



Association Between Prognostic Nutritional Index and Prognosis in Patients With Heart Failure: A Meta-Analysis

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Background: The prognostic nutritional index (PNI) has been proposed as a marker of malnutrition and associated with the prognosis of cardiovascular disease. However, whether PNI can serve as a potential biomarker for the prognosis of heart failure (HF) upon those established risk factors were still controversial. This meta-analysis aimed to generate comprehensive evidence on the prognostic value of PNI in patients with HF.

Methods: Multiple databases (PubMed, Embase, the Cochrane Library, and Google Scholar) were searched for related studies up to January 31, 2022. Observational studies accessed associations between PNI levels and the prognosis in patients with HF were included for meta-analysis. The hazard ratios (HRs) and 95% confidence intervals (CI) were calculated.

Results: Fourteen studies, comprising 19,605 patients with HF were included for meta-analysis. The median follow-up duration was 18.5 months. Compared with those with higher PNI (normal nutritional status), patients with HF with lower PNI (malnourished) were associated with a higher risk of all-cause mortality (HR 1.53, 95% CI 1.27–1.85) and composite major adverse cardiac outcomes (MACEs; HR 2.26, 95% CI 1.54–3.31) in the multivariable-adjusted model. Furthermore, when PNI was defined as per 1 increment as a continuous metric, higher PNI was associated with a decrease in all-cause mortality (per 1 increment of PNI: HR 0.94, 95% CI 0.88–0.96) and MACEs (per 1 increment of PNI: HR 0.97, 95% CI 0.95–0.98).

Conclusions: The PNI can serve as an easily calculated bedside “malnutrition-inflammation” biomarker in HF. Lower PNI was associated with a worse prognosis in patients with HF.

Keywords: prognostic nutritional index, heart failure, all-cause mortality, cardiovascular disease, prognosis

INTRODUCTION

Heart failure (HF) is the end state of various heart diseases. It was estimated that over 37.7 million individuals were affected with HF worldwide (1, 2). During the past decades, there have been significant improvements in the management of HF, especially with the use of new drugs, including angiotensin receptor neprilysin inhibitors and sodium-glucose cotransporter-2 inhibitors, and the

prognosis of HF had been improved (3). However, the risk of mortality and re-hospitalization are still high, which become a growing public health burden worldwide (4–6). Therefore, it was important to further address novel pathogenic mechanisms, prognostic factors, and treatment modalities in HF (7–9).

Malnutrition is an important prognostic factor in HF. It was estimated that up to 50% of patients with HF were malnourished (10). Current guidelines for the management of HF recommend assessment of nutritional status in chronic HF (3, 11); however, there is no consensus on the tools or metrics for measuring malnutrition. Recently, a novel and simple metric, the prognostic nutritional index (PNI), had been proposed to evaluate the nutritional status in multiple clinical settings, including cancers, and post-operative pneumonia (12, 13). Recent studies also showed that lower PNI is associated with an increased risk of mortality or major adverse cardiac events (MACEs) in patients with acute or chronic HF (14–18). However, whether PNI can serve as a potential biomarker for the prognosis of HF upon those established risk factors were still controversial.

Herein, we conducted a systematic review and meta-analysis of observational studies to generate comprehensive evidence on the prognostic value of PNI in patients with HF, and further explore whether such a relationship is modified by other risk factors.

MATERIALS AND METHODS

Search Strategies and Study Selection Criteria

This study was performed under the guideline of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group (19). We searched multiple databases (PubMed, Embase, the Cochrane Library, and Google Scholar) from inception until January 31, 2022. The search was developed by combining the MeSH heading and text strategies, with the terms “prognostic nutritional index,” “PNI” or “malnutrition” and “heart failure,” “cardiac failure,” “myocardial failure,” “cardiac dysfunction,” or “myocardial dysfunction.” The search was limited to human studies and writing in English or Chinese. We also manually checked the reference lists of the included studies to identify other potential related articles.

The inclusion criteria for meta-analysis were: (1) observational studies involving adult participants with a diagnosis of HF; (2) the PNI was recorded at enrolment; and (3) the association between PNI score and the prognosis [including all-cause mortality or composite major adverse cardiac outcomes (MACEs)] of HF were reported during follow-up. The PNI value was calculated as: $PNI = 10 \times \text{serum albumin concentration (g/d6)} + 0.005 \times \text{total lymphocyte count (per mm}^3\text{)}$ (20).

The exclusion criteria were: (1) cross-sectional studies without follow-up evaluation; (2) reported other nutritional indexes but not PNI; and (3) duplicated publications from the same observational studies in such situations, only the most recently published data were included for analysis.

