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REVIEW

Heart failure and fracture risk: a meta-analysis

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Abstract

This meta-analysis was conducted to investigate whether heart failure is associated with an increased risk of fractures by summarizing all the available evidence. The PubMed, EMBASE, and Cochrane Library databases were searched for all relevant studies published from the date of database inception to April 2018. Studies that investigated the association between heart failure and fracture risk and conducted a comparison with controls were included. Seven cohort studies were finally identified as eligible for inclusion in the meta-analysis. All included studies were of high quality as evaluated by the Newcastle-Ottawa Scale. There was a significantly higher risk of any fracture in patients diagnosed with heart failure ($N = 53{,}038$) than in controls ($N = 126{,}727$) (RR 1.66, 95% CI 1.14–2.43, $I^2 = 94\%$, $P = 0.008$). The results were the same for hip (RR 3.45, 95% CI: 1.86–6.40, $I^2 = 95\%$, $P < 0.0001$) and humerus fractures (RR 1.91, 95% CI 1.07–3.40, $I^2 = 39\%$, $P = 0.03$) but not for vertebral and forearm fractures. To conclude, this meta-analysis demonstrated that patients with heart failure had an increased risk of fractures, especially hip and humerus fractures. Patients with heart failure may need to pay greater attention to their bone health. This meta-analysis found a significantly higher risk of fractures in patients with heart failure than in those without heart failure. Greater attention should be paid to bone health in patients with heart failure.

Keywords Fracture · Heart failure · Hip fracture · Meta-analysis

Introduction

Heart failure (HF) is a common disease that leads to acute care hospitalizations, morbidity, and mortality. It has a prevalence of 1–2% in adults and ≥ 10% in those > 70 years of age in developed countries. In Asian countries, the estimated prevalence for HF ranges from 1.26 to 6.7% [1] in the general population. With improved treatment, patients with HF may live longer and may be more prone to developing age-related comorbidities such as osteoporosis and the consequent fragility-related fractures. With aging, fractures become one of the most common causes of disability and a major public health burden, affecting more than 9 million patients worldwide each year [2, 3]. Many patients with HF have been found to develop fractures in clinical practice, partially due to the increased prevalence of both conditions with aging, such that they commonly coexist. However, recent studies have indicated that fractures and HF share a number of common risk factors, such as aging, menopause, smoking, and diabetes mellitus [1, 4, 5], and some medications for HF have the potential to cause bone loss [6]. Therefore, HF might be associated with fracture, a supposition that has been supported by several cohort and case-control studies that have shown that patients with HF have a greater risk of fractures [7–12]. However, the results of studies exploring the association between HF and fractures are inconsistent. The study by Gerber et al. [13] did not show an association between heart failure and fractures, and the extent to which heart failure increases the risk of fracture is inconsistent in different studies. To the best of our knowledge, no systematic review or meta-analysis has been performed on this topic. We performed a systematic review and meta-analysis to examine whether patients with HF have a greater risk of fractures by summarizing and pooling all the available data.

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Materials and methods

Data sources and searches

The PubMed, EMBASE, and Cochrane Library databases were searched for all relevant studies published from the date of database inception to April 2018. The search strategy included the MeSH terms "fractures, bone" and "heart failure," and the keywords related to these MeSH terms were also searched. This search was conducted with the help of a master librarian.

Study selection

Two independent investigators selected the eligible studies by reading the titles and abstracts. A third investigator was involved if there was a lack of consensus. All three investigators were well trained in performing systematic reviews and meta-analyses. Studies were included if they (i) were cohort or case-control studies; (ii) investigated the association between HF and fracture risk; and (iii) reported relative risks (RR), odds ratios (OR), or hazard ratios (HR) for fractures or raw data were provided with which those outcomes could be calculated. If several publications were included from the same cohort, only the study with the most comprehensive data was included. Only studies published in English were included. Studies were excluded if they (i) were reviews, editorials, commentaries, case reports, or letters or (ii) lacked key data needed to analyze the fracture risk in patients with HF compared to the control group.

