The Analysis for Anemia Increasing Fracture Risk

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Fractures are a major public health problem for elderly people throughout the world. Anemia is also a common, important health problem among elderly populations. The aim of this article was to estimate the association between anemia and fracture incidence via a systematic review and meta-analysis.

Material/Methods: The participant, intervention, observation, and study design (PICOS) reporting guidelines were followed, and databases were searched from their inception to May 2020 to identify relevant studies. When heterogeneity was significant, and a random-effects model was used. Subgroup analysis was conducted to explore the source of heterogeneity based on sex, study design, and region.

Result: We found that anemia significantly increased fracture risk [relative risk (RR)=1.26, 95% confidence interval (CI)=1.14–1.39, *P*<0.001], specifically, hip fracture (RR=1.44, 95% CI=1.29–1.61), spine fracture (RR=1.15, 95% CI=1.08–1.23), and nonspine fracture (RR=1.42, 95% CI=1.33–1.52). Males with anemia had a 1.51-fold higher fracture risk, females had a 1.09-fold higher fracture risk. And the association was stronger in Asian (RR=1.22, 95% CI=1.07–1.40), but not in American and European study populations.

Conclusions: In conclusion, a significantly increased fracture risk was observed, and anemia can be a predictor of fracture risk.

MeSH Keywords: **Anemia • Fractures, Bone • Meta-Analysis**

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Background

Fractures are a major public health problem for elderly people throughout the world [1,2]. As the aging of the population progresses, with the number of people over 65 increasing, the incidence of fracture will increase [3,4]. Fractures are well known to be associated with adverse outcomes, such as the loss of physical function [5], disability, and even mortality [6] in elderly people compared to young people. Thus, identifying risk factors for fractures that can help prevent fracture in elderly people is important.

Interestingly, anemia, which is defined by the World Health Organization (WHO) as a hemoglobin level of less than 13 g/dL in males and less than 12 g/dL in females [7,8], is also a common important health problem among elderly populations. Based on previous findings, diagnosed anemia or low hemoglobin levels in older adults has been associated with cardiovascular disease [9], low skeletal muscle mass and strength, declines in physical function [10], impaired cognitive performance [11], and low bone density [12]. These factors are highly correlated with an increased risk of fracture; therefore, anemia may elevate the risk of fracture [13].

Several previous studies have evaluated the relationship between anemia and fracture risk. One study observed a 1.38-fold increased hip fracture risk in multiethnic postmenopausal women with anemia compared with women without anemia; the difference was significant [14,15]. Fracture risk differs by sex, age, and fracture site. Jorgensen et al. found that males aged 55–74 years with anemia had a 2.15-fold increased nonvertebral fracture risk, whereas females with anemia did not have an increased nonvertebral fracture risk (RR=0.98, 95% CI=0.57–1.67) [16]. Whether anemia is one of the risk factors for fracture is unclear.

To date, no meta-analysis has determined the association between anemia and fracture risk Therefore, we aimed to evaluate the risk of fracture among populations with anemia by performing a meta-analysis. This study will increase awareness of the potential association of anemia and fracture. The findings highlight the importance of fracture prevention for those at risk of anemia and can be used to inform clinical practice.

Material and Methods

Search strategy and data sources

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17] were used to plan and execute this meta-analysis. PubMed and EMBASE were searched from their inception to May 2020 to identify observational studies on

Table 1. PICOS criteria for inclusion and exclusion of studies.

Parameter	Inclusion	Exclusion
Participants	Men and women	None
Interventions	Anemia	Combined with multiple diseases
Comparison	Same group	None
Outcomes	Fractures	None
Study design	Observational studies	None
	Retrospective study	
	Prospective study	

PICOS – participant, intervention, observation, and study design.

the relationship between anemia and fracture incidence. We did not apply any language restrictions during the search. The following search terms were used: 1) Anemia [Title/Abstract] OR "Anemia" [MeSH]; 2) fracture* [Title/Abstract] OR "Fractures, Bone" [MeSH]. We also searched to identify any additional studies. Additional eligible studies on anemia and the risk of fracture were identified by reviewing the references of relevant articles.

