HD, hemodialysis; KT, kidney transplantation; PD, peritoneal dialysis.

between patients undergoing dialysis and KT, data from this meta-analysis (Figures 1 and 2) indicate that the proportions and incidence rate of hip fractures in patients on KT were significantly lower than those of patients on dialysis. Certainly, further research will be needed to fully validate this finding. Based on these results, however, greater attention should be paid to dialysis patients, especially those on HD, by offering them osteoporosis therapy, improved health education, fall prevention strategies, and other techniques aimed at reducing their risk of hip fracture.

This meta-analysis does have several limitations. For one, the 14 studies included in this meta-analysis were all retrospective cohort studies based on historical data. Unlike prospective cohort studies, the quality of these retrospective cohort studies was not controlled by the researchers, so if there were other confounding factors then the reliability

and integrity of the study was likely to be low, affecting the quality and reliability of our meta-analysis. However, all meta-analyses are limited by such constraints on the quality and quantity of published studies, and they remain the best approach to resolving such problems at present, serving as a basis for decision making by clinicians and patients. Secondly, the present meta-analysis revealed high heterogeneity between studies, which was not explained by any one of the included studies and which may reduce the overall reliability of this study. This high heterogeneity may be associated with differences in age, gender, sample size, or follow-up time between the included studies. Caution is therefore required in the interpretation of our conclusions. Thirdly, the current meta-analysis lacks a pre-registered review protocol and there may be small biases, but we strictly follow the systematic evaluation process (PRISMA). Finally, we were not able to

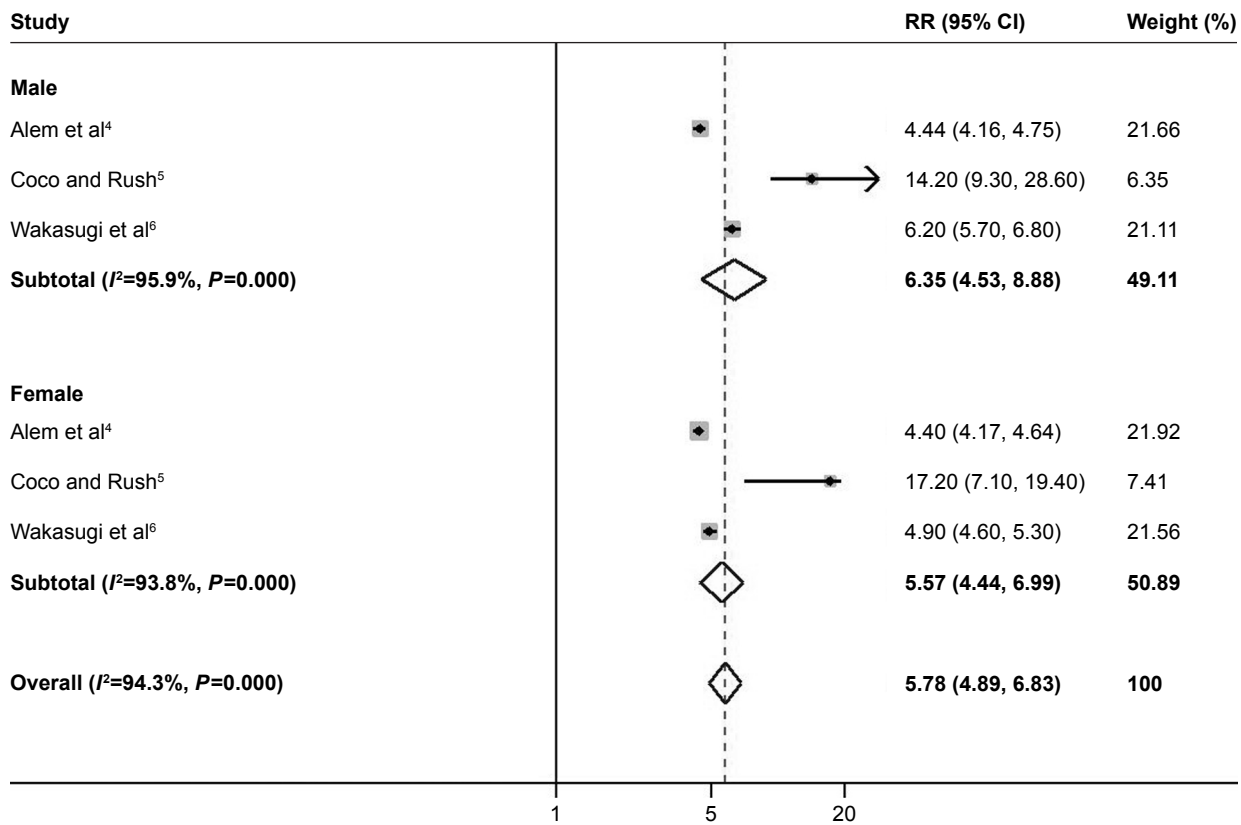


Figure 4 RR of hip fracture in patients on dialysis compared to the general population.