Data extraction and quality assessment

Data were extracted by two investigators independently, and disagreements were resolved by involving a third investigator. All relevant information pertaining to the study features, population characteristics, and outcomes were collected. The 9-point Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the included studies, which assesses the participant selection (0–4 points), comparability (0–2 points), and outcomes/exposures (0–3 points). A study with a score of 7–9 points was defined as high quality.

Data synthesis and analysis

RevMan 5.1 software (The Nordic Cochrane Center, Copenhagen, Denmark) was used for the meta-analysis. The heterogeneity of the included studies was measured using the

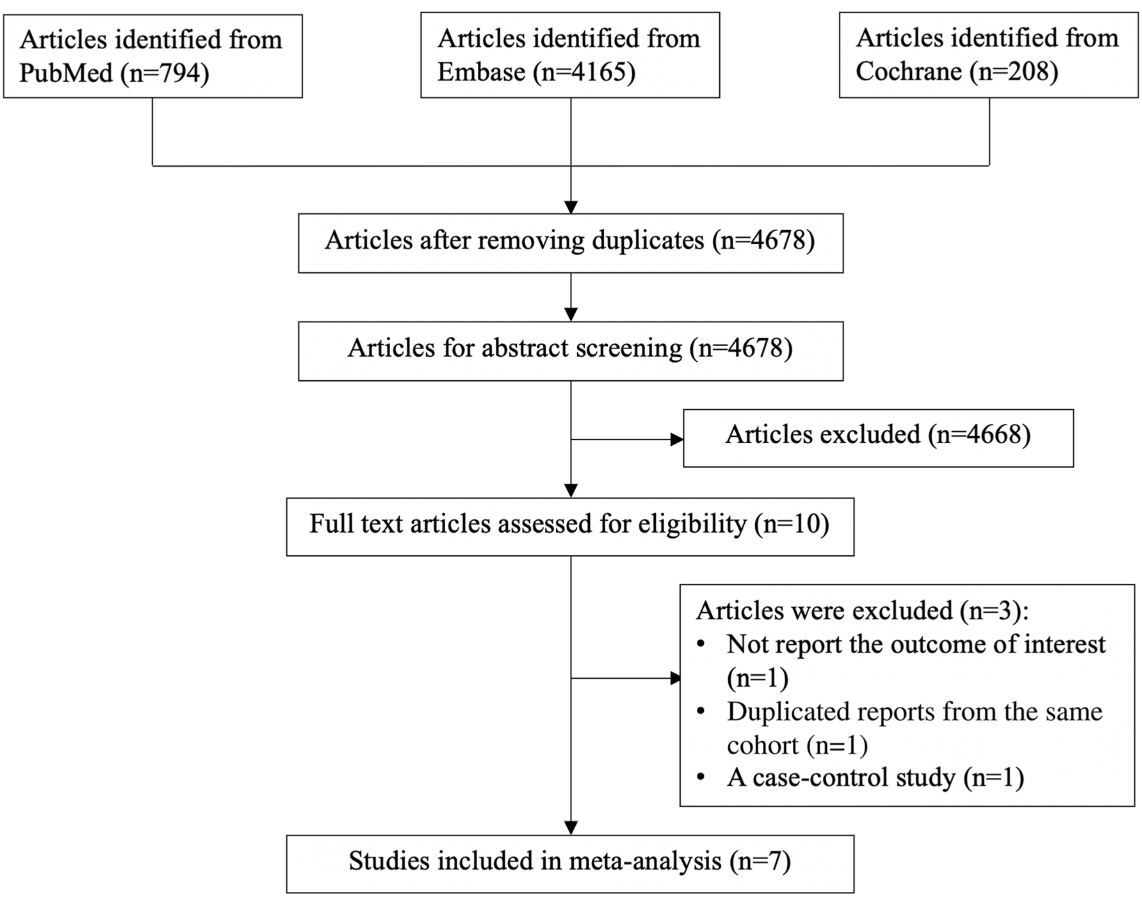

Fig. 1 Flow diagram of the study selection process

Higgins I^2 statistic [14]. A random effects model was used when heterogeneity was detected ($I^2 \geq 50\%$); otherwise, a fixed effects model was used ($I^2 < 50\%$). A sensitivity analysis was conducted to determine the source of heterogeneity. Adjusted ORs, HRs, and risk ratios were preferred over crude ratios if available; otherwise, crude ratios were used. The combined RRs from cohort studies were calculated with the 95% confidence interval (95% CI), and a $P < 0.05$ indicated a statistically significant difference. Begg's and Egger's tests were used to assess publication bias with Stata 12.0 statistical software (StataCorp, College Station, TX, USA), and a $P < 0.1$ indicated a statistically significant difference [15, 16].

Results

Search results and quality assessments

In total, 4678 studies were obtained from the PubMed, Cochrane, and EMBASE databases after 509 duplicate articles were removed. After reading the titles and abstracts, we excluded 4668 articles. The remaining ten studies were assessed by reading the full article. One study was excluded because it lacked the outcome of interest, and another study was excluded because it was a duplicated publication with the same cohort as another study. Therefore, eight studies were finally included, with seven cohort studies and one case-control study [7, 8, 10–13, 17, 18] (Fig. 1). One abstract by Gerber et