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Meta-analysis

Association between non-alcoholic fatty liver disease and risk of incident heart failure: a meta-analysis of observational studies

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Abstract

Background and aims: Recent research has associated non-alcoholic fatty liver disease (NAFLD) with an increased risk of atherosclerotic cardiovascular disease. Previous studies that evaluated the association between NAFLD and risk of heart failure (HF) yielded inconsistent results, however. This meta-analysis aimed to evaluate the association between NAFLD and the risk of HF.

Methods: We searched multiple electronic databases, including PubMed, Google Scholar, Embase and Web of Science for potential studies published from inception until 30 October 2021. Cohort studies reported multivariable-adjusted risks of incident HF in NAFLD patients comparing those without NAFLD were included.

Results: Six cohort studies comprising 10,979,967 participants (women = 55.5%) were included in the study. The median prevalence of NAFLD in these studies was 22.2%. During a median follow-up duration of 7.0 years, 92,915 HF cases were detected. In the unadjusted model, patients with NAFLD had a greater risk of incident HF [random-effect hazard ratio (HR) = 1.47, 95% confidence interval (CI) = 1.25–1.75, I^2 = 99%], compared with those without NAFLD. After multivariable adjustment of confounding risk factors, NAFLD was still linked with a higher risk of HF incidence (random-effect HR = 1.36, 95% CI = 1.16–1.58, I^2 = 98%). The risk of HF was increased not only in patients with progressive NAFLD severity but also in those with simple steatosis. The absolute risk difference of HF in NAFLD patients compared with those without NAFLD was 11.0 (95% CI = 4.9–17.7) per 10,000 person-years after multivariable adjustment.

Conclusion: This meta-analysis suggests that NAFLD may be associated with an increased risk of incident HF. Owing to the high heterogeneity of the published studies, however, further high-quality studies are still needed.

Keywords: cardiometabolic risk factors, cohort study, heart failure, non-alcoholic fatty liver disease, risk

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Introduction

The term non-alcoholic fatty liver disease (NAFLD) encompasses a range of liver conditions, including simple steatosis (non-alcoholic fatty liver, NAFL), non-alcoholic steatohepatitis (NASH) and NASH-related cirrhosis. Epidemiological data showed that NAFLD has become one of the most common chronic liver diseases globally, affecting about 25–45% of the adults in the general population.[1] Furthermore, with increasing epidemics of obesity and type 2 diabetes mellitus, the global prevalence of NAFLD will dramatically increase.[2] Besides liver complications, accumulating data indicate that NAFLD is an important risk factor for atherosclerotic cardiovascular disease (CVD),[3] chronic

kidney disease,[4] and cardiac arrhythmia.[5] Thus, NAFLD had been considered a 'multisystem' disease, requiring multidisciplinary intervention to treat both liver and cardiometabolic diseases.[2]

Similar to NAFLD, heart failure (HF), the end-stage of CVD, is an increasing public health burden, with high morbidity and mortality worldwide.[6] NAFLD often coexists with HF as they have similar pathophysiological characteristics and share multiple risk factors (e.g. obesity, diabetes mellitus and physical inactivity) in common. Furthermore, NAFLD is closely related to adverse cardiac remodelling, cardiac hypertrophy and diastolic dysfunction,[7–9] which may lead to emerging HF over time. The aforementioned cross-sectional features are incapable of establishing the causality between NAFLD and HF, however. Several longitudinal studies that evaluated the relation between NAFLD and future risk of HF produced inconsistent results.[10–15] Better clarification of the relation between NAFLD and HF risk is important to develop public health policy and clinical interventions for the treatment of HF. Therefore, we conducted this meta-analysis of existing longitudinal cohort studies to explore whether NAFLD is associated with the risk of HF.

Methods

Data sources, search strategies and study selection

This meta-analysis was not registered previously. We conducted the study according to the guideline from the MOOSE (Meta-analysis of Observational Studies in Epidemiology) Group.[16] We searched multiple electronic databases, including Embase, Google Scholar, PubMed and Web of Science for potential observational studies up to 30 October 2021, using terms related to 'NAFLD' and 'HF'. The detailed methods for PubMed searches are listed in online Supplementary File 1. Search strategies for other electronic databases were similar, but modified as necessary. We further checked the most updated reviews, meeting abstracts and the reference lists of the included studies to identify other relevant studies.

