INTRODUCTION

Heart failure (HF) is a clinical syndrome caused by structural and/or functional cardiac abnormality, resulting in pulmonary and/or systemic congestion and insufficient organ perfusion. It usually manifests typical symptoms such as breathlessness, fatigue, and lower limb swelling, which may be accompanied by signs such as pulmonary crackles, peripheral edema, jugular vein engorgement or even distension. The diagnostic workup of HF requires a thorough assessment of symptoms, signs, clinical history, blood biomarkers (eg, B-type natriuretic peptide, N-terminal pro-B-type natriuretic peptide), and echocardiographic estimates (eg, ejection fraction). Its incidence increases with age. It is reported to be the most common cardiovascular reason for hospitalization in people over 60 years of age and it is associated with a poor prognosis.

OBJECTIVES

We aimed to summarize available evidence to evaluate whether osteoporosis was associated with an increased risk of incident HF.

PATIENTS AND METHODS

Major databases, including PubMed, Embase, the Cochrane library, Web of Science, and ClinicalTrials, were searched for cohort studies reporting the hazard ratio (HR) for incident HF in patients with osteoporosis. The pooled hazard ratios (HRs) and 95% CIs were estimated by using a random-effects model. Heterogeneity was evaluated by the $I^2$ statistics and the $\chi^2$ test.

RESULTS

Three studies with a total of 70,697 patients were included, with the mean (SD) age of 62.9 (13.3) years. Osteoporosis was associated with an increased overall risk of incident HF (pooled HR, 1.17; 95% CI, 1.08–1.26; $P < 0.001$; heterogeneity $I^2 = 13.28\%$, $P = 0.32$). The risk of incident HF was elevated in osteoporotic men (HR, 1.3; 95% CI, 1.05–1.62; $P = 0.02$; $I^2 = 71.57\%$, $P = 0.03$); however, no significant association was found for women (HR, 1.14; 95% CI, 0.94–1.37; $P = 0.19$; $I^2 = 64.66\%$, $P = 0.06$). The association between osteoporosis and incident HF risk was positive among individuals of Asian ethnicity (HR, 1.18; 95% CI, 1.06–1.3; $P = 0.002$; $I^2 = 52.61\%$, $P = 0.15$).

CONCLUSIONS

Osteoporosis was associated with a modest but significantly increased risk of incident HF. Considering the limited number and quality of available studies, future high-quality data are required to further demonstrate the association between osteoporosis and incident HF.
WHAT'S NEW?

The association between bone health and cardiovascular diseases was observed in previous studies. However, whether osteoporosis is related to incident heart failure remains debatable. Data concerning the risk of incident heart failure in osteoporotic patients were systematically reviewed in the present study. We reported an increased overall hazard ratio of incident heart failure in patients with osteoporosis when compared to those without.

PATIENTS AND METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. (Supplementary material, Tables S1 and S2)

Search strategy

Two independent reviewers (CC and ZLY) performed database searches in PubMed, Embase, the Cochrane library, Web of Science, and ClinicalTrials by using the following items: (heart failure OR heart insufficiency OR cardiac insufficiency OR myocardial insufficiency OR myocardial failure OR cardiac failure OR heart decompensation OR cardiac decompensation OR myocardial decompensation) AND (osteoporosis OR osteopenia OR bone mineral density OR bone density OR bone densit OR bone content OR bone loss), from inception to April 16, 2019. There was no language restriction in our searches. We also performed a limited updated search from April 16, 2019 to June 21, 2020. Detailed search strategies in each database are reported in Supplementary material, Tables S3-S7.

Eligibility criteria and study selection

Studies were eligible if they met the following criteria: 1) had a longitudinal design; 2) included patients with osteoporosis or osteopenia (defined by bone mineral density [BMD] assessment using any validated tool according to a clear standard diagnostic criteria or any documented medical or insurance records); 3) included a control group (with normal BMD, or without osteoporosis); 4) the endpoints were incident HF (defined as diagnosis information from any medical or insurance records or self-reported HF based on a physician diagnosis confirmed by standard diagnostic criteria using medical records documenting series of symptoms, physical signs, and other supporting clinical findings); and 5) provided hazard ratio (HR) for incident HF. The primary outcome of our analysis was the risk of incident HF in patients with osteoporosis, assessed through HRs for incident HF.