Data Extraction and Study Quality Evaluation

Two researchers (CM and JW) conducted the literature searching and item screening independently. Potentially related articles were reviewed and study information was extracted into a predefined form. We evaluated the quality of the included studies according to NOS (the Newcastle–Ottawa Quality Assessment Scale for cohort studies), which assesses the selection, comparability, and exposure/outcome, respectively (21). Up to a maximum of nine points can be awarded in NOS and we defined studies were graded in quality as poor (<4 points), fair (4–6 points), or good (≥ 7 points), respectively (7, 22).

Statistical Analysis

We assessed whether PNI was associated with the prognosis in patients with HF. The primary outcome was all-cause mortality. The secondary outcome was MACEs, including all-cause mortality, and HF re-hospitalization or all-cause re-hospitalization. The association of the outcomes and PNI value was reported in different ways in the included studies, such as per 1 increment as a continuous metric; or as normal/malnutrition in classified trait. Therefore, we calculated the hazard ratios (HRs) for per 1 score increment in PNI level, and also pooled data as malnutritional vs. normal nutritional status, respectively. To explore the effect of confounders on the estimated risks, unadjusted and multivariable-adjusted relative risks were both calculated. If multiple results were reported from different statistical adjustment models, we extracted the data which had adjusted the maximal number of confounders for analysis.

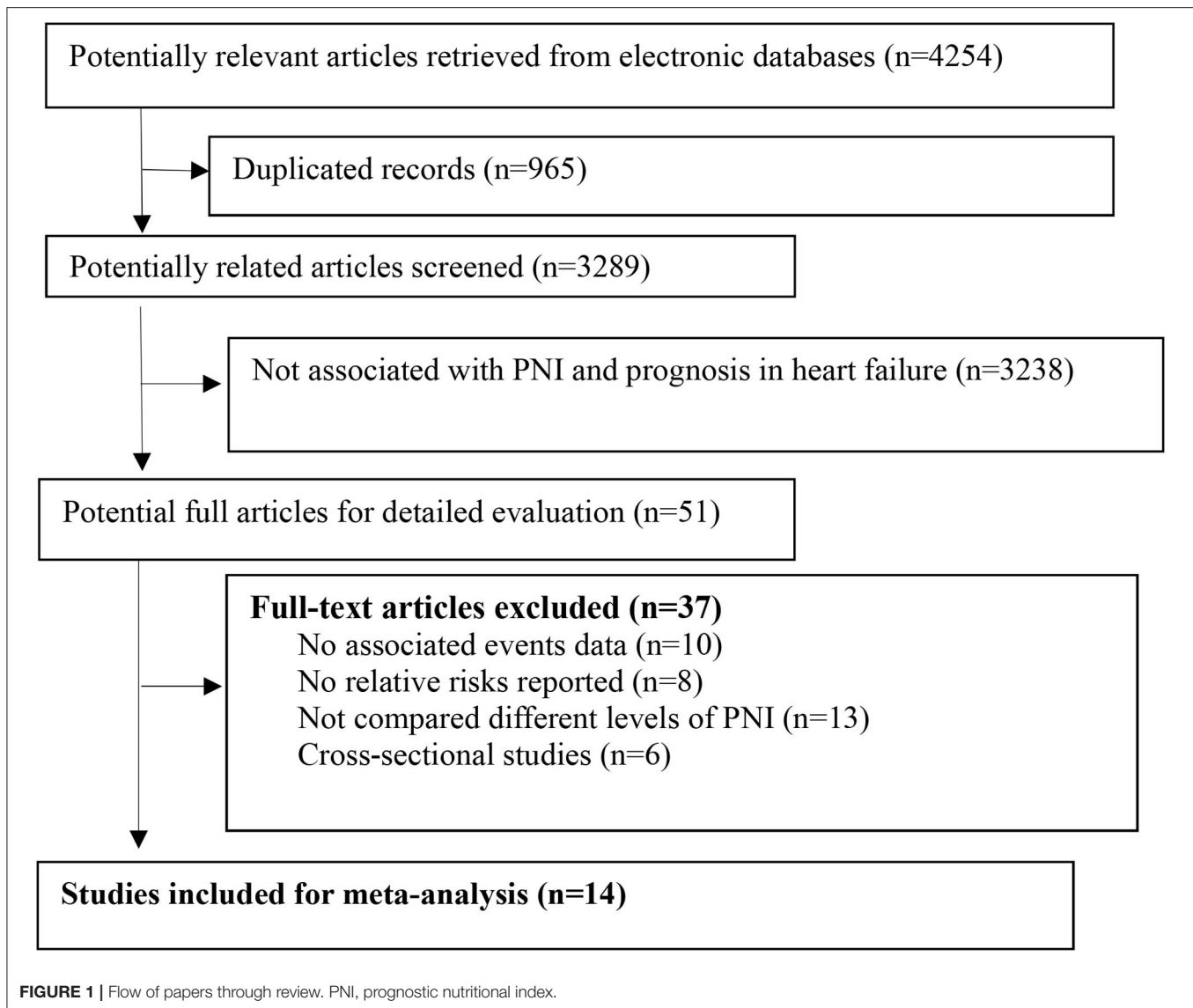
The HRs and their corresponding standard errors (SEs) were pooled by the inverse variance approach. In case outcomes were presented as odds ratios (ORs) or risk ratios (RRs), they were used as an approximate HR in meta-analysis (7, 22). We use the I^2 statistics to test heterogeneity, and an I^2 value of $>50\%$ or P for heterogeneity <0.1 was considered as statistically significant heterogeneity. A random-effects model was used to combine the pooled estimates if significant heterogeneity was observed. Otherwise, a fix-effects model was used.

