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Systematic review and meta-analysis of incidence and outcomes of hip and vertebral fractures hip fracture in patients with end-stage kidney disease

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This is the protocol for a systematic review and meta-analysis to systematically and quantitatively evaluate the mortality rate and time-period mortality after hip fracture and spinal fracture in patients with ESKD treated with hemodialysis, peritoneal dialysis, or kidney transplantation.

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Authors' Information

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Author contributions:
YS is the guarantor. YS, YK, and YT drafted the manuscript.
All authors contributed to the development of the selection criteria, the risk of bias assessment strategy, and data extraction criteria. YS, YK, and YT developed the search strategy. YK and YT provided statistical expertise. All authors read, provided feedback, and approved the final manuscript.

Introduction

2 Hip fracture is one of the major health problems in patients with end-stage kidney disease (ESKD) requiring renal replacement therapy, including hemodialysis, peritoneal dialysis, or kidney transplantation, because they have a higher risk for hip fracture than the general population [123]. In addition, several studies have demonstrated that hip fracture had a high burden of morbidity and mortality, and costs in patients with ESKD [456]. Along with the aging of

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the dialysis population, the increased risk of fractures may be explained by changes in phosphorus handling, vitamin D metabolism, and alternations in parathyroid hormone production and secretion associated with exacerbation of renal impairment [7].

Although prior studies have reported mortality rates after hip fracture in those with ESKD [789], the reported mortality rates vary across studies. Besides, a comprehensive and quantitative analysis of each finding in these studies has not been conducted.

Therefore, we aim to conduct a systematic review and meta-analysis to systematically and quantitatively evaluate the mortality rate and time-period mortality after hip fracture and spinal fracture in patients with ESKD treated with hemodialysis, peritoneal dialysis, or kidney transplantation.

Research Question

3 What are the mortality rate, 1-year mortality, and 5-year mortality after hip fracture and spinal fracture in patients with ESKD treated with hemodialysis or peritoneal dialysis, or kidney transplant?

Methods

4 We followed the Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 [10] for preparing this protocol.

4.1 Inclusion criteria of articles for the review

4.1.1. Types of included studies

We will include prospective and retrospective cohort studies, including cohorts from controlled trials, that describe outcomes after hip or spinal fracture in patients with ESKD treated with hemodialysis or peritoneal dialysis or kidney transplant. We will also include original reports such as case series in which all participants had mortality outcomes or cohort studies. We will not restrict publication date and status (full publication, conference abstract, and unpublished data).

We will exclude case reports with three cases or less, animal and laboratory studies, and literature reviews. We will also exclude not yet recruiting, recruiting, or withdrawn studies in Clinical.Trial.gov.

4.1.2. Study participants

Inclusion criteria:

We will include patients with ESKD treated with hemodialysis or peritoneal dialysis or kidney transplant, regardless of the etiology of chronic kidney disease, follow-up duration, and country of origin. We will include patients of any age, sex, and race.

Exclusion criteria:

None.

4.1.3. Intervention(s) or exposure(s)

Not applicable.

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4.1.4. Comparator(s) or control(s)

Not applicable.

4.2 Type of outcomes

4.2.1. Primary outcomes

1. Mortality rate, 1-year mortality, and 5-year mortality after hip fracture.
2. Mortality rate, 1-year mortality, and 5-year mortality after spinal fracture.

4.3 Search methods

4.3.1. Electronic search

We will search Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE via PubMed, and EMBASE via ProQuest Dialog. See Appendix 1, 2, and 3 for the search strategies.

4.3.2. Other sources

For ongoing or unpublished trials, we will also search World Health Organization International Clinical Trials Platform Search Portal (ICTRP) and ClinicalTrials.gov, as shown in Appendix 4 and 5. We will also confirm paper references including the extracted studies. We will ask the authors of original studies for unpublished or additional data.

4.4 Data collection and analysis

4.4.1. Selection of the studies

Two independent authors will screen the titles and abstracts of studies identified using the search strategy against the inclusion and exclusion criteria. The full text of the potentially eligible studies will be obtained and independently assessed for eligibility by two authors. If we are not sure whether the studies meet the inclusion criteria because of the abstract only, we will contact the original authors of these studies. Any disagreements will be resolved by discussion, and if this fails, a third reviewer will act as an arbiter.

