Systematic Review/Meta-Analysis

Association of metabolic traits with occurrence of nonalcoholic fatty liver disease-related hepatocellular carcinoma: A systematic review and meta-analysis of longitudinal cohort studies

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Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) has become one of the leading etiologies of hepatocellular carcinoma (HCC), but risk factors for NAFLD-related HCC occurrence have not been defined. NAFLD is often complicated by metabolic abnormalities, and there is a bidirectional association of metabolic abnormalities with NAFLD progression. This study aimed to systematically evaluate the relationship between metabolic traits and HCC occurrence in patients with NAFLD.

Method: This study reviewed eight eligible studies that included 297,956 participants, to determine the relationship between metabolic traits and the occurrence of HCC in patients with NAFLD.

Results: Presence of diabetes mellitus (DM) was associated with increased risk of HCC (HR: 2.65, 95%CI: 2.02 ~ 3.49, $P_{heterogeneity}$ = 0.589, I^2 = 0.0%). Stratified analysis revealed that this risk was higher in NAFLD patients with advanced fibrosis/cirrhosis (HR: 4.55, 95%CI: 2.34 ~ 8.87, $P_{heterogeneity}$ = 0.870, I^2 = 0.0%). Nonetheless even in patients without cirrhosis, DM remained a high risk factor for HCC incidence (HR: 1.80, 95%CI: 1.05 ~ 3.06, $P_{heterogeneity}$ = 0.291, I^2 = 10.4%). Overweight/obesity had a slight correlation with increased risk of HCC occurrence in NAFLD patients (HR: 1.31, 95%CI: 1.00 ~ 1.71, $P_{heterogeneity}$ = 0.888, I^2 = 0.0%), while presence of hypertension and dyslipidemia had no correlation.

Conclusion: DM and overweight/obesity are high risk factors for NAFLD-related HCC. In particular, DM increases 4-fold the risk of HCC incidence in NAFLD patients with advanced fibrosis/cirrhosis. There is a need to strengthen surveillance for HCC in NAFLD patients with DM, especially in those with advanced fibrosis/cirrhosis.

Keywords: Diabetes mellitus, dyslipidemia, hepatocellular carcinoma, hypertension, nonalcoholic fatty liver disease, obesity

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, the fifth most common cancer and the second leading cause of cancer-related mortality worldwide.[1,2] Chronic liver diseases such as hepatitis B virus (HBV), hepatitis C virus (HCV), and alcoholic liver disease are the most common causes of HCC. Nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases with a spectrum that ranges from simple steatosis to nonalcoholic steatohepatitis, with or without fibrosis.[3] Since viral hepatitis is preventable and treatable, NAFLD has gradually become a leading etiology of HCC.[4]

Clinical guidelines recommend cirrhotic patients be monitored every six months with abdominal ultrasonography, for occurrence of HCC.[5] Nonetheless, abdominal ultrasonography is limited by its low sensitivity and difficult definition of high-risk patients, therefore, most of those with NAFLD-related HCC are diagnosed at an advanced stage of disease (Barcelona Clinic Liver Cancer stage C or D), with a median survival time less than 11 months.[6] It is critical to identify risk factors for HCC progression in NAFLD. NAFLD is often complicated by metabolic abnormalities such as type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS). Metabolic abnormalities aggravate liver histological lesions in NAFLD, and in turn NAFLD presence increases the incidence of metabolic disorders and is correlated with increased risk of fatal cardiovascular disease (CVD).[7] Experiments have confirmed that NAFLD in the presence of metabolic stress can progress to HCC.[8] Lipotoxicity, chronic inflammation and gut dysbiosis are involved in the process of hepatocarcinogenesis in NAFLD.[9,10] Based on the above, metabolic abnormalities may be high risk factors for the occurrence of NAFLD-related HCC. Specific metabolic traits that are related to the occurrence of NAFLD-related HCC require systematic evaluation.

According to the results of previous clinical studies, the relationship between metabolic abnormalities and the occurrence of NAFLD-HCC remains controversial. Studies by Bertot *et al.*[11-15] indicated that DM was an independent risk factor for HCC incidence in NAFLD patients, but Grimaudo *et al.*[16-18] reported conflicting results. We conducted this systematic review and meta-analysis to assess the correlation of metabolic traits, including DM, overweight/obesity, hypertension and dyslipidemia, with NAFLD-related HCC incidence.