al. [10], which was published in *Circulation*, was included in our analysis, but we were unable to obtain detailed information after trying to contact the corresponding author and therefore could not evaluate the quality of the data. There was only one case-control study [17], and the data from it could not be combined with the data from the cohort studies, so we did not include it in our meta-analysis. The characteristics of the included studies are described in Table 1. All of the results are summarized in Table 2.

Any fracture risk for patients with or without a history of HF

After pooling data from five studies (two studies, Sennerby et al. [12] and Carbone et al. [9], only reported hip fractures, so they were excluded from this analysis), we found a significantly higher risk of any fracture in patients diagnosed with HF ($N = 49{,}242$) than in the controls ($N = 103{,}281$) (RR 1.66, 95% CI 1.14–2.43, $I^2 = 94\%$, $P = 0.008$, Fig. 2). A sensitivity analysis was performed, and the heterogeneity ($I^2 = 94\%$) originated from the 2008 study by van Diepen et al. [11]. The results were unchanged after excluding the two studies (RR 1.25, 95% CI 1.13–1.39, $I^2 = 27\%$), although the RR was smaller.

Table 1 Basic characteristics and quality evaluation of included studies

Study	Study design	Country	Number		Age (years, mean (SD))		Female (%)		BMI (mean (SD))		Follow-up years	Fracture (*n*)		Hip fracture (*n*)		Location of fractures	NOS score
			HF	Non-HF	HF	Non-HF	HF	Non-HF	HF	Non-HF		HF	Non-HF	HF	Non-HF		
van Diepen 2008	Cohort	Canada	2041	14,253	73 (NA)	78 (NA)	51.9	53.2	NA	NA	1	93	147	26	18	Any and hip	9
Sennerby 2009	Cohort	Sweden	2270	19,089	80 (4)	71 (8)	44.8	56	25.7 (3.7)	25.0 (3.3)	>40	113	526	113	526	Hip	9
Gerber 2011	Cohort	USA	961	961	75.5 (12.7)	75.4 (12.6)	54	54	26.9 (6.4)	25.4 (6.5)	7.5	222	181	NA	NA	Any and hip	8
Majumdar 2012	Cohort	Canada	1841	43,668	74 (9)	66 (10)	83	93	29 (6)	27 (5)	4–5	185	2310	55	249	Any and hip	8
Lai 2012	Cohort	Taiwan	43,874	43,874	NA	NA	NA	NA	NA	NA	6	NA	NA	NA	NA	Any and hip	8
Gerber 2014	Cohort	USA	525	525	NA	NA	NA	NA	NA	NA	6	NA	NA	NA	NA	Any	NA
Carbone 2009	Cohort	USA	1526	4087	73.9 (5.71)	72.3 (5.45)	52	60	27.4 (5.0)	26.4 (4.5)	11.5	159	316	159	316	Hip	9