Note: Weights are from random effects analysis.

Abbreviation: RR, relative risk.

include any unpublished data in this analysis, and so we may have overlooked some research that is eligible for publication. However, the problem is unlikely to be significant because the Egger and Begg’s tests indicated that there was no publication

bias in the current meta-analysis. Although our meta-analysis is subject to these limitations, it also has certain advantages. For one, this is a comprehensive literature review, and it is the first to our knowledge to analyze the risk of hip fracture

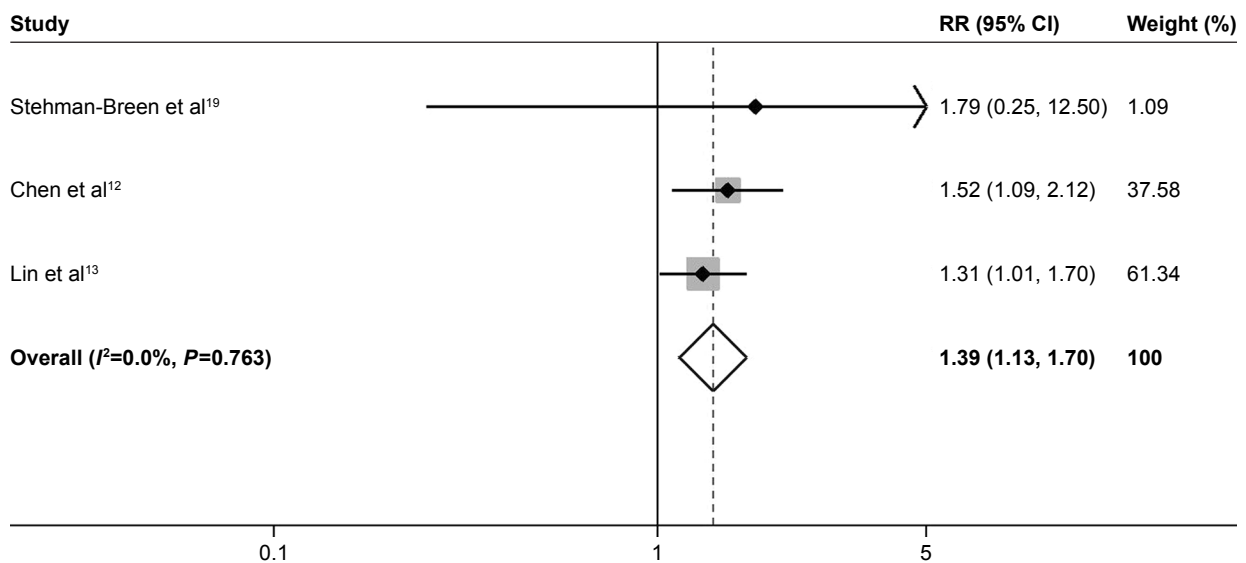


Figure 5 RR of hip fractures in patients on HD compared to those on PD.

Note: Weights are from random effects analysis.

Abbreviations: HD, hemodialysis; PD, peritoneal dialysis; RR, relative risk.

after dialysis or KT. In addition, in the present meta-analysis, many cohort studies included a large number of dialysis or KT patients and had long-term follow-up durations, greatly enhancing the statistical power of the combined results.

Conclusion

The present meta-analysis showed that about 2% of dialysis or KT patients go on to sustain a hip fracture during follow-up, with the overall hip fracture incidence rates being 8.95 per 1,000 person-years. The overall risk of hip fracture was more than 5-fold higher in dialysis patients than in the general population. Among patients on PD, HD, and KT, HD patients and KT patients had the highest and the lowest risk of hip fractures, respectively.

Author contributions

JT and JZ were involved with the concept and design of this manuscript. JT, YL and ZW were involved with the data collection, analysis, and writing of the paper. All authors contributed toward drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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