METHODS

Search strategy

Two authors (Jin Chen and Shu Song) independently searched for published articles in PubMed, Embase, and Cochrane databases up to and including April 2021, with no start date limit, using the following search terms: “diabetes”, “dyslipidemia”, “hyperlipidemia”, “hypertension”, “overweight”, “obesity” and "nonalcoholic fatty liver disease". Searches were limited to English publications and clinical studies. When population or results were investigated repeatedly in two or more studies, only the most recent and complete study was included. This study was conducted according to the PRISMA guidelines.[19]

Eligibility criteria and quality assessment

Studies were considered eligible for inclusion if they met the following criteria: 1) population-based longitudinal cohort study, 2) subjects were NAFLD patients, 3) exposure factors were defined at baseline: impaired fasting glucose regulation (IFG)/T2DM/DM (unspecified), overweight/obesity, dyslipidemia/hyperlipidemia/hypercholesterolemia/hyperlipoproteinemia, 4) definitive outcome during follow-up i.e., number of HCC cases, and 5) hazard ratios (HRs) calculated by Cox or competing risk regression. Studies were excluded if they were: 1) an animal study, 2) cross-sectional studies, 3) a systematic review or meta-analyses, 4) conference abstract, meeting proceedings, and letters to the editor, 5) had incomplete data, or 6) any research that was not related to the subject of this analysis. The quality of the included studies was assessed by the Newcastle-Ottawa scale[20] with the score ranging from 0 to 9, and comprised of a description of the participants selection (0-4), comparability of the groups (0-2), and ascertainment of outcomes (0-3).

Data extraction

The following data were extracted independently from original studies by two investigators (Jin Chen and Shu Song): the first author’s name, publication year, study country, study design, sample size, follow-up, outcome during follow-up, exposure factors, HRs for assessing the relationship between exposure factors and the outcome. In this study, we unified IFG/T2DM, T2DM and DM (unspecified) as DM, and dyslipidemia, hyperlipidemia, hypercholesterolemia, hyperlipoproteinemia as dyslipidemia. If there was disagreement on extracted data, a third investigator was consulted to resolve the inconsistency.

Statistical analysis

This meta-analysis was performed using STATA 14.0 software (College Station, TX, USA). The association

between metabolic traits and NAFLD-related HCC incidence was estimated by using hazard ratios (HRs), with 95% confidence interval (95% CI). Pooled HRs were calculated through a random effects model (inverse-variance model), and a *P* value < 0.05 was considered statistically significant. Heterogeneity was assessed by the Q test and Higginss inconsistency index (I^2), and a *P* value < 0.05 or an I^2 value exceeding 50% indicated significant heterogeneity. Sensitivity analyses were performed by removing studies one by one from the meta-analysis to assess the stability of results. Begg's and Egger's tests were used to evaluate publication bias, and a symmetrical funnel plot and *P* value > 0.05 indicated that publication bias in this meta-analysis was not significant.

RESULTS

Eight longitudinal cohort studies,[11-18] containing a total of 297,956 NAFLD patients with or without metabolic traits, were included in this meta-analysis [Figure 1]. All investigated the association between DM and HCC incidence, four evaluated the association of overweight/obesity with HCC incidence, four estimated the association between hypertension and HCC occurrence, and five studied the association between dyslipidemia and HCC incidence in NAFLD patients. The mean/median follow-up ranged from 46 months to 9.3 years, and patient numbers for HCC occurrence during follow-up ranged from 7 to 253. The included studies were all high-quality longitudinal cohort studies and no low-quality studies were identified for inclusion [Tables 1 and 2].