Study selection

A comprehensive literature search strategy was created using PICOS (participant, intervention, comparator, observation, and study design) reporting guidelines (Table 1) along with a customized coding scheme developed by Brown et al. [18]. The inclusion criteria were as follows: 1) observational studies; 2) studies in which anemia was the exposure of interest and that considered a diagnosis of anemia or fracture based on WHO criteria and including patients without any basic disease history, including chronic renal disease; 3) studies that evaluated the relationship between anemia and fracture risk; and 4) studies with sufficient data on hazard ratios (HRs), which were replaced by relative risks (RRs) or adjusted RRs and their 95% confidence intervals (CIs). The exclusion criteria terms were as follows: 1) case reports, reviews, meta-analyses, letters or notes, editorials, or conference abstracts; (2) duplicate reports; and 3) nonhuman research studies. When the same participant was studied in more than one study or the data were duplicated, we chose the study with the largest sample size and the most recent or complete study.

Data extraction and quality assessment

According to the predetermined selection criteria, 2 authors (TYR and TZW) independently estimates the eligibility of the records and extracted the data. The following data were extracted: name
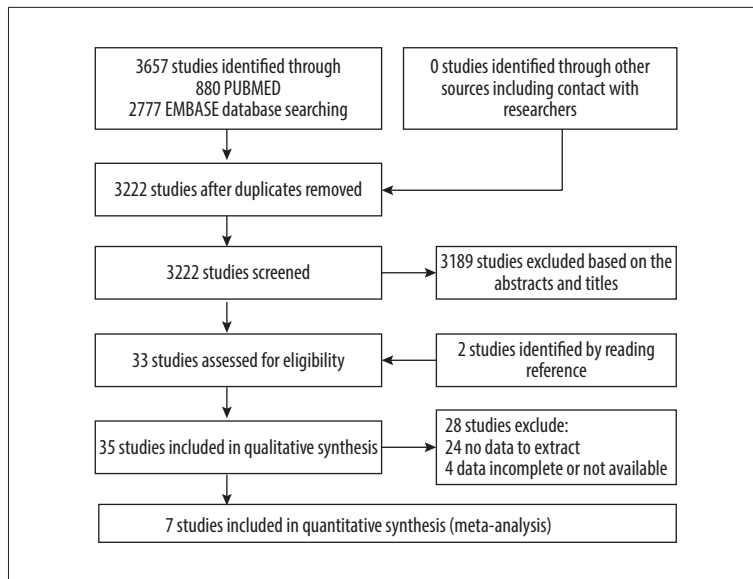
Figure 1. Flow chart of the meta-analysis.

of the first author, publication year, study location, ages, fracture type/assessment, study design, study size, follow-up time, study models, HRs or RRs and 95% CIs, and statistical adjustments for covariates. Any foreign-language articles were not translated into English. Any disagreements were resolved by discussion and corresponding authors' agreement. The methodological quality assessment was accorded with the Newcastle-Ottawa Scale (NOS) [19]. The total NOS score was 9. Studies were deemed low quality if the NOS score was <7.0 and high quality if the NOS score was ≥7.0.

Statistical analyses

We calculated a pooled RR and 95% CI from the RRs and 95% CIs reported in each study. We used Cochran Q and I^2 statistics to assess heterogeneity [20]. A random-effects model (DerSimonian and Laird method) [21] was applied, when heterogeneity existed (the P value was <0.1 and the I^2 value was >50%). Otherwise, a fixed-effects model [22] was used. Subgroup meta-analysis according to sex, study design, and region were performed to explore the origin of the heterogeneity. Additionally, to evaluate the stability of the results, a sensitivity analysis was aimed to assess the influence of individual records on the pooled result by excluding each single study in turn [23]. Finally, Begg's test (rank correlation method) [24] was used to assess potential publication bias. Data analyses were conducted using STATA statistical software version 14.0 (STATA Corp. LLC, College Station, TX, USA).

Results

Literature search and study characteristics

Our search in the aforementioned databases from their inception through May 2020 identified 3657 articles that included

2 216 000 individuals aged ≥55 years old. A total of 3222 articles remained after the removal of duplicates. Based on title and abstract screening, 3819 records were excluded, and 33 studies were retrieved. After reading the full texts, 2 additional eligible articles were identified by reviewing the references of the relevant articles. Finally, 7 studies [14–16,25–28] were included in our analysis (Figure 1). The characteristics of those studies and the NOS scores are shown in Table 1. Of the 7 studies, 3 were from the USA, and 4 were from other countries, including Norway, Spain, and Korea. Three were prospective studies, and 4 were retrospective studies. All of the studies were high-quality studies (scores ≥7.0) (Table 2).

Main analysis

Anemia was significantly associated with increasing fracture risk (RR=1.26, 95% CI=1.14–1.39); substantial heterogeneity was observed (P=0.000, I^2=77.3%) (Figure 2A).