Observational cohort studies were included for our meta-analysis if (1) the studies involved adult participants (age ⩾18 years), (2) indicators defining NAFLD were evaluated and (3) a multivariable-adjusted risk of future incident HF associated with NAFLD patients was determined compared with those without NAFLD. We excluded the study if (1) they were case–control or cross-sectional studies with no follow-up evaluation, (2) they only defined NAFLD using serum liver enzymes (serum alanine transaminase or gamma-glutamyltransferase levels), (3) they did not adjust for other confounding risk factors for the risk of HF in NAFLD, (4) they were <1-year follow-up duration and (5) they were duplicate data from the same cohort study.

Data extraction and study quality assessment

After conducting the literature search, two investigators (W.L. and M.Q.) screened the retrieved items and read through the relevant studies, independently. Discussions were made with a third investigator (Y.H.) to resolve the discrepancies. Original information such as study design, authors, region, sample size, definition and prevalence of NAFLD, sex, age, outcome events, follow-up duration and adjusted risk factors were recorded in standard forms. If needed, we contacted the authors of the included studies to obtain additional data.

The quality assessment of the included studies was based on the Newcastle–Ottawa Quality Assessment Scale (NOS) for cohort studies, which evaluates the study quality based on the following: selection (four items, up to 4 stars totally), exposure/outcome (three items, up to 3 stars totally) and comparability (one item, up to 2 stars).[17] The included studies were classified as poor (<4 stars), fair (4–6 stars) and good quality (⩾7 stars), respectively, in this meta-analysis.[18,19] We also assessed whether the included studies were adjusted adequately for covariates (at least six of seven confounders including sex, age, blood pressure/hypertension/anti-hypertensive treatment, blood glucose metrics/diabetes mellitus, body mass index/obesity/overweight, serum cholesterol levels/dyslipidemia and smoking).

Statistical analysis

This meta-analysis was executed using RevMan 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). For the main analysis, the relative risk (RR) or hazard ratio (HR) of HF associated with NAFLD adjusted for the maximal number of covariates was extracted, and the log HRs were combined using the inverse variance method.

RRs were regarded as approximate to HRs and directly used in the meta-analysis.[20,21] We also compared the pooled HRs adjusted for the maximal number of covariates with those unadjusted to explore the confounder strength on the risk of HF. Heterogeneity among the studies was evaluated by the I^2 statistics. If significant heterogeneity was observed ($I^2 \geqslant 50\%$ or $p \geqslant 0.1$), meta-analysis was performed using the random-effects model. Otherwise, a fixed-effects model was used. We interchanged the random-effects model and fixed-effects model in the meta-analysis to conduct the sensitivity analyses. We also recalculated the pooled HRs by removing one study each time. The potential publication bias was evaluated by inspecting the funnel plots.

Subgroup analyses were performed based on ethnicity (non-Asian *versus* Asian), enrolment population (general population *versus* special clinical condition), study design (retrospective *versus* prospective), age (average $\geqslant$60 years *versus* $<$60 years), the definition of NAFLD [computed tomography (CT) *versus* fatty liver index (FLI) *versus* biopsy], follow-up duration (10 years *versus* $\geqslant <$ 10 years), type of HF [heart failure with reduced ejection fraction (HFrEF) *versus* heart failure with preserved ejection fraction (HFpEF)] and adjustment of potential confounders (adequate *versus* inadequate). We also performed subgroup analyses according to the severity of NAFLD (different FLI levels and liver histology).

The absolute risk difference for the incident HF associated with NAFLD was calculated by multiplying the (pooled HR-1) by the assumed comparator risk.[22] The median absolute risk of incident HF in the control group across the included studies was defined as the assumed comparator risk. The absolute risk difference in this study was calculated in events per 10,000 person-years. p-value < 0.05 was considered with statistical significance, and all p-values were two-tailed.