The likelihood was that HCC incidence in NAFLD patients with DM was significantly higher than

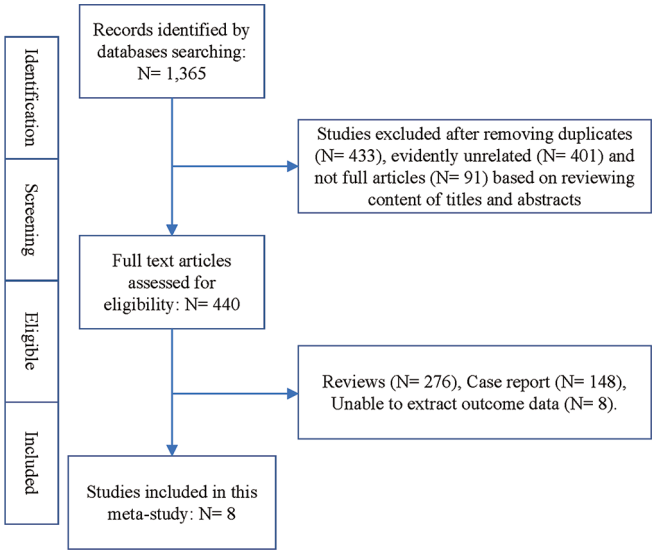

Figure 1: Flow chart of this study design

that in patients without DM, with a pooled HR of 2.65 (95%CI: 2.02 ~ 3.49). The statistical heterogeneity was insignificant ($P_{heterogeneity}$ = 0.589), with an I^2 of 0.0% [Figure 2a]. Moreover, stratified analysis based on NAFLD severity revealed that DM presence was associated with high incidence of HCC, regardless of the presence of cirrhosis: pooled HR in patients without cirrhosis was 1.80 (95%CI: 1.05 ~ 3.06, $P_{heterogeneity}$ = 0.291, I^2 = 10.4%) and pooled HR in patients with advanced fibrosis/cirrhosis was 4.55 (95%CI: 2.34, 8.87, $P_{heterogeneity}$ = 0.870, I^2 = 0.0%) [Figure 2c].

The relationship between presence of overweight/obesity and hypertension, and NAFLD-related HCC incidence is shown in Figure 3. Overweight/obesity NAFLD patients were at higher risk of developing HCC than those without overweight/obesity, with a pooled HR of 1.31 (95%CI: 1.00 ~ 1.71, $P_{heterogeneity}$ = 0.888, I^2 = 0.0%) [Figure 3a]. Nonetheless our results showed that hypertension presence was not associated with the risk of NAFLD-related HCC incidence, with a pooled HR of 1.08 (95%CI: 0.71 ~ 1.65, $P_{heterogeneity}$ = 0.406, I^2 = 0.0%) [Figure 3c].

We also evaluated the relationship between presence of dyslipidemia and NAFLD-related HCC. As shown in Figure 4a, dyslipidemia in NAFLD patients had no correlation with HCC development: pooled HR was 0.80 (95%CI: 0.45 ~ 1.40, $P_{heterogeneity}$ = 0.072, I^2 = 53.5%). Since there was a high heterogeneity in the results, we deleted the study with the largest heterogeneity but the result (HR: 0.98, 95%CI 0.62-1.55, $P_{heterogeneity}$ = 0.224, I^2 = 31.4%) was consistent with the previous one [Figure 4c]. Furthermore, we conducted sensitivity analysis by eliminating included studies one by one, and the result was again consistent with the previous result [Figure 4d].

Finally, we investigated publication bias in these results. As shown in Figures 2b, 2d, 3b, 3d and 4b, funnel plots of all pooled HRs were morphologically symmetrical and there was no significant difference in any results on Begg and Egger tests.

DISCUSSION

In recent years, the increasing incidence of NAFLD and absence of treatment approaches have led to a gradual increase in patients with NAFLD-related HCC.[21] Identification of the population of patients with NAFLD at high risk of developing HCC is vital. Nonetheless known risk factors for HCC are not completely applicable in such patients.[6] Metabolic abnormalities are not only common complications of NAFLD, but also positively correlated