Two authors (GZJ and YYY) developed the lists of studies independently during the selection process. A third author (CC) was prepared to adjudicate the lists, and discussed with the above 2 authors to reach a consensus if discrepancies were found. If 2 studies were based on the same cohort, the study with bigger sample size was included. The references of included articles were searched to identify additional potentially relevant publications. We also considered conference abstracts in our database searches. We contacted the corresponding authors to acquire the data to evaluate the eligibility of potentially relevant conference abstracts.

Data extraction and quality assessment

Two reviewers (CC and ZLY) independently extracted data from the included studies using a standard form. Disagreements between the 2 reviewers were solved by a formal discussion to reach a consensus. Data were extracted on: 1) basic characteristics of included studies (first author, publication year, country, race, number of patients, mean age, percentage of female patients, follow-up period, adjusted covariates; 2) descriptions of exposure measurement (osteoporosis or osteopenia) and endpoint (incident HF); and 3) outcome data (hazard ratio). The quality of prognostic studies was assessed according to the recommendations by Hayden et al11 using the following domains: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and control, and analysis. Two reviewers (GZJ and YYY) performed the quality assessment of each of the included studies independently. Discrepancies were solved by discussion with a third reviewer (ZLY). The domains would be rated as yes, partly, unsure, or no for its appropriateness, respectively.

Statistical analysis

We performed a random-effects meta-analysis using Comprehensive Meta-Analysis (CMA) 2.0 (Biostat, Englewood, New Jersey, United States).12 In the primary analysis, we calculated the pooled HR and 95% CI from all included studies. We only included the HR adjusted for the highest number of covariates for each study. The same procedure was performed in the post hoc subgroup analysis. Study heterogeneity was evaluated by using the I² statistics and the χ² test. A value of over 50% for the former and a P value of less than 0.05 for the latter suggested significant moderate or higher heterogeneity.13
Sensitivity analyses were conducted as follows: First, a fixed-effect model was additionally used to estimate the pooled HR of all included studies in order to compare with a random-effects model. Secondly, we estimated the respective HRs by a random-effects model by excluding one study at a time. Publication bias was not performed because of the limited number of included studies (less than 10) in the present review. A P value of less than 0.05 was considered significant.

Ethics statement This study was approved by the Academic Administration Committee of Maoming People’s Hospital. Informed consent was not required.

RESULTS Description of included studies A total of 5451 articles were identified in the search. All articles were derived from the abovementioned databases, and no other sources of studies or unpublished studies were used. Then, 5428 articles were excluded after the screening of their titles and abstracts. Twenty-three articles (5 in PubMed, 9 in Web of Science, 9 in Embase) were reviewed. Thirteen duplicated articles were excluded. Out of the 10 remaining full-text studies, 7 were further excluded (mainly because of overlapping cohorts, case series reports, and missing HR data for incident HF) (Supplementary material, Table S8), and 3 studies were ultimately included (figure 1). Among included studies, the cohort study conducted in the United States had a prospective design, while the other 2 from Taiwan had a retrospective design. The main features of the included studies are shown in Table 1. All participants were recruited from patients with end-stage renal disease (ESRD) in the study of Yu et al. The sample sizes ranged from 1250 to 57,148, with 70,697 people analyzed in total. The mean (SD) age of all included people was 62.9 (13.3) years. Ninety-eight percent of the people were of Asian ethnicity, and the rest were mostly Caucasians. Only a small number of Black people were included in the study by Fohtung et al in this review. However, no Black individuals were included in the final analysis in that study since scant osteoporosis was diagnosed in this subpopulation. More women, accounting for 76.7% of all included people, were included than men. The follow-up period varied from 6.9 to 10.5 years, but 1 study did not provide relevant data. All studies listed detailed adjusted covariates, mainly including age, sex, smoking, alcohol consumption,
### TABLE 1  Characteristics of included studies