Results

Studies included and main characteristics

In the 1024 article items returned from the initial search, 55 papers were qualified for a full-article review after screening the titles and abstracts. Finally, 6 cohort studies comprising 10,979,967 participants (women = 55.5%) were included in the meta-analysis (Figure 1).[10–15] Key characteristics of the six studies included in the meta-analysis are presented in Table 1. There were three prospective cohort studies and three retrospective cohort studies, respectively. Four of them were derived from the general population, one was from Medicare patients and one included patients with diabetes. The FLI was used to define NAFLD in three studies, one study defined NAFLD with CT, one study detected NAFLD based on database records and one study documented NAFLD by biopsy. In these studies, the prevalence of NAFLD ranged from 3.2 to 35.2% (median = 22.2%), and 92,915 HF cases were detected during a median follow-up duration of 7.0 years. The exclusionary criteria used to accurately categorize a patient as having NAFLD (i.e. alcohol use, secondary causes of steatosis and other chronic liver diseases) in these cohorts were presented in Supplementary File 2.

According to the NOS assessment, two studies were graded as fair, and four studies were with good quality (Supplementary File 3). The adjusted confounders in the maximal adjusted statistical models are presented in Supplementary File 4, and five studies were defined as with adequate adjustment.

NAFLD and risk of incident HF

In the unadjusted model, compared with those without NAFLD, the risk of incident HF was increased significantly in NAFLD patients [HR = 1.47, 95% confidence interval (CI) = 1.25–1.75; Figure 2]. Significant heterogeneity was observed among the included studies ($I^2 = 99\%$, $p < 0.001$), however. In the multivariable-adjusted model, NAFLD was still associated with a significant increase in HF risk (HR = 1.36, 95% CI = 1.16–1.58; Figure 3). Owing to the limited number of studies included ($n = 6$), we cannot formally exclude the presence of any publication bias by inspection of the funnel plot (Supplementary File 5). The sensitivity analyses documented further evidence for the association between NAFLD and risk of incident HF, which did not change when using statistical models (interchanging the fixed-effects model and random-effects model) or recalculating the HRs with removing one study at a time (Supplementary File 6).

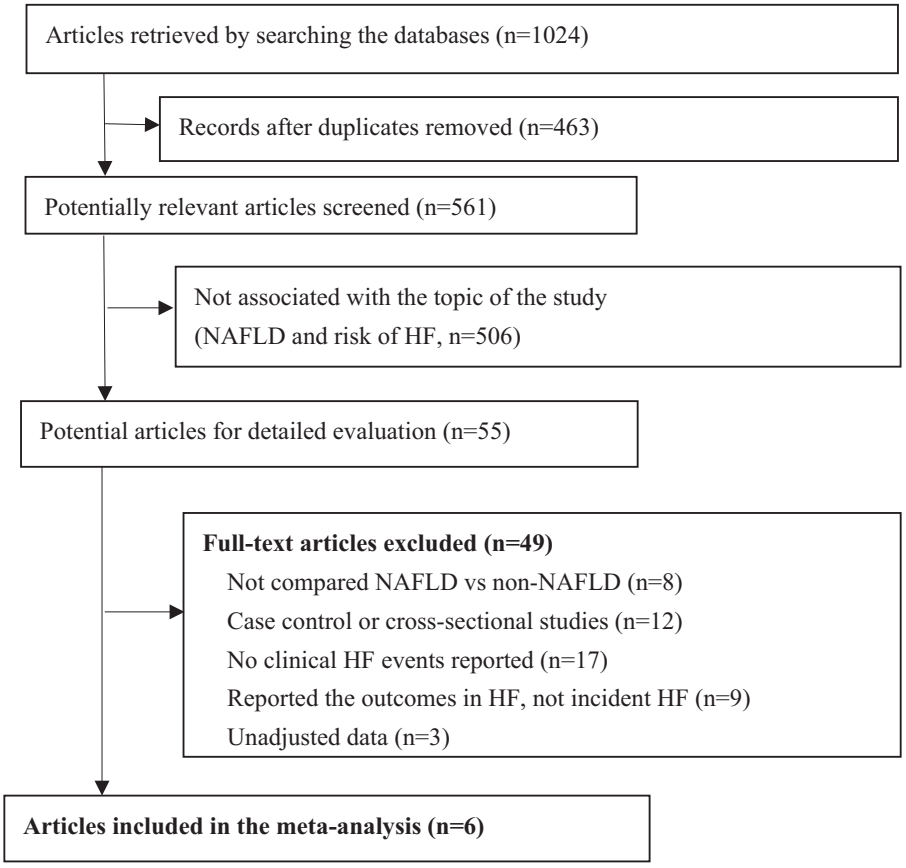

Figure 1. Flow of papers through review.
HF, heart failure; NAFLD, non-alcoholic fatty liver disease.