Table 1 Characteristics of included studies and quality assessment

Authors & Years	Country	Study Design	Sample Size (*n*)	NAFLD definition	Advanced fibrosis/ cirrhosis definition	Follow-up	HCC presence (*n*)	Metabolic traits	Research quality[a]
Bertot, 2018	Australia	Prospective longitudinal cohort study	NAFLD: 284	Liver biopsy showing >5% steatosis or fatty infiltration confirmed by imaging and excluding other types of liver diseases	Advanced fibrosis: fibrosis stage 3-4 confirmed by liver biopsy; Cirrhosis: fibrosis stage 4 by liver biopsy	51 months (median)	28	T2DM	8
Kanwal, 2020	USA	Retrospective longitudinal cohort study	NAFLD: 271,906; NAFLD without cirrhosis: 271,906	Elevated ALT values appearing more than twice, with more than 6 months apart, and excluding other types of liver diseases	Cirrhosis: ≥2 outpatient or ≥1 inpatient ICD-9 code	9.3 years (mean)	253 (NAFLD); 64 (NAFLD without cirrhosis)	T2DM; Obesity (BMI >30 kg/ m^2); Dyslipidemia; Hypertension	9
Yang, 2020	USA	Prospective longitudinal cohort study	NAFLD with cirrhosis: 354	Clinical, radiologic or histologic evidence of fatty liver disease or cryptogenic liver disease with metabolic syndrome in the absence of other causes	Cirrhosis: liver histology, features of portal hypertension or radiographical evidence (nodular contour of the liver or increased liver stiffness >5 kPa measured by MR elastography)	46-47 months (median).	30	DM (unspecified); Hyperlipidemia; Hypertension	7
Grimaudo, 2020	Italy	Prospective longitudinal cohort study	NAFLD: 471	The presence of ultrasonography-assessed steatosis plus at least one criterion of the metabolic syndrome and excluding other types of liver diseases	Cirrhosis: liver histology or liver stiffness measurement >11.5 KPa for M probe or >11 KPa for XL probe	64.6 months (median)	13	IFG/T2DM; Obesity (BMI ≥30 kg/m^2)	9
Lee, 2017	China Taiwan	Retrospective longitudinal cohort study	NAFLD without cirrhosis: 18,080	ICD-9 code: 571.8 and excluding other types of liver diseases based on ICD-9 code	Not included	6.32 years (median)	41	T2DM; Hypercholesterolemia; Hypertension	8
Ito, 2020	Japan	Prospective longitudinal cohort study	NAFLD: 179	Fatty changes in the liver observed by imaging and excluding other types of liver diseases	Cirrhosis: fibrosis stage 4 confirmed by liver biopsy	7.9 years (median)	7	DM (unspecified); Overweight (BMI ≥25 kg/m^2); Dyslipidemia; Hypertension	7
Kawamura, 2012	Japan	Retrospective longitudinal cohort study	NAFLD: 6,508	Ultrasonography finding of bright liver with stronger echoes in the hepatic parenchyma than in the renal or spleen parenchyma and excluding other types of liver diseases	Cirrhosis: fibrosis stage 4 confirmed by liver biopsy	2,051 days (median)	16	T2DM; Overweight (BMI ≥25 kg/m^2); LDL cholesterol ≥140mg/ dl	8
Vilar-Gomez, 2018	Europe, Asia, Australia and USA	Prospective longitudinal cohort study	NAFLD with advanced fibrosis (F3/F4): 458	Liver biopsy showing >5% steatosis and excluding other types of liver diseases	Advanced fibrosis: fibrosis stage 3-4 confirmed by liver biopsy; Cirrhosis: fibrosis stage 4 confirmed by liver biopsy	5.5 years (mean)	41	T2DM	8

Note: a: Research quality was assessed by Newcastle-Ottawa scale and the score ranged from 0 to 9 points. USA: United States of America, NAFLD: Nonalcoholic fatty liver disease, HCC: Hepatocellular carcinoma, T2DM: Type 2 diabetes mellitus, BMI: Body mass index, LDL: Low density lipoprotein

Table 2: Association between metabolic traits and NAFLD-related HCC occurrence in included studies