Due to the limited number of available studies, we did not perform subgroup analyses for the association between PNI and the prognosis in patients with HF. The sensitivity analyses were conducted by interchanging the statistical models (random-effects models vs. fixed-effects models) or by omitting one study at a time. Publication bias was evaluated by inspecting the funnel plot for the outcomes. Due to the limited number of studies for each analysis (all $n < 10$), we did not further perform Begg’s test or Egger’s test to explore the publication bias. All the meta-analyses were conducted using RevMan 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). We consider a P -value <0.05 as statistically significant.

RESULTS

Studies Retrieved and Characteristics

We retrieved 4,254 related articles from the databases. After deleting the duplicate items, two authors independently screened the titles and abstracts and reviewed the full text of 51



articles (**Figure 1**). Finally, according to the predefined inclusion and exclusion criteria, we included 14 studies comprising 19,605 patients with HF for analysis (14–18, 20, 23–30). The median follow-up duration was 18.5 months. The main baseline characteristics of the included studies are presented in **Table 1**. Most of the included studies adjusted the important confounders for the prognosis of HF (**Supplementary File 1**). According to the predefined NOS assessment, we graded 4 studies with fair study quality and 10 studies with good quality (**Supplementary File 2**).

PNI and Risk of All-Cause Mortality in Patients With HF

In the unadjusted model, patients with lower PNI (malnourished) were associated with a 108% increase in all-cause mortality (HR 2.08, 95% CI 1.63–2.64; $I^2 = 89%$, P for heterogeneity <0.001), compared with those with higher PNI (normal nutritional status;

Figure 2). In the multivariable-adjusted model, the association between lower PNI and risk of all-cause mortality was still with statistical significance (HR 1.53, 95% CI 1.27–1.85; $I^2 = 71%$, P for heterogeneity = 0.004; **Figure 3**).

When PNI was defined as per 1 increment as a continuous metric, we observed that higher PNI was associated with a decrease in all-cause mortality in the unadjusted model (per 1 increment of PNI: HR 0.90, 95% CI 0.87–0.94; $I^2 = 93%$, P for heterogeneity <0.001 ; **Figure 4**), as well as in the multivariable-adjusted model (per 1 increment of PNI: HR 0.94, 95% CI 0.88–0.96; $I^2 = 78%$, P for heterogeneity <0.001 ; **Figure 5**).

PNI and Risk of MACEs in Patients With HF

Patients with lower PNI were associated with a 154% increase in MACEs (HR 2.54, 95% CI 1.48–4.38; $I^2 = 85%$, P for heterogeneity <0.001), compared with those with higher PNI in the unadjusted model (**Figure 6**). In the multivariable-adjusted

TABLE 1 | Characteristics of studies evaluated the association between prognostic nutritional index (PNI) and the outcomes in patients with heart failure (HF).