<table>
<thead>
<tr>
<th>Study, country, Setting, Participants, n</th>
<th>Race, %</th>
<th>Female sex, %</th>
<th>Follow-up, y</th>
<th>Age, y, mean (SD)</th>
<th>Adjusted covariates, n</th>
<th>Match</th>
<th>Exposure measure</th>
<th>HF ascertainment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fohtung et al, United States Community 1250 (1014 non-Black participants)</td>
<td>Non-Black, 81; Black, 19</td>
<td>59 (58.1 among non-Black participants)</td>
<td>10.5</td>
<td>76.7 (5)</td>
<td>16e</td>
<td>No</td>
<td>BMD (DXA at total hip or femoral neck), classified into osteoporosis, osteopenia, and normal BMD</td>
<td>Medical record (adjudication by an expert panel)</td>
</tr>
<tr>
<td>Chiu et al, Taiwan Nationwide population 57 148</td>
<td>Asian, 100</td>
<td>78.3</td>
<td>Osteoporosis group, 7.07 (3.49); control group, 6.9 (3.5)</td>
<td>Osteoporosis group, 63.9 (12.8); control group, 63.1 (13.1)</td>
<td>19b</td>
<td>Yes</td>
<td>Osteoporosis (health information from the National Health Insurance Research Database)</td>
<td>Health information from the National Health Insurance Research Database</td>
</tr>
<tr>
<td>Yu et al, Taiwan Nationwide population 12 535</td>
<td>Asian, 100</td>
<td>71</td>
<td>NA</td>
<td>Osteoporosis group, 59.8 (13.5); control group, 58.5 (14.2)</td>
<td>8c</td>
<td>Yes</td>
<td>Osteoporosis (Health information from the National Health Insurance Research Database)</td>
<td>Health information from the National Health Insurance Research Database</td>
</tr>
</tbody>
</table>

**a** Age, body mass index, systolic blood pressure, antihypertensive medication, diabetes mellitus, smoking, alcohol consumption, physical activity, estrogen replacement (women), prevalent coronary heart disease, prevalent stroke or transient ischemic attack, prevalent peripheral arterial disease, prevalent atrial fibrillation, estimated glomerular filtration rate, forced expiratory volume in 1 second, and C-reactive protein

**b** Age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, chronic kidney disease, stroke, chronic obstructive pulmonary disease, asthma, alcohol-related illness, coronary artery disease, and liver diseases, and medications including prednisolone, estrogen, statin, angiotensin-converting enzyme inhibitors, angiotensin receptor blocker, spironolactone, and thiazides

**c** Age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, mental disorders, hepatitis B infection, and hepatitis C infection

Abbreviations: BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; HF, heart failure; NA, not available

### TABLE 2  Quality assessment of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Study participationa</th>
<th>Study attritionb</th>
<th>Osteoporosis or osteopenia ascertainmentc</th>
<th>Outcome defined and described appropriatelyd</th>
<th>Control of confoundinga</th>
<th>Analysis described appropriatelyf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiu et al, Taiwan</td>
<td>Yes</td>
<td>Unsure</td>
<td>Unsure</td>
<td>Unsure</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fohtung et alUnited States</td>
<td>Yes</td>
<td>Unsure</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Yu et alTaiwan</td>
<td>Yes</td>
<td>Unsure</td>
<td>Unsure</td>
<td>Yes</td>
<td>Partly</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Each bias was assessed as yes, partly, no, and unsure.

**a** The study sample represents the population of interest on key characteristics to sufficiently limit the potential bias.

**b** Loss to follow-up (from sample to study population) is not associated with key characteristics (the study data adequately represent the sample), sufficiently limiting potential bias.

**c** The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias.

**d** The outcome of interest is adequately measured in study participants to sufficiently limit potential bias.

**e** Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest.

**f** The statistical analysis is appropriate for the design of the study, limiting potential for presentation of valid results.
comorbidities, and medications. The mean number of adjusted covariates was 14.

Osteoporosis and HF were ascertained directly by documented information from health insurance databases in the 2 studies from Taiwan. In the study from the United States, osteoporosis was identified through measurements of individuals’ BMD according to the World Health Organization classification of osteoporosis using T-scores, and HF was confirmed by an expert panel based on standard diagnostic criteria through careful evaluation of medical records documenting series of symptoms, physical signs, and other supporting clinical findings.

Quality assessment of included studies According to the quality assessment criteria of prognosis studies in systemic reviews (Table 2), the study participation was adequate in all 3 included studies. We were unsure about the study attrition in all 3 studies not reporting relevant data about loss to follow-up. We were also unsure about the appropriateness of ascertainment of osteoporosis and HF in 2 studies from Taiwan since the criteria for diagnosis were not provided. Potential confounders were adequately accounted for in 2 studies, except for the study from Yu et al16 rated as partly for this domain. An appropriate statistical analysis was employed in all studies and sufficiently limited the potential for the presentation of invalid results. Taken together, one study was considered to be of good quality, while the other 2, of moderate quality. The major insufficiencies were derived from the measurements of exposure and outcome in the 2 retrospective cohorts. These 2 studies identified osteoporosis and incident HF through documented medical records, in which diagnostic information was missing and inconsistent diagnostic criteria might have been used. It possibly resulted in inconsistencies in exposure and outcome measurements and caused heterogeneity among included studies.