Authors & Years	HRs calculation	Outcome	Exposure factors				Adjusted factors
			DM	Over weight or obesity	Dyslipidemia	Hypertension	
Bertot, 2018	Cox regression	HCC	In all NAFLD patients: T2DM 2.9 95% CI (1.2-7.3)	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Kanwal, 2020	Cox regression	HCC	In all NAFLD patients: T2DM 2.77 95% CI (2.03-3.77); In NAFLD patients without cirrhosis: T2DM 2.15 95% CI (1.20-3.85),	In all NAFLD patients: Obesity 1.31 95% CI (0.98-1.74); In NAFLD patients without cirrhosis: Obesity 1.19 95% CI (0.69-2.07)	In all NAFLD patients: Dyslipidemia 1.31 95% CI (0.84-2.04); In NAFLD patients without cirrhosis: Dyslipidemia 1.73 95% CI (0.72-4.12)	In all NAFLD patients: Hypertension 1.25 95% CI (0.65-2.42); In NAFLD patients without cirrhosis: Hypertension 0.78 95% CI (0.27-2.27)	Age, Gender, Race, T2DM, Obesity (BMI >30 kg/m^2), Dyslipidemia, Hypertension
Yang, 2020	Cox regression	HCC	In NAFLD patients cirrhosis: DM 4.18 95% CI (1.23-14.2)	Not mentioned	In NAFLD patients cirrhosis: Hyperlipidemia 0.98 95% CI (0.43-2.20)	In NAFLD patients cirrhosis: Hypertension 0.67 95% CI (0.30-1.46)	Only the association between DM and HCC was adjusted by age and albumin.
Grimaudo, 2020	Cox regression	HCC	In all NAFLD patients: IFG/T2DM 2.9 95% CI (1.2-7.3)	In all NAFLD patients: Obesity 0.87 95% CI (0.21-3.56)	Not mentioned	Not mentioned	Age, Obesity (BMI ≥30 kg/m^2), PLT, Albumin, IFG/T2DM, PNPLA3 polymorphism, Advanced Fibrosis/Cirrhosis
Lee, 2017	Cox regression	HCC	In NAFLD patients without cirrhosis: T2DM 1.19 95% CI (0.47-3.02)	Not mentioned	In NAFLD patients without cirrhosis: Hypercholesterolemia 0.41 95% CI (0.15-1.11)	In NAFLD patients without cirrhosis: Hypertension 1.14 95% CI (0.46-2.80)	Age, Gender, ALT, Hypertension, Hypercholesterolemia, T2DM, Gout, Statin use, Metformin use, Aspirin use
Ito, 2020	Cox regression	HCC	In all NAFLD patients: DM 1.832 95% CI (0.354-9.469)	In all NAFLD patients: Overweight 1.068 95% CI (0.207-5.508),	In all NAFLD patients: Dyslipidemia 0.213 95% CI (0.048-0.953),	In all NAFLD patients: Hypertension 2.810 95% CI (0.545-14.490)	Unadjusted
Kawamura, 2012	Cox regression	HCC	In all NAFLD patients: T2DM 3.21 95% CI (1.09-9.50)	In all NAFLD patients: Overweight 1.69 95% CI (0.63-4.55)	In all NAFLD patients: LDL cholesterol≥140mg/dl 1.07 CI (0.40-2.89)	Not mentioned	Only the association between T2DM and HCC was adjusted by Age, ALT and PLT
Vilar-Gomez, 2018	Competing risk regression	HCC	NAFLD patients with advanced fibrosis: T2DM 4.72 95% CI (2.13-10.45)	Not mentioned	Not mentioned	Not mentioned	Cirrhosis, Gender, Race, Age, Smoking, BMI, Hypertension, History of vascular events or malignant neoplasm, Statin therapy, Glucose-lowering medications, Anti-hypertensive medications, Aspirin, INR, Albumin, Total bilirubin, AST/ALT, PLT, MELD score

HCC: Hepatocellular carcinoma, NAFLD: Nonalcoholic fatty liver disease, T2DM: Type 2 diabetes mellitus, IFG: Impaired fasting glucose regulation, BMI: Body mass index, LDL: Low density lipoprotein, PLT: Platelet, ALT: Alamine aminotransferase, AST: Aspartate transaminase