Study	Country/region	Study design	Cohort characteristics	PNI covariate definition	Sample size (% women)	Age (year) (mean or median)	Follow-up (months)	Events for analysis
Kawata et al. (14)	Japan	Retrospective cohort study	AHF	Continuous	141 (46.8%)	84	12.0	MACEs
Ju et al. (15)	China	Retrospective cohort study	AHF	Continuous	8,893 (55%)	81	3.0	All-cause mortality
Çinier et al. (16)	Turkey	Retrospective cohort study	HFrEF	Quartiles	1,100 (20.5%)	60.9	48.0	All-cause mortality
Sze et al. (17)	UK	Prospective cohort study	CHF	Continuous Malnourished (PNI ≤ 38.0)	467 (33.0%)	76.0	18.5	All-cause mortality MACEs
Candeloro et al. (18)	Italy	Prospective cohort study	AHF	Continuous Malnourished (PNI ≤ 34)	344 (54.1%)	84.0	5.3	All-cause mortality
Alataş et al. (23)	Turkey	Retrospective cohort study	AHF	Malnourished (PNI ≤ 41.2)	628 (53.7%)	74.7	NA	All-cause mortality
Zencirkiran and Kahraman (24)	Turkey	Prospective cohort study	HFpEF	Malnourished (PNI < 37.0)	285 (54.4%)	68.0	12.0	MACEs
Chien et al. (25)	China	Retrospective cohort study	HFpEF	Malnourished (PNI < 38.0)	1,120 (60.6%)	77.2	41.8	All-cause mortality MACEs
Takikawa et al. (26)	Japan	Prospective cohort study	AHF	Malnourished (PNI < 38.0)	457 (46.6%)	79.0	12.0	All-cause mortality
Sze et al. (27)	UK	Prospective cohort study	CHF	Malnourished (PNI < 38.0)	3,386 (39.0%)	75.0	52.4	All-cause mortality
Shirakabe et al. (28)	Japan	Retrospective cohort study	AHF	Malnourished (PNI < 38.0)	458 (34.0%)	76.0	12.0	All-cause mortality
Cheng et al. (29)	China	Prospective cohort study	AHF	Continuous Malnourished (PNI ≤ 44.8)	1,673 (32.0%)	76.0	31.5	All-cause mortality
Sze et al. (30)	UK	Prospective cohort study	AHF	Malnourished (PNI ≤ 38.0)	265 (38.0%)	82.0	19.9	All-cause mortality
Narumi et al. (20)	Japan	Prospective cohort study	CHF	Malnourished (PNI ≤ 38.0)	388 (40.0%)	69.6	28.4	MACEs

AHF, acute heart failure; CHF, chronic heart failure; HF, heart failure; HFrEF, heart failure with preserved ejection fraction; HFpEF, heart failure with preserved ejection fraction; MACEs, major adverse cardiac events; NA, not available; PNI, prognostic nutritional index.

model, lower PNI was still associated with an increased risk of MACEs (HR 2.26, 95% CI 1.54–3.31; $I^2 = 64\%$, P for heterogeneity = 0.04; **Figure 7**).

Only two studies defined PNI as per 1 increment as a continuous metric and evaluated the association between the risk of MACEs. Higher PNI was associated with a decrease of MACEs in the unadjusted model (per 1 increment of PNI: HR 0.95, 95% CI 0.91–1, **Supplementary File 3**), as well as in the multivariable-adjusted model (per 1 increment of PNI: HR 0.97, 95% CI 0.95–0.98, **Supplementary File 4**).

Sensitivity Analyses and Publication Bias Evaluation

Our sensitivity analyses confirmed that the association of PNI with the risks of all-cause mortality and MACEs did not change with the use of fixed-effects models for the random-effects models or recalculation of the relative risks by omitting one study at a time in the meta-analysis. We did not observe significant publication bias for all-cause mortality or MACEs

associated with PNI by visual inspection of the funnel plot (**Supplementary Files 5–12**).

DISCUSSION

To the best of our knowledge, this is the first meta-analysis evaluating the prognostic effect of PNI in patients with HF. We found that PNI can serve as an important biomarker in predicting a worse prognosis, including all-cause mortality and/or re-hospitalization in HF, either used as a continuous level or a category metric for defining the nutritional status. Although attenuated, the association between PNI and prognosis of HF was still significant after adjustment for multiple confounders, indicating that the prognostic effect of PNI was independent of other established risk factors.

Malnutrition is common in patients with HF and has been proposed as a modifiable risk factor for improving the prognosis in these patients (31). Nutritional intervention in HF can improve the life quality and reduce the risk of mortality (32).

