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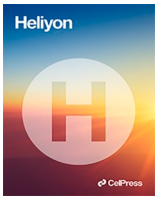

Presence of diabetes further heightens hepatocellular carcinoma risk in patients with hepatitis B or hepatitis C virus-related cirrhosis: A meta-analysis

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ABSTRACT

Objective: Impact of diabetes mellitus on the development of hepatocellular carcinoma (HCC) remained controversial in cirrhotic patients. This meta-analysis aimed to investigate the association of diabetes and the occurrence of HCC in patients with hepatitis B or hepatitis C virus-related cirrhosis.
Methods: Two authors comprehensively searched PubMed and Embase databases until June 22, 2023, to identify studies that evaluated the association of diabetes with the occurrence of HCC in patients with hepatitis B or hepatitis C virus-related cirrhosis.
Results: Sixteen retrospective/prospective cohort studies reporting on 15 articles (5357 cirrhotic patients) were included. The prevalence of diabetes in hepatitis B and hepatitis C virus-related cirrhosis patients ranged from 4 to 46%. Diabetes was associated with higher risk of HCC (risk ratio [RR] 1.74; 95% confidence intervals [CI] 1.24–2.45) in patients with hepatitis C virus-related cirrhosis. However, no significant relationship of diabetes with the occurrence of HCC was present in studies with less than 48-month follow-up among patients with hepatitis C virus-related cirrhosis (RR 1.28; 95% CI 0.68–2.43). Moreover, diabetes also conferred an increased risk of HCC (RR 2.67; 95% CI 2.03–3.51) in patients with hepatitis B virus-related cirrhosis.
Conclusion: Presence of diabetes significantly predicted the occurrence of HCC in patients with hepatitis B or hepatitis C virus-related cirrhosis.

1. Introduction

Liver cirrhosis refers to a late stage of chronic liver disease characterized by regenerative nodules and fibrosis (scarring) [1]. The common causes of cirrhosis include hepatitis B or C virus (HBV or HCV) infection and alcohol/non-alcohol related fatty liver disease. The global health burden of cirrhosis is increasing due to population growth and aging [2]. Despite advances in evidence-based medicine, there is still lack of effective treatment for liver cirrhosis. Irrespective of the etiology of liver disease, cirrhotic patients

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are at higher risk of hepatocellular carcinoma (HCC) occurrence [3]. The annual incidence of HCC in the cirrhotic stage of HBV and HCV infection was 3.23% and 4.81%, respectively [4]. Therefore, identification of risk factors and surveillance for HCC is very urgent in liver cirrhosis.

Diabetes mellitus is a well-known risk factor for developing several malignancies, including HCC [5]. Diabetic patients conferred an approximately 2-fold risk of developing HCC than those without diabetes [6]. Moreover, individuals with HBV and HCV infection conferred a 37% and 76% higher risk of HCC, respectively [7]. The presence of diabetes in cirrhotic patients with HBV or HCV infection may promote the development of HCC through the metabolic pathway and hepatocarcinogenic potential of the HBV/HCV. Several studies have demonstrated the direct hepatocarcinogenic effect of diabetes among cirrhosis patients [8–11]. However, the impact of diabetes mellitus on the HCC occurrence remained under debate in patients with HBV [12] or HCV [13–16]-related cirrhosis. These conflicting findings may be partly due to antidiabetic agents potentially modify the risk of HCC [17]. Particularly, metformin use has been linked to a reduced risk of HCC in patients with diabetes and chronic hepatitis C [18].

Previous meta-analysis has not specially addressed the association between diabetes and the occurrence of HCC in HBV or HCV-related cirrhotic patients. Therefore, we conducted this updated meta-analysis to summarize the role of diabetes in prediction of HCC among cirrhotic patients with HBV or HCV infection.

2. Material and methods

2.1. Search strategy

This meta-analysis was conducted on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement [19]. We systematically search the articles indexed in PubMed, Web of Science, and Embase database based on the "patients, exposure, outcome, and time/design" criteria. The following combined items were used for literature search without language restriction (Supplemental Text S1): "cirrhotic" OR "liver cirrhosis" OR "liver fibrosis" AND "diabetic" OR "diabetes" AND "hepatocellular carcinoma" OR "liver cancer" OR "liver neoplasms" AND "follow up" OR "follow-up". The last search date was until June 22, 2023. To avoid missing any studies, we manually scanned the reference lists of related articles.