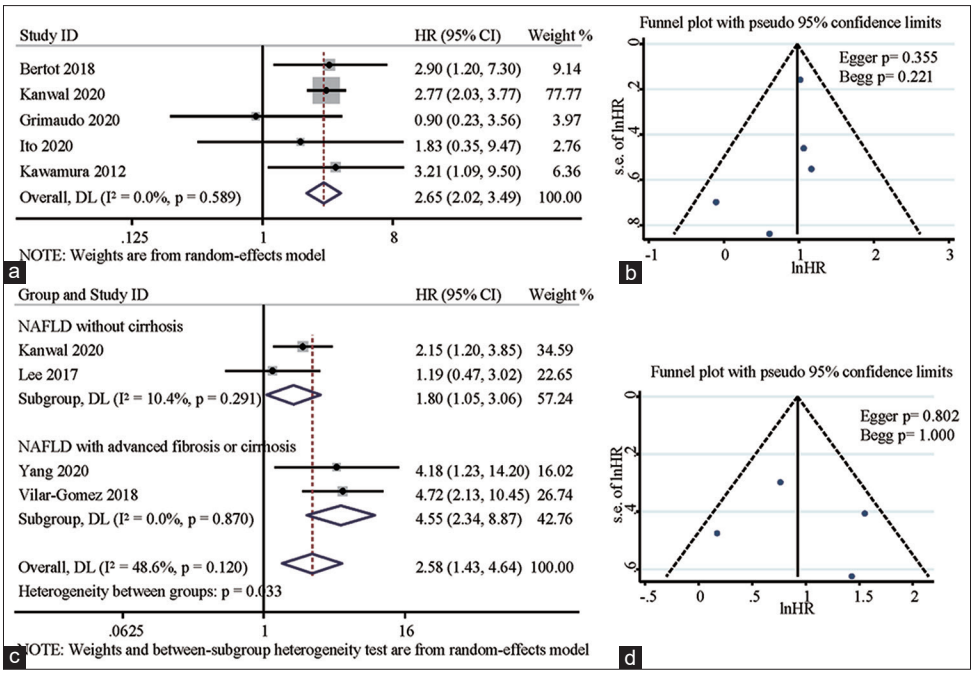

Figure 2: Forest plots depicting the correlation between DM and NAFLD-related HCC incidence (a), and correlation of DM with HCC incidence in noncirrhotic and cirrhotic NAFLD (b). Funnel plots depicting potential publication bias in pooled HRs of the association between DM and NAFLD-related HCC incidence (c), and pooled HRs of the association between DM and HCC incidence in noncirrhotic and cirrhotic NAFLD (d)

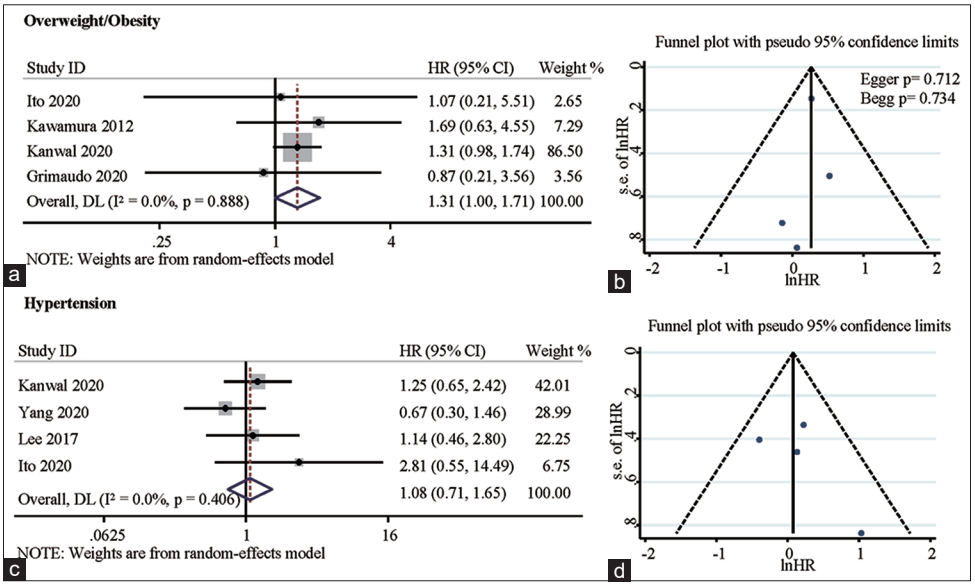

Figure 3: Forest plots depicting the correlation between overweight/obesity and NAFLD-related HCC incidence (a), and correlation between hypertension and NAFLD-related HCC incidence (b). Funnel plots depicting potential publication bias in pooled HRs of the association between overweight/obesity and NAFLD-related HCC incidence (c), and pooled HRs of the association between hypertension and NAFLD-related HCC incidence (d)

with the severity of histological injury.[22] In this systematic review and meta-analysis, DM and overweight/obesity were associated with an increased risk of HCC incidence in NAFLD patients, especially DM, when the risk increased 4-fold if advanced fibrosis/cirrhosis was also present.