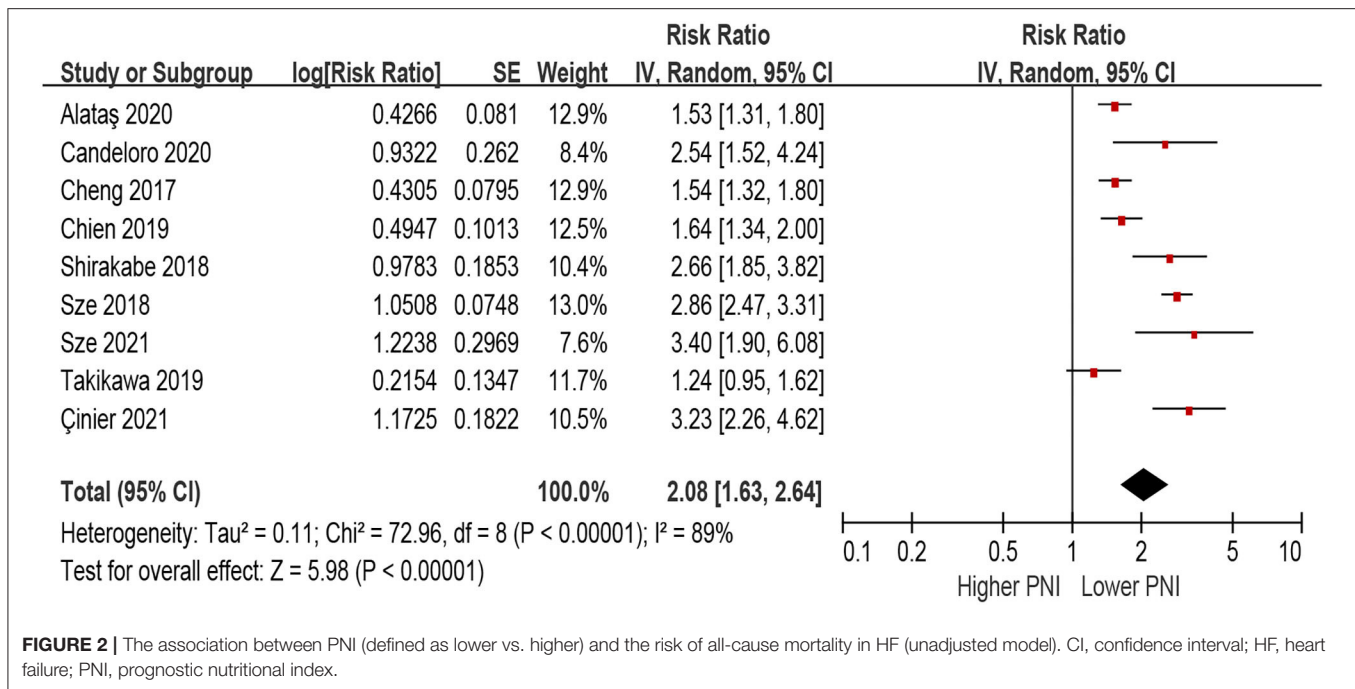


FIGURE 2 | The association between PNI (defined as lower vs. higher) and the risk of all-cause mortality in HF (unadjusted model). CI, confidence interval; HF, heart failure; PNI, prognostic nutritional index.