The absolute risks of HF in NAFLD (median = 58.7 per 10,000 person-years) and non-NAFLD (median = 30.6 per 10,000 person-years) across the included studies were shown in online Supplementary File 7. The absolute risk difference of incident HF between NAFLD and non-NAFLD was 11.0 (95% CI = 4.9–17.7) per 10,000 person-years after multivariable adjustment.

Subgroup analyses

The pooled results of all subgroup analyses are shown in Table 2. There was no significant heterogeneity observed among the subgroup analyses according to participants' average age, ethnicity and adjustment of confounders. One study with CT evaluated the association between NAFLD and risk of HF in type 2 diabetic patients, and found no association between NAFLD and risk of HF in patients with type 2 diabetes. There was significant heterogeneity compared with the studies that included the general population, however. Furthermore, the RR of HF associated with NAFLD was higher in prospective studies and those with a follow-up duration of more than 10 years. The risk of HF by ejection fraction was separately reported in only one study, which showed that patients with NAFLD had a higher risk of HFpEF (HR = 1.24, 95% CI = 1.14–1.34), but had no association with HFrEF (HR = 1.09, 95% CI = 0.98–1.21).[15] According to the level of FLI, the HF risk was already increased in those with mild NAFLD (FLI <60, HR = 1.21, 95% CI = 1.03–1.42), as well as severe NAFLD (FLI ⩾60, HR = 1.54, 95% CI = 1.09–2.18) (p for subgroups' heterogeneity = 0.21). Furthermore, based on biopsy, patients with simple steatosis and NASH without fibrosis carried about a 60% higher risk of HF than those without NAFLD, and the risk of HF was more significantly increased in those with non-cirrhotic fibrosis (HR = 2.04, 95% CI = 1.66–2.51) and cirrhosis

(HR = 2.84, 95% CI = 2.08–3.85) (p for heterogeneity = 0.003).

Discussion

In this large sample meta-analysis with approximate 11.0 million participants, we found that after adjusting for other cardiometabolic risk factors, NAFLD was associated with a 36% increased RR of future HF incidence compared with the people without liver diseases. The absolute risk difference of incident HF in NAFLD was 11.0 per 10,000 person-years. The increased risk was already increased in mild NAFLD (defined as simple steatosis by biopsy or mild elevated FLI).

Another meta-analysis published recently also reported that NAFLD was associated with an increased HF risk [odds ratio (OR) = 1.61, 95% CI = 1.43–1.84].[23] In four included studies in that meta-analysis, however, one was cross-sectional studies,[24] one was with data of subclinical HF[25] and two extract HF data unadjusted for other risk factors for analysis.[12,26] Salah *et al.* also included a total of 5 studies comprising 1,433,066 subjects for meta-analysis, and their results showed that NAFLD was associated with increased risk of HF (OR = 1.60, 95% CI = 1.24–2.05). Both these previous reports proposed that there was a link between NAFLD and HF.[27] In this study, we only included cohort studies with multivariable-adjusted data for analysis, which mitigated the influence of other confounders on the association between NAFLD and HF risk. We showed that the association between NAFLD and HF (adjusted HR = 1.36) was only mildly decreased compared with unadjusted data (unadjusted HR = 1.47). These data supported the notion that NAFLD was a risk factor for HF, independent of other cardiometabolic risk factors. Moreover, most of the included studies in the current meta-analysis were published recently and not included in the prior meta-analysis, which provided the most updated evidence for analysis.

Besides comorbidity of cardiometabolic risk factors, several mechanisms may contribute to the relation between NAFLD and HF risk. First, insulin resistance, impaired glucose and lipid metabolism were the core pathophysiological feature in NAFLD, which will finally result in a decrease of myocardial energy metabolism and caused cardiac dysfunction.[2,28,29] Second,

Table 1. Characteristics of included studies in the meta-analysis.