Interestingly, the pooled results showed that anemia contributed significantly to the risk of each fracture type, including hip fracture (RR=1.44, 95% CI=1.29–1.61, P=0.080, I^2=52.1%) (Figure 2B), spine fracture (RR=1.15, 95% CI=1.08–1.23, P=0.301, I^2=18%) (Figure 2C) and nonspine fracture (RR=1.42, 95% CI=1.33–1.52, P=0.072, I^2=46.1%) (Figure 2D). Statistical heterogeneity was observed for only hip fracture risk (Figure 2B).

Subgroup meta-analysis

The study showed heterogeneity in anemia and hip fracture risk. To examine these heterogeneities, we conducted a subgroup meta-analysis accorded with sex, study design, and region, as shown in Table 3. The results indicated that anemia led to a higher fracture risk in most of subgroup meta-analysis.
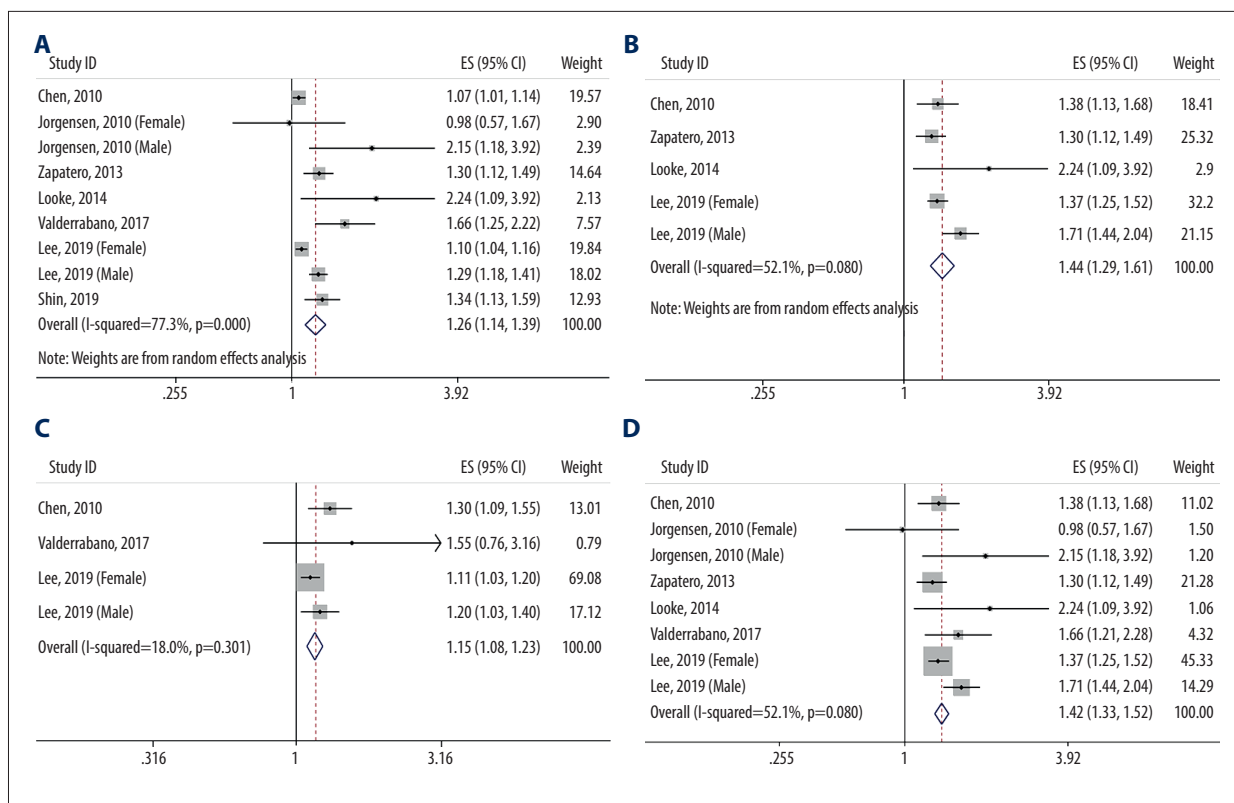
Figure 2. Forest plot. (**A**). Forest plot of the of anemia association with fracture risk. (**B**) Forest plot of anemia association with hip fracture risk. (**C**) Forest plot of anemia association with spine fracture risk. (**D**) Forest plot of anemia association with nonspine fracture risk. (CI – confidence interval).