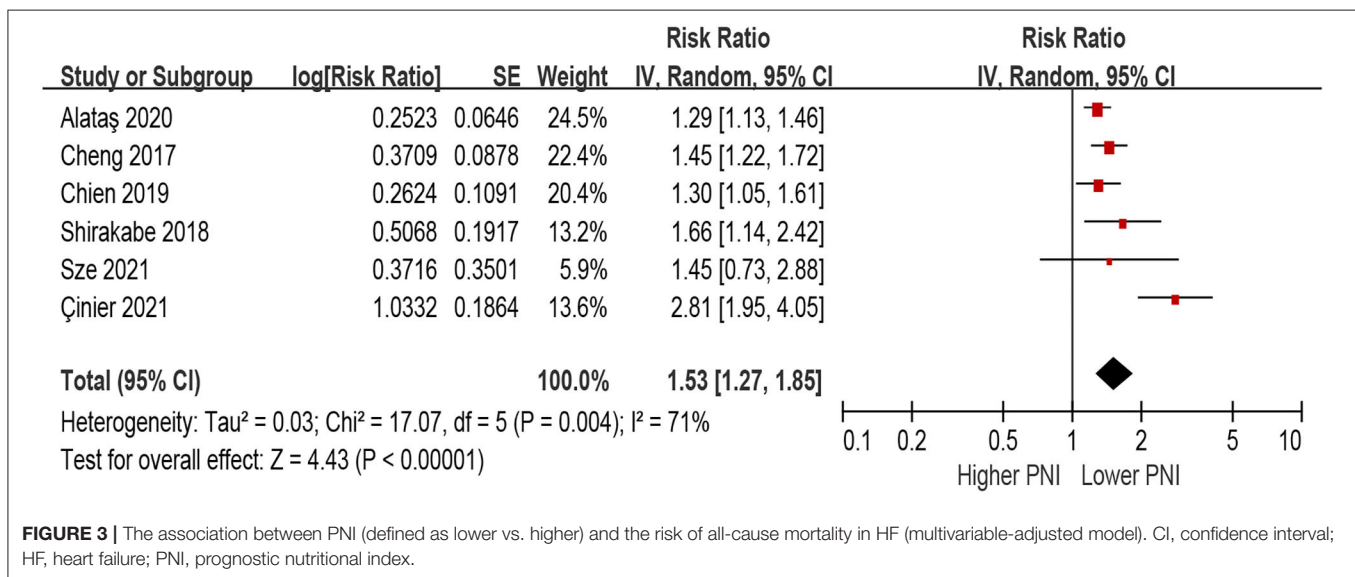
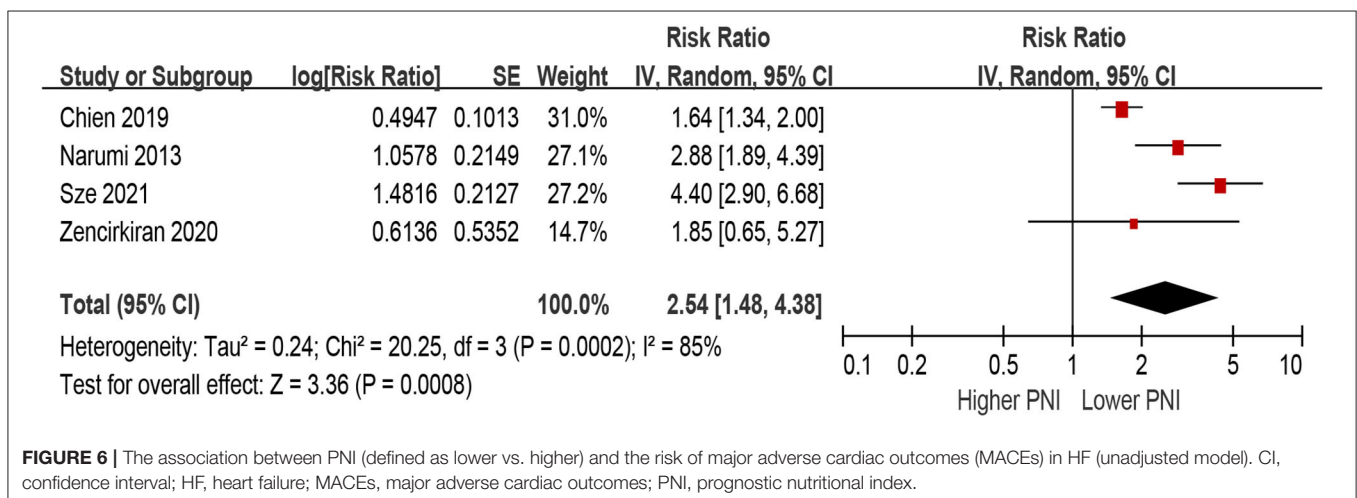
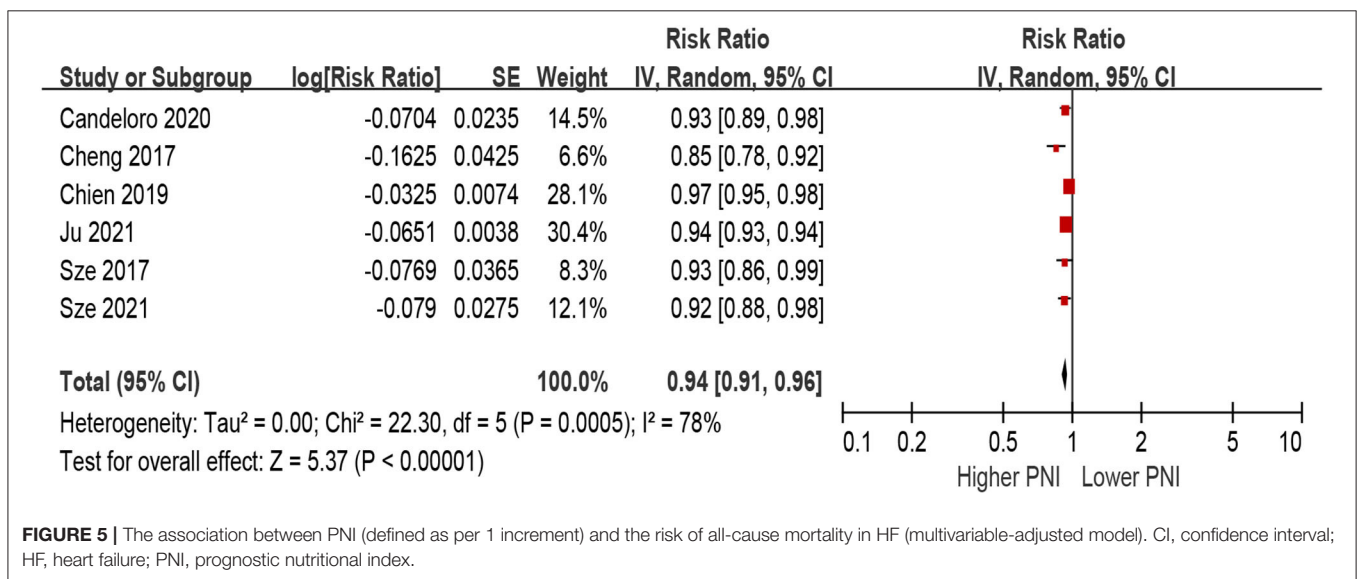
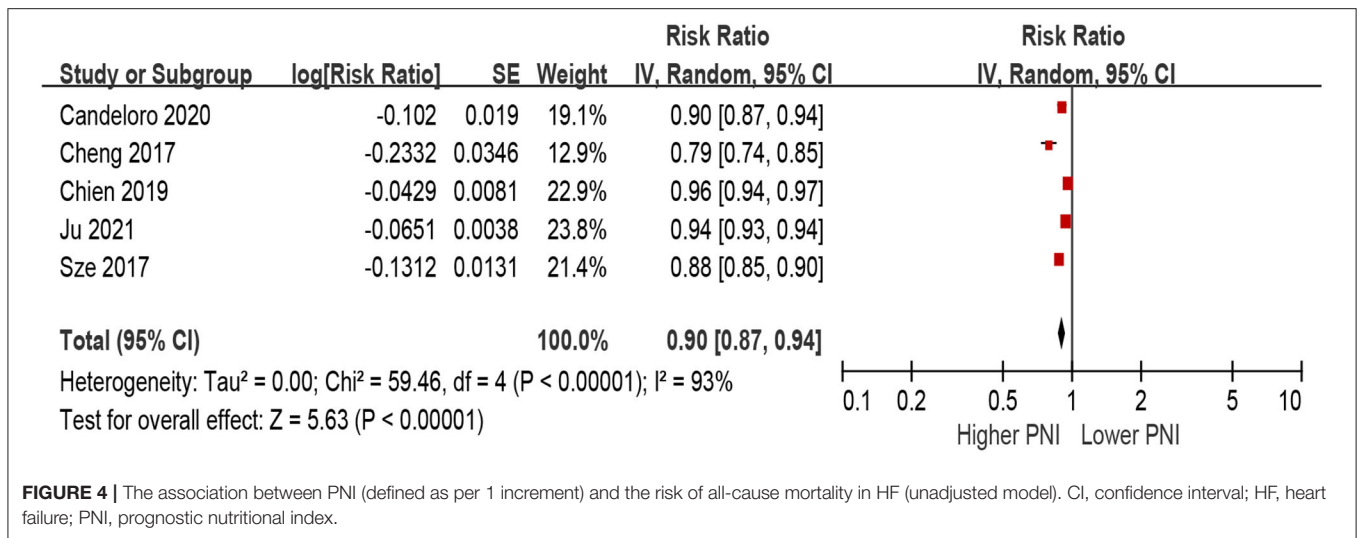