Study	Country/ region	Study design	Cohort characteristics	NAFLD definition and prevalence (%)	Sample size (% women)	Mean age (years)	Follow-up (years)	HF diagnosed methods	Incident HF (*N*)	Baseline CVD excluded
Dunn *et al.*[14]	USA	Retrospective cohort study	Type 2 diabetes	Computed tomography (9.9%)	2343 (54.4)	65.8	5.0	ICD-9	772	No
Roh *et al.*[13]	Korea	Prospective cohort study	General population	Fatty liver index ⩾30 (26.1%)	308,578 (50.7)	41.4	5.4	ICD-10	2532	Yes
Park *et al.*[10]	Korea	Retrospective cohort study	General population	Fatty liver index ⩾20 (35.2%)	778,739 (60.5)	52.4	8.5	ICD-10	28,524	Yes
Simon *et al.*[11]	Sweden	Prospective cohort study	General population	Biopsy-confirmed (18.3%)	56,959 (45.9)	51.4	13.6	ICD-10	4988	Yes
Lee *et al.*[12]	Korea	Prospective cohort study	General population	Fatty liver index ⩾30 (28.0%)	8,962,813 (55.1)	50.5	10.1	ICD-10	12,432	Yes
Fudim *et al.*[15]	USA	Retrospective cohort study	Medicare patients	Database record (3.2%)	870,535 (56.9)	74.5	1.2	ICD-9/ICD-10	43,667	No

CVD, cardiovascular disease; HF, heart failure; ICD, the International Statistical Classification of Diseases and Related Health Problems; NAFLD, non-alcoholic fatty liver disease.

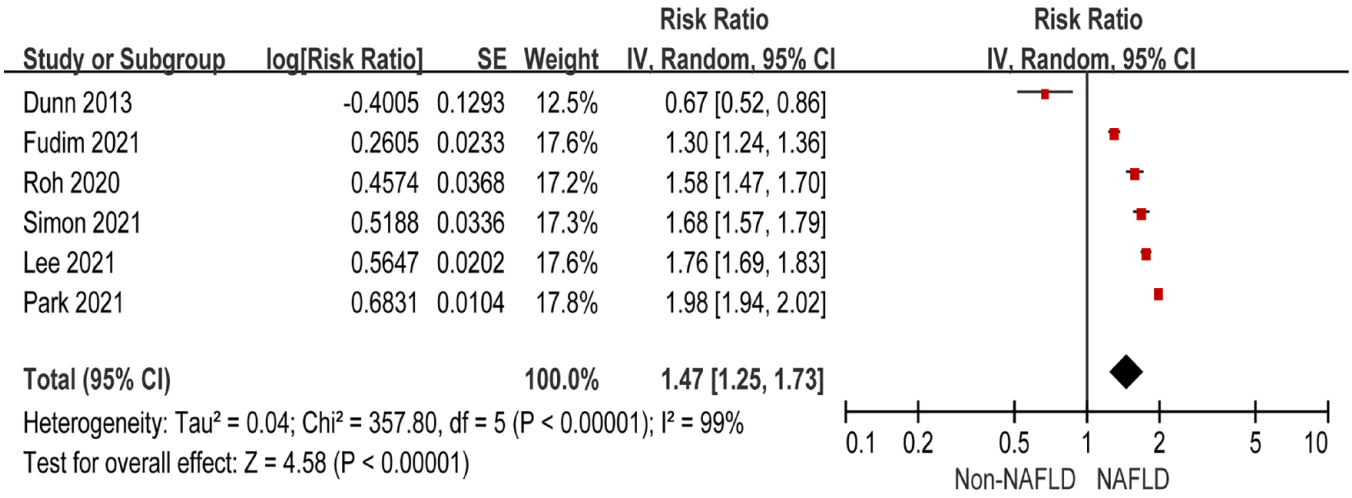

Figure 2. Forest plot of crude risk of HF associated with NAFLD.
CIs, confidence intervals; HF, heart failure; NAFLD, non-alcoholic fatty liver disease.