4.4.2. Data extraction and management

Two review authors will perform data extraction for the studies independently. The 1-year and 5-year mortality will be extracted, but the mortality less than 1 year will not be extracted. We will extract the data if studies report the mortality of more than 1 year and less than 5 years (e.g., 2-year mortality), but do not report either 1-year or 5-year mortality. In that case, the outcome data for less than 3 years will be included as 1-year mortality, and the data for 3 to 5 years will be included as 5-year mortality. We will perform a sensitivity analysis excluding the outcome data other than 1-year and 5-year mortality to confirm the robustness of the main results. Any disagreements will be resolved by discussion, and if this fails, a third reviewer will act as an arbiter. We will contact the original authors if necessary. We will use data extraction which was checked beforehand for 10 randomly selected studies.

4.5 Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias for each study

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using the Joanna Briggs Institute Prevalence Critical Appraisal Tool [1112]. We will assess the following domains:

1. Was the sample frame appropriate to address the target population?
2. Were study participants sampled in an appropriate way?
3. Was the sample size adequate?
4. Were the study subjects and the setting described in detail?
5. Was the data analysis conducted with sufficient coverage of the identified sample?
6. Were valid methods used for the identification of the condition?
7. Was the condition measured in a standard, reliable way for all participants?
8. Was there appropriate statistical analysis?
9. Was the response rate adequate, and if not, was the low response rate managed appropriately?

Any disagreements will be resolved by discussion, and if this fails, a third reviewer will act as an arbiter. In this study, the overall risk of bias will be calculated as the number of "Yes" responses for each domain divided by the total number of domains and expressed as a percentage. The overall risk of bias will be defined based on the calculated percentage as follows: <50%: high risk of bias; 50% to 80%: moderate risk of bias; >80%: low risk of bias).

4.6 Measures of treatment effects

Incidence rate and risk (incidence proportion) with 95% confidence intervals (CIs) and 95% prediction intervals. Incidence rate will be measured as the number of incident cases per measure of exposure and incidence proportion will be measured as the number of incident cases over a specified time frame. The statistical heterogeneity will be assessed using τ^2 statistics, which provide a logit scale measure of between-study variance, represented in a more readily interpretable way by the 95% prediction intervals.

4.7 Handling of missing data

We will not complement the missing values.

4.8 Assessment of heterogeneity

We will evaluate the statistical heterogeneity by visual inspection of the forest plots and calculating the I^2 statistic (I^2 values of 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity). If heterogeneity is detected (I^2>50%), we will verify the possible causes. Cochrane Chi-square test (Q-test) will be performed to calculate I^2 statistic, and *P* value less than 0.10 will be defined as statistically significant.

4.9 Assessment of reporting bias

We will search the clinical trial registry system (ClinicalTrial.gov and ICTRP) to

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identify completed but unpublished studies. We will assess the potential publication bias by visual inspection of the funnel plot. Egger test will also be performed. Funnel plots are likely to be inaccurate in meta-analyses of prevalence studies with low proportions of outcomes [14], we will not conduct the test and visual inspection if we find less than 20 studies [1516]or studies that have similar sample sizes.

4.10 Meta-analysis

We will use a single-arm analysis. For categorical variables, the percentage, mean, and standard deviation were calculated. We will calculate pooled incidence rate and incident proportion of death in patients with ESKD after hip fracture as well as in those with ESKD after spinal fracture. The random-effects model (DerSimonian and Laired method) will be used for pooled estimates to consider the variance between and among the studies. We will conduct statistical analyses using the R software (R Development Core Team 2019), with packages meta version 4.15-0 and metaphor version 2.4-0.

4.11 Subgroup analysis

To evaluate the clinical heterogeneity of study participants, we will perform subgroup analyses for primary outcomes with sex (men versus. women), race (Black versus. non-Blacks), presence or absence of cardiovascular diseases [hypertension, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease], presence or absence of diabetes mellitus, types of renal replacement therapy (hemodialysis, peritoneal dialysis, or kidney transplant, and participants' age category (Age ≥75 versus. Age <75), if possible.