Table 3 shows that the source of statistical heterogeneity was sex, not study design or region. Males with anemia had a higher fracture risk (RR=1.51, 95% CI=1.16–1.95) than females (RR=1.09, 95% CI=1.04–1.13), and the association was stronger in Asian (RR=1.22, 95% CI=1.07–1.40), but not in American (RR=1.47, 95% CI=0.96–2.23) or European (RR=1.35, 95% CI=0.98–1.85) in the study.

Sensitivity analysis

A sensitivity analysis was used to assess the stability of our analysis when each study was excluded, the overall combined result did not change (Figure 3), which indicated that this analysis was robust.

Publication bias

Begg's rank correlation test showed no evidence of publication bias among the studies ($P>|z|=0.536$).

Discussion

To enhance the understanding of fracture incidence, we performed a comprehensive meta-analysis of eligible studies to describe the relationship between the risk of fracture and anemia. To the best of our knowledge, this is the first specific meta-analysis to explore this potential relationship. The primary results from our study consistently suggested that the risk of fracture was increased 1.26-fold in patients with anemia. When the fractures in patients with anemia were restricted to specific sites, the risk of fractures was inconsistent; for example, the risk of spine fractures increased 1.15-fold, the risk of hip fractures increased 1.44-fold, and the risk of nonspine fractures increased 1.42-fold. In the present study, although heterogeneity was observed, no publication bias was found, and the sensitivity analysis showed stable and robust results. Therefore, it may be possible to prevent fractures and related adverse events by treating anemia.

In this study, we found that males with anemia had a higher fracture risk than females. There are many results consistent with ours. A study by Jorgensen et al. [16] indicated a 2.19-fold higher fracture risk in males than in females. A study involving a population aged more than 65 years in Korea also showed

Table 2. Characteristics of 6 studies included in the final analysis of anemia and fracture risk.

Author, year (location)	Age	Fracture type/ assessment	Study design	Study size	Follow-up time	Models	Adjustment for covariates	NOS
Chen, 2010 (United States)	63.2±7.2 y	Hip/medical records spine/ Self-reported any/Self-reported	P, C	8739	7.8 y	Cox proportional hazards models	Arm assignment, interventions, race/ ethnicity, age, height, weight, self-reported general health, baseline number of falls, diabetes	9
Jorgensen, 2010 (Norway)	55 to 74 y	Nonspine/ radiographic archives of the University Hospital of North Norway	P	5286	8.3 y	Cox regression analyses	Age, height, BMI, serum total cholesterol, HDL-cholesterol, serum triglycerides, serum creatinine, smoking, use of alcohol, grip strength, and distal forearm BMD	9
Zapatero, 2013 (Spain)	71.3±16.8 y	Hip/ICD-9 codes	RO	1991911	NA	logistic regression analysis	–	7
Looke, 2014 (United States)	≥65 y	Hip/ICD-9 codes	RO	2122	NA	Cox proportional hazards models	Age, sex, ever smoked, femur neck BMD, iron/ folate deficiency, inflammation, renal insufficiency, BMI, timed chair stand	7
Valderrabano, 2017 (United States)	≥65 y	Any/Self-report nonspine/Self-report spine/ Self-report	P, C	3632	7.2 y	Cox proportional hazards models	–	9
Lee, 2019 (South Korea)	≥65 y	Any/ICD-10 codes spine/ICD-10 codes hip/ ICD-10 codes	R, C	72131	8.0 y	Cox proportional hazards models	Age, sex, BMI, alcohol, smoking history, and physical activity	8
Shin, 2019 (Korea)	58.4±11.8 y	Any/Self-report	R, C	133179	4.5 y	Cox proportional hazards models	Age, sex, residence, income, and disability	9

y – years; P – prospective; R – retrospective; C – cohort; RO – retrospective observational; BMI – body mass index; BMD – bone mineral density; HDL – high density lipoprotein; NOS – Newcastle-Ottawa Scale.

that anemia may be more strongly related to hip fracture in males (RR=1.71, 95% CI=1.44–2.04) than in females (RR=1.37, 95% CI=1.25–1.52) [25]. Based on the aforementioned findings, sex differences may play an important role in the effects of anemia on fracture. However, it is unclear why the risk of fracture differs between sexes.