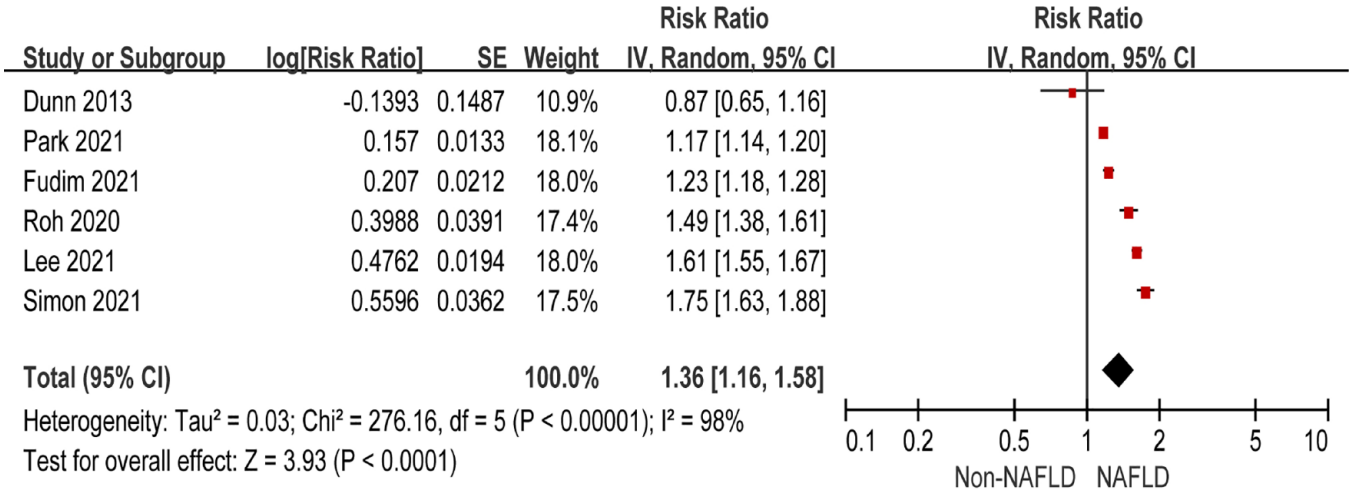

Figure 3. Forest plot for multivariable-adjusted risk of HF associated with NAFLD.
CIs, confidence intervals; HF, heart failure; NAFLD, non-alcoholic fatty liver disease.

NAFLD is a status of a low-grade inflammatory disorder;[30] higher levels of pro-inflammatory cytokines and reactive oxygen species, including interleukin-6, interleukin-1β and tumour necrosis factor-α, were observed in NAFLD.[28,31] The activation of chronic inflammation could contribute to associated pathologies of HF. Third, increased activity of the renin–angiotensin–aldosterone system and sympathetic nervous system, expression change of adipokines and gut microbiota–derived metabolite may also play a link between the development of HF in patients with NAFLD.[32–35]

Considering the high prevalence and dramatic increase incidence of NAFLD, as well as the high morbidity and mortality of HF, our study has several important clinical implications. First, our results showed an increased risk of HF even in patients with mild NAFLD. Further risk stratification combined with echocardiography or serum

Table 2. Subgroup analyses of the association between NAFLD and risk of HF.

Subgroup	Number of studies	RR (95% CI)	*p*[a]
Ethnicity			0.59
Asians	3	1.41 (1.11–1.78)	
Non-Asians	3	1.27 (0.94–1.72)	
Study design			<0.001
Prospective cohort	3	1.61 (1.50–1.74)	
Retrospective cohort	3	1.18 (1.11–1.26)	
Participant's average age			0.10
<60 years	4	1.49 (1.21–1.83)	
⩾60 years	2	1.07 (0.76–1.49)	
Exclusion of baseline CVD			0.10
Yes	4	1.49 (1.21–1.83)	
No	2	1.07 (0.76–1.49)	
Methods for defining NAFLD			<0.001
Biopsy-confirmed	1	1.75 (1.63–1.88)	
Fatty liver index	3	1.41 (1.11–1.78)	
Computed tomography	1	0.87 (0.65–1.16)	
Databases record	1	1.23 (1.18–1.28)	
Enrolment			0.01
General population	4	1.49 (1.21–1.83)	
Diabetes	1	0.87 (0.65–1.16)	
Medicare patients	1	1.23 (1.18–1.28)	
Follow-up duration			<0.001
<10 years	4	1.24 (1.11–1.37)	
⩾10 years	2	1.67 (1.54–1.81)	
Adjustment of confounders			0.66
Adequate[b]	4	1.39 (1.19–1.62)	
Not adequate	2	1.20 (0.66–2.20)	
Type of HF			0.06
HFrEF	1	1.09 (0.98–1.21)	
HFpEF	1	1.24 (1.14–1.34)	

(Continued)

Table 2. (Continued)