4.12 Sensitivity analysis

We will perform a sensitivity analysis limited to population-based cohort studies that describe outcomes after hip or spinal fracture in patients with ESKD treated with hemodialysis or peritoneal dialysis or kidney transplant. We will also perform a sensitivity analysis excluding the outcome data other than 1-year and 5-year mortality to confirm the robustness of the main results.

Conflicts of interest

5 None.

6

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#1	[mh “Kidney Diseases”]
#2	[mh “Renal Replacement Therapy”]
#3	#1 OR #2
#4	ESRD:ti,ab
#5	“end stage renal disease”:ti,ab
#6	CKD:ti,ab
#7	“chronic kidney disease”:ti,ab
#8	“chronic kidney failure”:ti,ab
#9	“renal transplantation”:ti,ab
#10	#4 OR #5 OR #6 OR #7 OR #8 OR #9
#11	#3 OR #10
#12	[mh “Femoral Fractures”]
#13	“femoral fracture”:ti,ab
#14	“femoral neck fracture”:ti,ab
#15	“fracture, hip”:ti,ab
#16	#13 OR #14 OR #15
#17	#12 OR #16
#18	[mh “Spinal Fractures”]
#19	“vertebral fracture”:ti,ab
#20	#18 OR #19
#21	#17 OR #20
#22	#11 AND #21

Appendix 1: CENTRAL search strategy

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#1	Kidney Diseases [mh]
#2	Renal Replacement Therapy [mh]
#3	#1 OR #2
#4	ESRD [tiab]
#5	“End Stage Renal Disease” [tiab]
#6	CKD [tiab]
#7	“Chronic Kidney Disease” [tiab]
#8	“Chronic Kidney Failure” [tiab]
#9	“Renal Transplantation” [tiab]
#10	#4 OR #5 OR #6 OR #7 OR #8 OR #9
#11	#3 OR #10
#12	Femoral Fractures [mh]
#13	“Femoral Fracture” [tiab]
#14	“Femoral Neck Fracture” [tiab]
#15	“Fracture, Hip” [tiab]
#16	#13 OR #14 OR #15
#17	#12 OR #16

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#18	Spinal Fractures [mh]
#19	“Vertebral Fracture” [tiab]
#20	#18 OR #19
#21	#17 OR #20
#22	#11 AND #21

Appendix 2: MEDLINE (via PubMed) search strategy

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S1	“EMB.EXACT.EXPLODE(“kidney diseases”)
S2	“EMB.EXACT.EXPLODE(“renal replacement therapy”)
S3	S1 OR S2
S4	ab(ESRD) OR ti(ESRD)
S5	ab(end stage renal disease) OR ti(end stage renal disease)
S6	ab(CKD) OR ti(CKD)
S7	ab(chronic kidney disease) OR ti(chronic kidney disease)
S8	ab(chronic kidney failure) OR ti(chronic kidney failure)
S9	ab(renal transplantation) OR ti(renal transplantation)
S10	S4 OR S5 OR S6 OR S7 OR S8 OR S9
S11	S3 OR S10
S12	“EMB.EXACT.EXPLODE (“femoral fractures”)
S13	ab(femoral fracture) OR ti(femoral fracture)

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S14	ab(femoral neck fracture) OR ti(femoral neck fracture)
S15	ab(fracture, hip) OR ti(fracture, hip)
S16	S13 OR S14 OR S15
S17	S12 OR S16
S18	“EMB.EXACT.EXPLODE (“spinal Fractures”)
S19	ab(vertebral fracture) OR ti(vertebral fracture)
S20	S18 OR S19
S21	S17 OR S20
S22	S11 AND S21

Appendix 3: EMBASE search strategy (ProQuest Dialog)

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#1 Conditions: (Kidney Diseases, Renal Replacement Therapy, Femoral Fractures, Spinal Fractures)
#2 Intervention: Not applicable
Recruitment status is ALL.

Appendix 4: ICTRP search strategy

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Condition or disease: (Kidney Diseases OR Renal Replacement Therapy) AND (Femoral Fractures OR Spinal Fractures)
Intervention: Not applicable

Appendix 5: ClinicalTrial.gov search strategy

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