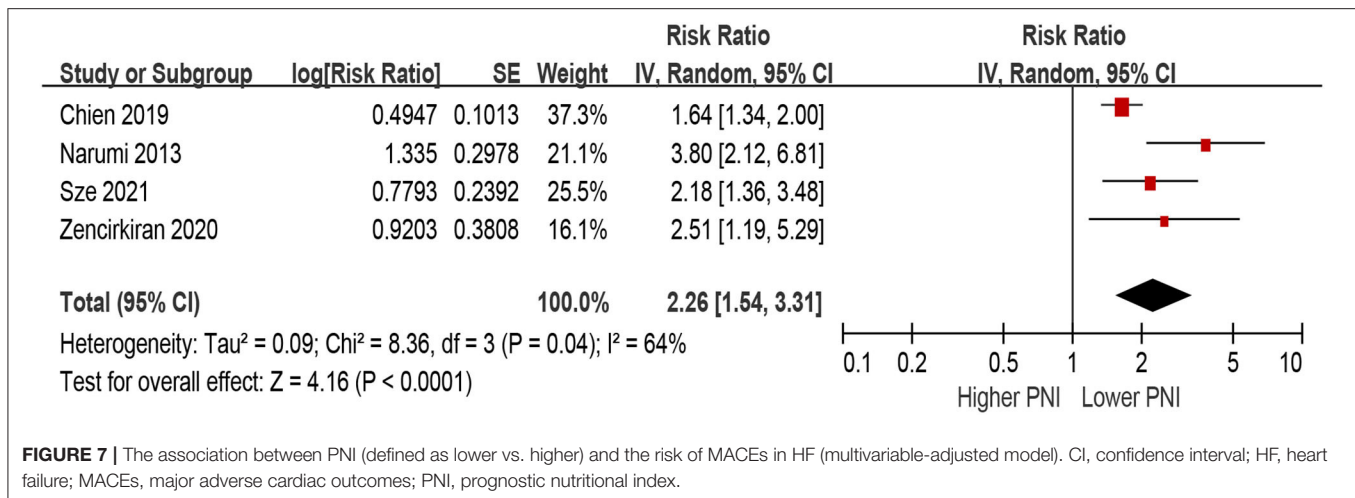
FIGURE 3 | The association between PNI (defined as lower vs. higher) and the risk of all-cause mortality in HF (multivariable-adjusted model). CI, confidence interval; HF, heart failure; PNI, prognostic nutritional index.