Analysis of included studies We first evaluated the estimated HRs for female and male patients and the entire cohort in the study from Fohtung et al14 since they only provided HRs based on bone sites and sex.

As reported in Figure 2, patients with osteoporosis had an increased overall risk of incident HF using a random-effects model (pooled HR, 1.17; 95% CI, 1.08–1.26; P < 0.001), as was the case with the fixed-effect model (pooled HR, 1.16; 95% CI, 1.09–1.23; P < 0.001). There was modest heterogeneity among included studies (I² = 13.28%, P = 0.32). Due to the relatively low number of included studies (less than 10), evaluations of publication bias were not performed. Sensitivity analyses were conducted to test the influence of each included study on the overall effect estimate by excluding one study at a time. There were consistent HRs observed favoring osteoporosis in increasing the risk of incident HF in sensitivity analyses (Supplementary material, Table S9).

Post hoc subgroup analyses Sex and race were demonstrated to be important factors for HF,17,18 meaning that they could be clinically-associated effect modifiers. The subgroup analysis regarding sex, as shown in Figure 3, indicated that osteoporosis was positively associated with increased risk of incident HF for males (HR, 1.3; 95% CI, 1.11–1.54; P < 0.001) but not males of Asian ethnicity with osteoporosis were at increased risk of incident HF (2 studies, I² = 0.15%) (HR, 1.18; 95% CI, 1.06–1.3; P = 0.002; P = 52.61%, P = 0.15) (Figure 4). However, we failed to assess the risk for non-Asian patients (mostly Caucasians) because only 1 study was available in the present analysis.

DISCUSSION In the present meta-analysis including 3 cohort studies with a total of 70,697 participants, we observed a 17% increase in the overall risk of incident HF in people with osteoporosis (mean [SD] age of 62.9 [13.3] years) compared with those without. In post hoc analyses by sex, the risk of incident HF increased by 30% in men with osteoporosis. A slightly raised
We suggested that osteoporosis was independently associated with an increased risk of incident HF. However, the underlying mechanisms still remain unclear. One potential explanation could be the activation of renin-angiotensin-aldosterone system (RAAS) in these conditions. Accumulating data suggested that RAAS might contribute to osteoporosis and its progression. For instance, in vitro studies found that angiotensin II could activate osteoclasts, key mediators in osteoporosis.\textsuperscript{22, 23} Animal studies in mice or rats showed that renin and angiotensin accelerated BMD decrease and that their blockage could improve bone quality.\textsuperscript{22-27} Furthermore, a significant increase of serum angiotensin-converting enzyme activity was revealed in osteoporotic women.\textsuperscript{28} A long-term intervention with RAAS inhibitors reduced osteoporotic fracture in postmenopausal women\textsuperscript{29} and protected against bone loss in hypertensive Black men.\textsuperscript{30} It was also demonstrated that in a cohort from Taiwan, a long-term use of RAAS inhibitors lowered the risk of osteoporotic fracture in a hypertensive population.\textsuperscript{31} All these data consistently indicated that the RAAS might be involved in osteoporosis. It was well demonstrated that the RAAS activation plays an important part in various conditions, such as hypertension, endothelial dysfunction, myocardial remodeling, atherosclerosis, and risk of incident HF was also seen in women with osteoporosis (HR, 1.14); however, it lacked statistical significance. Although an outstanding study by Veronese et al\textsuperscript{5} showed an association between low BMD and future cardiovascular diseases, they did not account for patients with HF in their analysis.\textsuperscript{5} Our study specifically synthesized available data to date to demonstrate that osteoporosis could be a risk factor for incident HF, which summarized the current knowledge in this field. However, this observation should be interpreted cautiously, since people at the mean (SD) age of 62.9 (13.3) years mostly have other comorbidities including a variety of causes and risk factors of HF (eg, CAD, hypertension, valvular heart disease, cardiomyopathy, diabetes mellitus, obesity, and so on).\textsuperscript{19} These covariates could be confounders when examining the association between osteoporosis and incident HF. In the present review, there were some important covariates not considered in adjustment among included studies. For example, CAD, an established cause of HF, was not included in covariates adjustment in the study by Yu et al.\textsuperscript{16} Adequate adjustment for causes and risk factors of HF should be emphasized in the future studies. On the other hand, low BMD itself is found to be related to other comorbidities such as cardiovascular calcification, chronic obstructive pulmonary disease,\textsuperscript{20, 21} which may potentially indicate that people with osteoporosis themselves may have more pathological conditions, thus predisposing to HF.