The first important finding was that DM and overweight/obesity were both risk factors for HCC incidence in NAFLD. In noncirrhotic and cirrhotic NAFLD patients, DM remained a high risk factor. Streptozotocin (STZ), a chemical agent that destroys pancreatic β cells and causes increased blood glucose, has been proven to induce NAFLD-related HCC in rodents fed a high fat diet (HFD).[8] This indirectly suggests that elevated blood glucose might be a key factor in the development of NAFLD-related HCC. An increasing number of studies

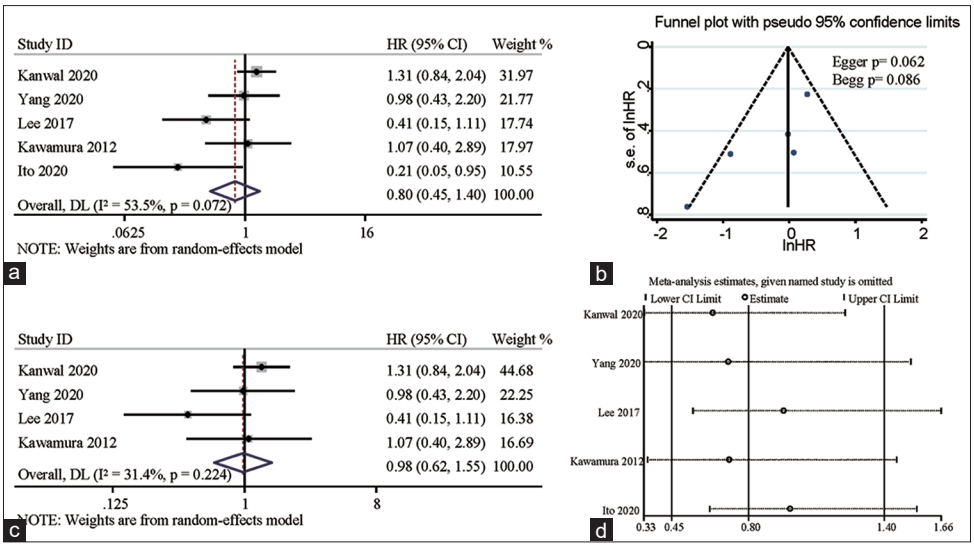

Figure 4: Forest plots depicting the correlation between dyslipidemia and NAFLD-related HCC incidence (a). Funnel plots depicting potential publication bias in pooled HRs of the association between dyslipidemia and NAFLD-related HCC incidence (b), and results from the sensitivity analysis of pooled HRs of the association between dyslipidemia and NAFLD-related HCC incidence (c and d)

has shown that reprogramming of glucose metabolism is crucial for tumor formation and development, including HCC.[23,24] Glucose is the most important nutrient *in vivo*, and in HCC development, insufficient glucose supply can induce hypoxia and up-regulation of hypoxia inducible factor (HIF) signal, further activating oncogenes and deactivating tumor suppressor genes.[25] This hypoxia signal is also involved in tumor epithelial mesenchymal transition (EMT), metastasis and other biological behaviors. Glucose uptake and utilization in the peripheral tissues of patients with DM has been shown to be impaired and may be an important reason for the hypoxic environment and NAFLD-related HCC development.

The relationship between obesity and tumorigenesis has been reported by many studies.[26] In NAFLD patients, obesity is also associated with more severe histological injury.[22] Obesity is characterized by the expansion of adipose tissue, and often accompanied by inflammation of adipose tissue. Studies have shown that peritumoral adipocytes, also known as cancer-associated adipocytes (CAAs), interact directly with cancer cells to promote tumor growth. CAAs have been shown to secrete numerous proteases and cytokines, including IL-6 and IL-8, to promote tumor growth, invasion and migration.[27] This suggests that obesity might participate in the development of NAFLD-related HCC by inducing adipose tissue inflammation and CAA formation. Our findings showed that obesity was a risk factor for NAFLD-related HCC, but the impact of overweight/obesity on NAFLD-related HCC occurrence was mild compared with that of DM. In this study, overweight/obesity was measured by BMI. A previous large-scale clinical study revealed that BMI was associated with HCC incidence, with a modest HR of 1.19.[28] This modest risk was likely due to the limitations of BMI in assessment of overweight/obesity. Although BMI is the easiest and most available clinical measure for body/obesity types, it is not able to differentiate fat and skeletal muscle mass.[29] Unlike fat, skeletal muscle plays a protective role in cancer progression. Previous studies showed that skeletal muscle loss was not only associated with increased incidence of HCC, but also served as a poor prognostic marker of HCC.[30] Skeletal muscle, as an endocrine organ, can secrete a series of myokines such as irisin and IL-15 to inhibit cancer development.[31] Therefore, a more comprehensive assessment of body/obesity types is needed to clarify the relationship between obesity and NAFLD-related HCC occurrence.