Subgroup	Number of studies	RR (95% CI)	*p*[a]
Severity of NAFLD (by FLI)			0.21
Mild (FLI <60)	2	1.21 (1.03–1.42)	
Severe (FLI ⩾60)	2	1.54 (1.09–2.18)	
Severity of NAFLD (by biopsy)			0.003
Simple steatosis	1	1.65 (1.51–1.80)	
NASH without fibrosis	1	1.60 (1.28–2.00)	
Non-cirrhotic fibrosis	1	2.04 (1.66–2.51)	
Cirrhosis	1	2.83 (2.08–3.85)	

CI, confidence interval; CVD, cardiovascular disease; FLI, fatty liver index; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; RR, relative risk.
[a]For heterogeneity among subgroups.
[b]Adequate adjustment denoted adjustment of at least six of seven confounders including sex, age, hypertension or blood pressure or anti-hypertensive treatment, body mass index or other measure of overweight/obesity, cholesterol, diabetes or blood glucose metrics and smoking.

biomarkers for screening early stages of HF would be important to develop patient-centred, precision preventative and treatment strategies.[36] It should be noted that N-terminal prohormone of brain natriuretic peptide (NT-proBNP), a wildly used biomarker for predicting and diagnosing HF, was lower expressed in patients with NAFLD.[37,38] None of these studies included patients with over HF, however. Therefore, whether in patients with HF and NAFLD, the expression of NT-proBNP levels was different needed further exploration. Second, lifestyle (diet and exercise) modification to achieve the proper weight is the core stone in NAFLD treatment;[39] however, it is difficult to achieve and sustain in long-term duration.[40] Therefore, pharmacological management beneficial to both NAFLD and HF would play a significant role in the field. In recent years, the novel anti-diabetic drugs, glucagon-like peptide 1 receptor agonists and sodium–glucose cotransporter-2 inhibitors have shown promising results in CVD and NAFLD. Further studies are urgently needed to evaluate whether the anti-diabetic drugs above can prevent the risk of HF in NAFLD.[41,42]

Several limitations should be noted in the current meta-analysis. First, our subgroup analyses found that the RR of HFpEF, but not HFrEF, was increased in NAFLD patients. Only one study, however, provided data for the HF subtypes (HFpEF and HFrEF) analysis, and the heterogeneity among subgroups was not statistically significant. Therefore, whether NAFLD was an independent risk factor for HFrEF needs further studies. Second, the definition methods of NAFLD in the included studies were different, and the NAFLD prevalence was with a wild range in these studies (3–35%). Furthermore, significant heterogeneity existed among the included studies. The results showed that the HF risk was higher in NAFLD evaluated by FLI and biopsy, but not observed in a study with CT. The underlying reason for the inconsistency was unclear and needed further exploration. Third, there were prospective and retrospective cohort studies in the meta-analysis, which may contribute to the significant heterogeneity among the studies. Owing to the high heterogeneity of the published studies, the results should be still interpreted with caution, and further high-quality studies are needed. High-quality prospective studies with adequately long follow-up durations and echocardiographic data are still needed to better examine the association between NAFLD and risk of incident HF. Forth, only one study evaluated the association between NAFLD and risk of HF in type 2 diabetic patients, and found no significant association. There was significant heterogeneity compared with studies that

included the general population, however. Therefore, further studies are needed to explore the risk of HF in diabetic patients with NAFLD. Finally, only one study reported the severity of NAFLD by biopsy and reported data for cirrhosis and the association with HF. This is an important limitation as cirrhosis can raise the risk of certain types of HF.

Conclusion

The results of this meta-analysis suggest that NAFLD may be associated with an increased risk of incident HF, especially for HFpEF. The risk of HF was increased even in patients with simple steatosis, and more significant with the progression of the NAFLD severity. Because of the high heterogeneity of the published studies, however, further high-quality studies are still needed.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Wensheng Li: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Weixing Wen: Data curation; Formal analysis; Investigation; Methodology; Software; Validation.

Dongxiao Xie: Supervision; Visualization; Writing – original draft; Writing – review & editing.

Min Qiu: Data curation; Formal analysis; Software.

Xiaoyan Cai: Conceptualization; Project administration; Resources.

Sulin Zheng: Conceptualization; Project administration; Resources.

Yuli Huang: Conceptualization; Funding acquisition; Supervision; Validation; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Availability of data and material

The data sets and/or analyses during this study are available from the corresponding author on reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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