In addition to sex, region and ethnicity are also risk factors for fracture because of gene-environmental interactions. A significantly increased fracture risk was observed in multiethnic postmenopausal women with anemia in the United States [14]. But in our study, we detected different results regarding a stronger association in Asian (RR=1.22, 95% CI=1.07–1.40) than in

American countries (RR=1.47, 95% CI=0.96–2.23) or Europe countries (RR=1.35, 95% CI=0.98–1.85). There were racial differences in the association between WHO-defined anemia and adverse health events, including fracture.

The underlying mechanisms of the relationship between anemia and fracture are unclear. Many risk factors for anemia in elderly people were also risk factors for fracture, such as chronic inflammation and nutrient deficiency, including deficiencies in iron, cobalamin B12, and folate. Therefore, the direct, indirect, or combined effects of anemia on fracture risk were observed and are summarized as follows. On the one hand, low bone density plays a very important role in the occurrence and development

Table 3. Subgroup analyses of the association between anemia and fracture risk.

	Factor	No. of studies	RR (95% CI)	Heterogeneity P (I² %)
Sex	Male	3	1.51 (1.16–1.95)	0.074 (61.5)
	Female	3	1.09 (1.04–1.13)	0.747 (0.0)
	Male/Female	3	1.35 (1.18–1.55)	0.266 (24.4)
Study design	Prospective study	4	1.34 (0.96–1.87)	0.003 (78.0)
	Retrospective study	5	1.26 (1.12–1.42)	0.001 (77.7)
Region	America	3	1.47 (0.96–2.23)	0.001 (85.1)
	Europe	3	1.35 (0.98–1.85)	0.154 (44.6)
	Asia	3	1.22 (1.07–1.40)	0.003 (83.1)

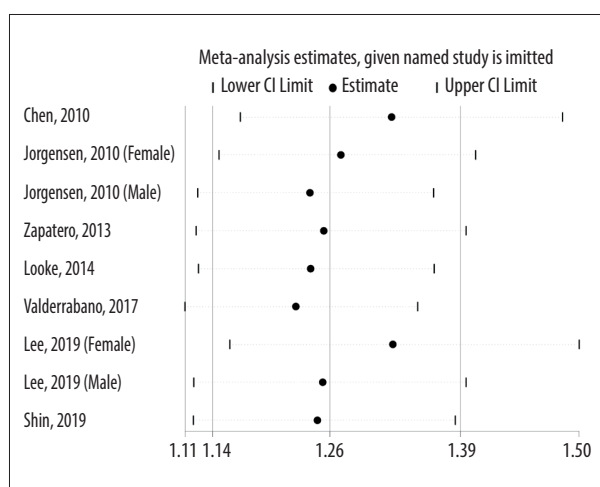RR – relative risk; CI– confidence interval.

Figure 3. Sensitivity analysis. The analysis was performed via recalculation of the pooled results of the primary analysis after exclusion of one study per iteration.

of fracture. One study found that low hemoglobin levels were associated with low bone density [12]. Anemia is caused by blood loss, and the body compensates for hematopoiesis through hematopoietic cell proliferation, which leads to the absorption of bone tissue and ultimately a reduction in bone density [30].

On the other hand, anemia affects oxygen delivery to the skeletal muscles; therefore, physical performance and the mass or strength of the muscle are negatively impacted [10,31] and dizziness, as a symptom of anemia, is clearly related to falls and fractures in elderly people. Another effect of anemia on fracture risk in older persons is inflammation [32], which has been significantly associated with poor physical performance, muscle strength [33,34], and the risk of fracture.

Despite its advantages, this study also had some limitations. First, we searched all studies describing the association between anemia and fracture; however, the amount of relevant trials was still relatively small. Second, some published studies in journals or books not available in the online databases were missed. Besides, studies with nonsignificant or negative results may not be published. Third, the adjustment for confounding covariates, such as age, sex, comorbidities, body mass index, and others, were significantly different among the studies; 2 of the 6 studies did not mention confounders. Fourth, participants with osteoporosis and without osteoporosis may influence the estimates; however, we could not gain enough data to conduct the subgroup analysis. Finally, our results were of good quality but not the most comprehensive study. Thus, high-quality, comprehensive analyses are still needed as more data are published in the future.

Conclusions

In this study, we found that anemia played an important role in the development of fracture, and anemia may be significantly associated with an increased fracture risk. Patients with anemia, especially elderly patients, should actively prevent the occurrence of fractures. To prevent fracture and provide additional convincing evidence for clinical practice and patients, high-quality, comprehensive analyses are still needed in the future.

Conflicts of interest

None.

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