Therefore, it is important to evaluate the nutritional status and aid in risk stratification and treatment strategies in the clinical setting. Some multi-dimensional nutritional screening tools, including the Nutritional Risk Screening (NRS-2002), and Mini Nutritional Assessment–Short Form (MNASF) have been developed for evaluating the nutritional risks in patients with HF (33, 34). However, these tools include multiple clinical indexes and dietary factors extracted by questionnaires, which are time-consuming to perform, with limited generalizability in routinely use, and may be confounded by recall bias from the patients.

In contrast, the PNI is a simple metric that can be easily calculated from serum albumin level and lymphocyte

count, which are available in most clinical laboratories. Lower PNI (malnutrition) in patients with HF may be contributed to both reduced albumin and lymphocyte count. The components of the PNI, serum albumin, and lymphocyte count, may indicate independent prognostic information in patients with HF. Reduced serum albumin levels may be influenced by malnutritional status or an indication of renal and liver dysfunction. Low lymphocyte count could indicate immune hypo-responsiveness and increased cortisol levels, which could harm the prognosis of HF. Therefore, a lower PNI is not only a metric of malnutrition but also an indication of pro-inflammation status, which provides objective





information on “malnutrition-inflammation” complex syndrome for determining increased mortality in HF (33, 34). Similar to PNI, some other simple blood-based biomarkers have also been used to assess the nutritional status in HF, such as the controlling nutritional status (CONUT) score (25, 35), and geriatric nutritional risk index (GNRI) (36, 37). However, the CONUT score is calculated from serum albumin, lymphocyte count, and cholesterol, which may be confounded by the broad use of statin in patients with HF. The GNRI requires body weight for calculation, which will be confounded by fluid overload status and dramatic change in HF treatment during hospitalization. Therefore, the PNI may be a more suitable index that can be easily calculated using routine laboratory parameters and offers a practical tool for evaluating the nutritional risk of HF. However, which index is better for predicting the prognosis in HF needed further exploration. Furthermore, the change of PNI during hospitalization would be important to evaluate the association between this metric and the prognosis of HF. Kawata et al. (14) showed that the changes in PNI on admission and at discharge during hospitalization, were associated with 1-year mortality in patients with acute HF. These findings further support the use of PNI to guide the risk stratification in HF.

Some limitations should be noted in the current study. First, the type and definition of HF were different in the included studies, which may contribute to the clinical heterogeneity. Second, the underlying inflammation status was not adjusted in most of the included studies. Therefore, it is difficult to attribute the prognostic effect of PNI to only malnutritional status or a combination of inflammation status. Third, we did not have individual patient data to perform the comprehensive subgroup analysis. Fourth, the cut-point for malnutritional status with PNI was different in the included studies, which would be an important heterogeneity among the studies.

In conclusion, PNI can serve as an easily calculated bedside “malnutrition-inflammation” biomarker in HF. Lower PNI was associated with a worse prognosis in patients with HF. Future

studies are needed to explore whether treatment targeting improving the PNI can provide a positive effect on the prognosis of HF.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

J-DW, J-QL, M-YC, and J-XW: research idea and study design. M-YC, J-XW, M-TL, and X-YJ: data acquisition. J-DW, X-LW, Z-WX, and J-QL: data analysis/interpretation. X-LW and Z-WX: statistical analysis. J-DW and J-QL: supervision and mentorship. All authors contributed important intellectual content during manuscript drafting or revision and accept accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fcvm.2022.918566/full#supplementary-material>

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