HF heart failure, *NA* not applicable, *BMI* body mass index

Table 2 Summary of meta-analysis results for HF and fractures

Analysis specification	Studies	RR (95% CI)	Heterogeneity I^2 (%)	*P* value
All	5	1.66 (1.14–2.43)	94	0.008
Fracture locations				
Hip	5	3.45 (1.86–6.40)	95	< 0.001
Vertebral	2	1.78 (0.88–3.58)	88	0.11
Humerus	2	1.91 (1.07–3.40)	39	0.03
Forearm	2	1.06 (0.80–1.41)	0	0.69

Hip fracture risk for patients with or without a history of HF

One cohort study reported the OR, and four cohort studies reported the HRs of patients who experienced hip fractures (Fig. 3). The OR in the 2008 study by van Diepen et al. [11] was transformed into a RR. The pooled analysis revealed a significantly higher risk of hip fracture in patients with HF than in those without HF (RR 3.45, 95% CI: 1.86–6.40, $I^2 = 95\%$, $P < 0.0001$). The sensitivity analysis showed that the heterogeneity came from the Carbone et al. [9] and Majumdar et al. [8] studies, and RR was markedly higher after excluding these two studies (RR 4.71, 95% CI 3.78–5.86, $I^2 = 0\%$).

Fracture risk at other sites for patients with or without a history of HF

Two studies reported fracture risks in the vertebrae, the humerus, and the forearm separately. The pooled analysis showed that patients with HF had a significantly higher risk of fracture in the humerus (RR 1.91, 95% CI 1.07–3.40, $I^2 = 39\%$, $P = 0.03$) and only a trend towards an increased risk of fracture in the vertebrae and forearm (RR 1.78, 95% CI 0.88–3.58, $I^2 = 88\%$, $P = 0.11$; RR 1.06 95% CI 0.80–1.41, $I^2 = 0\%$, $P = 0.69$) compared with those without a history of HF (Fig. 4).

Publication bias

There was no publication bias identified in any of the included studies. For the overall analysis, no obvious publication bias was identified by Begg's and Egger's tests ($P = 0.322$ and $P = 0.134$, respectively).

Discussion

This study is the first meta-analysis to examine the risk of fracture in patients with HF. We found a significantly increased risk of any fracture in patients with HF than in those without HF, especially for hip and humerus fractures. These data suggest that patients with HF may have an increased risk of fracture and may need to pay greater attention to bone health, especially patients at an advanced age.

The pathophysiological link between HF and fracture has not been clear, although several possible mechanisms have been proposed. First, HF and osteoporosis share some common etiological risk factors, such as aging, menopause, smoking, vitamin D deficiency, and diabetes mellitus [1, 4, 5, 19]. Second, hypoxemia has been identified in patients with stable HF, which may stimulate osteoclast formation and bone resorption, thus leading to bone loss [20]. Third, hyperaldosteronism and secondary hyperparathyroidism are common in patients with HF, which may stimulate calcium excretion and accelerate bone loss. Fourth, medications used for treating HF, such as loop diuretics, have been shown to stimulate bone loss and increase the risk of fractures [21–25]. Finally, patients with HF have been reported to have a higher risk of falls, possibly due to frailty in patients with advanced HF.

We found an increased risk of fracture in the hip but not in the vertebrae in patients with HF, although vertebral compression fractures are the most common osteoporotic fractures. This finding can be explained by the fact that the two included studies that reported the vertebral fracture risk, Gerber et al. [13] and Majumdar et al. [8], did not validate the fractures with radiographic imaging. Most vertebral fractures are

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Lai 2012	0.1717	0.0344	21.9%	1.19 [1.11, 1.27]
Majumdar 2012	0.2418	0.0936	20.9%	1.27 [1.06, 1.53]
Gerber 2011	0.281	0.1537	19.3%	1.32 [0.98, 1.79]
Gerber 2014	0.5306	0.1906	18.1%	1.70 [1.17, 2.47]
van Diepen 2008	1.3736	0.1403	19.7%	3.95 [3.00, 5.20]
Total (95% CI)			**100.0%**	**1.66 [1.14, 2.43]**

Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 71.53$, df = 4 ($P < 0.00001$); $I^2 = 94\%$
Test for overall effect: Z = 2.65 (P = 0.008)

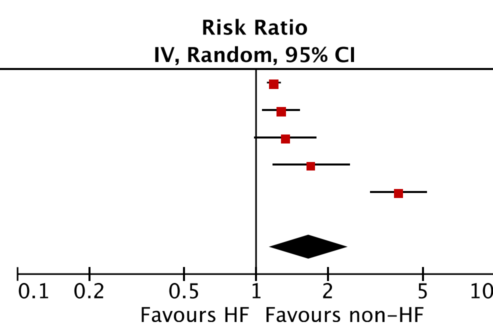

Fig. 2 Forest plots of any fracture risk between the HF group and non-HF group

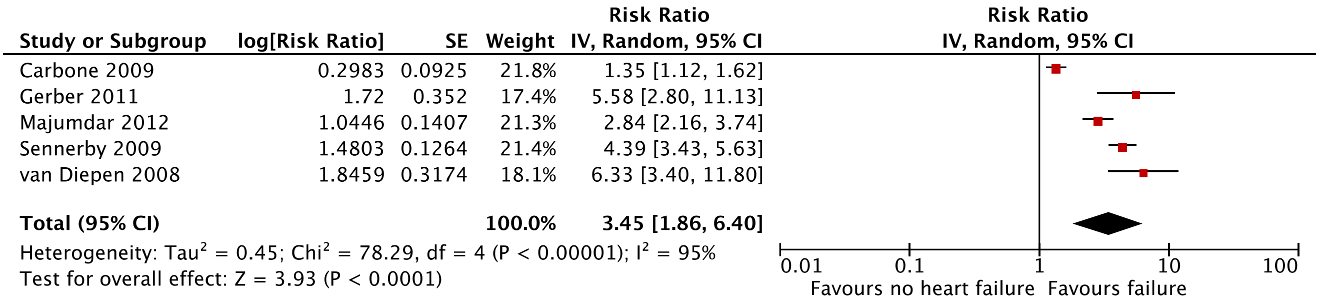

Fig. 3 Forest plots of risk of hip fracture between the heart failure group and non-heart failure group