We suggested that osteoporosis was independently associated with an increased risk of incident HF. However, the underlying mechanisms still remain unclear. One potential explanation could be the activation of renin-angiotensin-aldosterone system (RAAS) in these conditions. Accumulating data suggested that RAAS might contribute to osteoporosis and its progression. For instance, in vitro studies found that angiotensin II could activate osteoclasts, key mediators in osteoporosis.\textsuperscript{22, 23} Animal studies in mice or rats showed that renin and angiotensin accelerated BMD decrease and that their blockage could improve bone quality.\textsuperscript{22-27} Furthermore, a significant increase of serum angiotensin-converting enzyme activity was revealed in osteoporotic women.\textsuperscript{28} A long-term intervention with RAAS inhibitors reduced osteoporotic fracture in postmenopausal women\textsuperscript{29} and protected against bone loss in hypertensive Black men.\textsuperscript{30} It was also demonstrated that in a cohort from Taiwan, a long-term use of RAAS inhibitors lowered the risk of osteoporotic fracture in a hypertensive population.\textsuperscript{31} All these data consistently indicated that the RAAS might be involved in osteoporosis. It was well demonstrated that the RAAS activation plays an important part in various conditions, such as hypertension, endothelial dysfunction, myocardial remodeling, atherosclerosis, and
inflammation, which lead to HF. Whether osteoporosis could contribute to HF via RAAS activation warrants further investigations.

Another potential mediator could be osteoprotegerin (OPG). It was initially revealed to be a key regulatory protein in bone metabolism and was then found to be expressed in the heart and vasculature. Its expression was shown to increase with age. In animal studies, the OPG-knockout mice not only developed osteoporosis at an early age but also had increased numbers of apoptotic myocardial cells, cardiac eccentric hypertrophy, attenuated contractile function, and artery calcification. In clinical studies, serum OPG was demonstrated to be positively associated with BMD, and its expression was reported to be increased in patients with HF. Thus, OPG seemed to be a protective protein to HF and osteoporosis. The dysregulation of OPG might be involved in osteoporosis-associated incident HF. However, data were not consistent to date with regard to the expression of serum OPG in osteoporotic patients, especially women. Serum OPG expression might be influenced by estrogen, diabetes mellitus, chronic renal disease, or other metabolic disorders. Future studies with large sample sizes are necessary to elucidate the mechanism underlying the regulation of OPG expression in these 2 conditions.

Sex differences in HF were well demonstrated previously. It appeared that osteoporotic men might have a higher risk of incident HF compared with women in our analysis, although we failed to prove it with statistical approach. The discrepancy might be affected by the sex difference in overall lifetime risk of HF, which was shown to be greater in men and probably related to heavier burden and earlier onset of CAD as compared with women. In addition, risk factors such as smoking, alcohol consumption, inappropriate lifestyle are more common in men. Another explanation might be that osteoporosis in men was often secondary and associated with poor health status or with a greater number of risk factors, which might also have a negative impact on the cardiovascular system. However, whether men with osteoporosis carry a higher risk of incident HF than women still remains open for further discussion with more well-designed studies. Our analysis has several limitations. First, the number of included studies was relatively small, and the overall quality of included studies was moderate. Second, the sample sizes of included studies differed tremendously, and the pooled HR was mainly driven by 2 retrospective cohorts from Taiwan. Third, a large majority of included people were of Asians ethnicity, making the observation in our analysis possibly not fit for other races. Fourth, in this analysis, we were unable to further discuss the impact of covariates such as age, comorbidity, and medication on the relationship between osteoporosis and incident HF, which could be helpful in further understanding the underlying interactions between them. Accordingly, the results presented in our analysis should be interpreted with caution.

Conclusions In conclusion, the present meta-analysis showed that osteoporosis was associated with a modestly higher risk of incident HF. Given the limited quantity and quality of currently available data, more future good-quality studies are required to further demonstrate the association between osteoporosis or low BMD and the risk of incident HF, to evaluate whether proper management of osteoporosis could reduce HF incidence, and to elucidate the underlying mechanism of interaction between these 2 disorders.

SUPPLEMENTARY MATERIAL
Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION
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CONTRIBUTION STATEMENT ZG conceived the concept of the study, ZG and YY contributed to the design of the research. All authors were involved in data collection. ZG and YY analyzed the data. All authors edited and approved the final version of the manuscript.
CONFLICT OF INTEREST None declared.
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REFERENCES