Another interesting finding of this study was that hypertension and dyslipidemia have no significant correlation with the occurrence of HCC in NAFLD patients. Hypertension and dyslipidemia were recognized as high risk factors for cardiovascular events, but their correlation with tumorigenesis remains controversial. In kidney cancer, Flaherty *et al.*[32] reported that hypertension was not associated with cancer incidence, while Chow *et al.*[33] suggested that elevated blood pressure was associated with an increased risk of cancer. The same contradictory results were evident when assessing the relationship between dyslipidemia and tumorigenesis.[34,35] Our results indicated that these two factors were not related to NAFLD-related HCC incidence.

Compared with other types of liver disease, surveillance for HCC in NAFLD patients is difficult. A large UK cohort study showed that 56.7% of patients with NAFLD-related HCC had not been monitored prior to diagnosis, compared with only 13.3% of those with HCV-related HCC.[36] Another multicenter study indicated that the detection rate of HCC by ultrasonic surveillance in NAFLD was much lower than that in HCV.[37] This is probably due to the large population base of patients with NAFLD and the lack of reliable methods to stratify their risk of HCC. AASLD guidelines categorised HCC surveillance for NAFLD-related cirrhosis under "other conditions", with no specific recommendations.[38] EASL-EASD-EASO clinical practice guidelines concluded that surveillance for HCC in NAFLD was difficult to implement since high risk patients were not clearly identified.[39] Obesity, DM, hypertension and hyperlipidemia are common comorbidities in NAFLD and might have a causal relationship.[7] Whether these comorbidities can increase HCC risk is nonetheless unclear. Our findings emphasized the contribution of DM to NAFLD-related HCC and suggest that diabetic NAFLD patients constitute a high risk population for NAFLD-related HCC, especially in the presence of advanced fibrosis/cirrhosis. This provides supplementary knowledge for risk stratification and monitoring of NAFLD-related HCC.

The assessment of heterogeneity was an important part of the meta-analysis. Significant heterogeneity existed when assessing the relationship between dyslipidemia and NAFLD-related HCC incidence. This heterogeneity was mainly caused by the inclusion of Ito's study although removal of this study and performing sensitivity analysis did not alter our conclusion.

This study also had some limitations: metabolic traits often coexisted, but due to the lack of sufficient inclusion studies, we could not assess the additive risk of HCC when NAFLD patients simultaneously suffered from one or more traits. In addition, NAFLD severity was a key factor affecting the occurrence of HCC. In this study, there were insufficient included studies to perform stratified analysis of the relationship between metabolic traits and HCC occurrence according to the severity of NAFLD. Finally, metabolic comorbidities may have been subject to intervention. The lack of certainty about whether metabolic comorbidities were well controlled at baseline may have been an important confounding factor affecting the results. Future research needs to clarify the relationship between the intervention status of metabolic comorbidities and HCC occurrence in patients with NAFLD.

In conclusion, this systematic review and meta-analysis provides evidence that DM and overweight/obesity are risk factors for NAFLD-related HCC incidence. More importantly, DM increased the risk of HCC occurrence 4-fold in cirrhotic NAFLD patients. Since cirrhosis is a risk factor for HCC incidence, diabetic patients with NAFLD and advanced fibrosis/cirrhosis should be monitored closely for development of HCC.

Authors' contributions

Jin Chen and Shu Song equally contributed to this work. Jin Chen and Shu Song designed the study, analyzed the data and wrote the manuscript. Xiangsu Li and Dongxue Bian designed the search strategy and were involved in data analysis. Xudong Wu was responsible for the research design, data analysis, and manuscript revision. All authors gave their approval for submission of the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

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