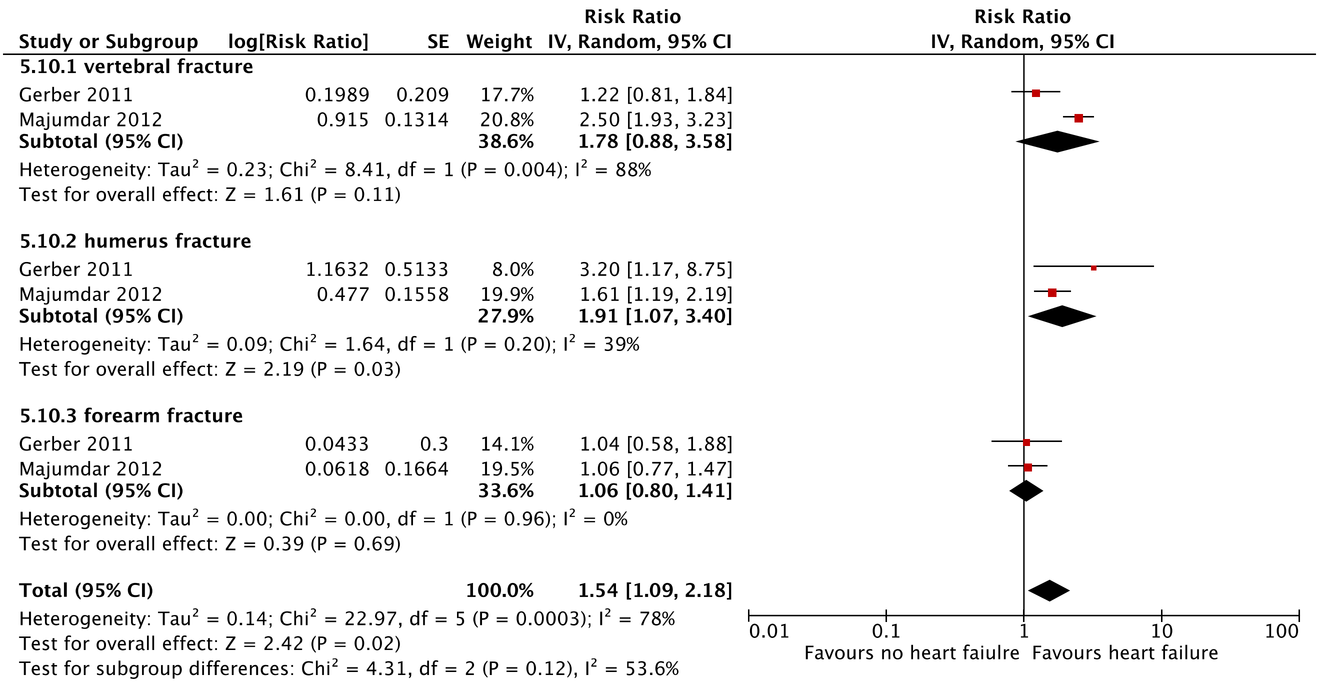

Fig. 4 Forest plots of fracture risk at different sites between the HF group and non-HF group

asymptomatic and cannot be detected without radiographic imaging [26]; therefore, the incidence rates in these two studies were underestimated. Another explanation is that only two studies reported vertebral fractures, and the number of vertebral fractures was quite small compared with the number of hip fractures, so the power may have been inadequate to identify a difference in the vertebral fracture risk of patients with HF compared to controls. More studies with larger sample sizes are needed to clarify whether patients with HF have an increased risk of vertebral fractures.

The 2008 study by van Diepen et al. [11] reported a higher risk of any fracture than was reported in any of the other 5

Table 3 Quality evaluation of included studies based on NOS score

Study	Selection	Comparability	Exposure/ Outcome	NOS score
van Diepen 2008	****	**	***	9
Sennerby 2009	****	**	***	9
Gerber 2011	***	**	***	8
Majumdar 2012	****	**	**	8
Lai 2012	***	**	***	8
Gerber 2014	NA	NA	NA	NA
Carbone 2009	****	**	***	9

studies and was identified as the main source of heterogeneity in the meta-analysis. This may be because that study was retrospective, while the other studies were prospective. Moreover, the heterogeneity in hip fracture risk analysis may have been due to the relatively high body mass index (BMI) of the patients in the studies by Carbone et al. [9] and Majumdar et al. [8], as a high BMI is a possible protective factor against future fracture [27–30].

There are unique strengths to our study. This is the first meta-analysis examining the association between HF and fracture risk that has pooled all the available data. All the included cohort studies were of high quality as assessed by the NOS (Table 3), except for one abstract [10]. Furthermore, instead of crude data, the adjusted ORs or HRs of the original studies were used so that possible confounders had been adjusted for and more reliable results were obtained.

Nonetheless, there are several limitations in our study. First, only observational studies were included instead of randomized controlled trials, which could provide more reliable evidence to clarify this topic. However, it is not possible to conduct randomized controlled trials to explore whether HF is a risk factor for fracture. The results from well-conducted observational studies with large sample sizes and long follow-up periods are also reliable. Moreover, the numbers of fractures in specific sites were limited so that the power to identify a difference in the risk of a specific fracture in patients with HF compared to those without HF may have been reduced.

In conclusion, this meta-analysis demonstrated that patients with HF have an increased risk of any fractures, especially hip and humerus fractures. As patients with HF live longer, more attention needs to be paid to their bone health, especially in those patients at advanced ages. Further studies are needed to clarify the association of HF with fractures at specific sites and the underlying pathophysiologic mechanisms.

Compliance with ethical standards

Conflict of interest None.

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