2.2. Inclusion and exclusion criteria

Two independent authors assessed the retrieved full-text potential articles using the following criteria for inclusion and exclusion. Studies were included if: 1) retrospective/prospective cohort studies or post hoc analysis of randomized controlled trials that enrolled patients with liver cirrhosis, 2) presence of diabetes mellitus as predictor, 3) occurrence of HCC as the outcome of interest, and 3) reported data on the adjusted relative risk of HCC for individuals with diabetes versus those without diabetes. The exclusion criteria included: 1) without specially reported the etiology of cirrhosis, 2) not reported outcome measures of interest, 3) lack of an adjusted risk estimate, and 4) cross-sectional or case-control as study design.

2.3. Data extraction and quality evaluation

The following data from eligible studies were extracted by two independent authors: surname of the first author, year of publication, study region, study design, number of patients, gender distribution, etiology of cirrhosis, mean or median age at enrollment, definition and prevalence of diabetes, mean or median follow-up time, adjusted risk summary of HCC, variables adjusted, and information for evaluating the study quality. Two independent authors assessed the methodological quality of the included studies using the Newcastle-Ottawa Scale (NOS) [20]. We defined the studies with a total score $\geq$7 points to have high quality. Disagreements in the above procedures were resolved by consensus.

2.4. Data analysis

All the meta-analyses were carried out using Stata 12.0 (Stata Corporation, USA). We pooled the fully adjusted risk ratio (RR) with 95% confidence intervals (CI) for patients with diabetes *vs*. those without. Study heterogeneity was examined using the Cochrane Q test and I^2 statistics. Significant heterogeneity was defined by the I^2 statistic exceeding 50% and $p < 0.10$ of Cochrane Q test. We selected a random effect model when significant heterogeneity was found; otherwise, a fixed-effect model was selected. We performed leave-one-out analyses to examine the effect of individual study on original pooling risk summary. Additionally, we performed the subgroup analysis based on the study design, patients' age, definition of diabetes, and length of follow-up. The funnel plot, Begg's test, and Egger's test ($p < 0.10$ considering statistically significant). Were used to assess the publication bias.

3. Results

3.1. Literature search and characteristics of included studies

A total of 2313 potentially relevant articles were obtained using the search strategy, 1032 of them were excluded for duplicate records. Following the assessing titles and/or abstracts, 1281 publications were further removed because of obviously irrelevant, and 53 full-text articles were collected for eligibility assessment. We further removed 38 articles because they did not specially enroll the

patients with HBV or HCV-related cirrhosis, provide unadjusted risk summary, or without reporting the outcome of interest. Ultimately, 15 articles [13–16,21–31] were included in this meta-analysis (Fig. 1). Of which, one article [15] reported the data of two cohort studies.

Table 1 lists the characteristics of the included studies. These eligible published between 2008 and 2023. Five studies [13,16,27,28,31] were prospective design, while the others were retrospective studies. Sample sizes varied from 138 to 1,038, with a total of 5357 cirrhotic patients. The follow-up duration ranged from 25 months to 7.8 years. HBV infection was ascertained by serologically positive for hepatitis B surface antigen. HCV infection was ascertained by positive anti-HCV antibodies and/or detectable HCV-RNA. Diabetes was diagnosed according to the medical records only in 9 studies [14–16,21,22,24,25,27,29,30], while the other studies diagnosed diabetes according to the fasting glucose, glucose tolerance test, or antidiabetic medications. The prevalence of diabetes in cirrhotic patients with hepatitis B and hepatitis C virus varied from 4% to 46%. The study quality was grouped as high with NOS score ranging between 7 and 9 points (Supplemental Table S1).

3.2. Association of diabetes with developing HCC in HCV-related cirrhosis

Ten studies [13–16,22,24–26,28–31] reported the association of diabetes with development of HCC in HCV-related cirrhotic patients. Considering presence of significant heterogeneity ($I^2 = 61.7\%$, $p = 0.004$), we therefore used a random effect model. Patients with diabetes had an increased risk of HCC occurrence (RR 1.74; 95% CI 1.24–2.45; Fig. 2) compared with patients without diabetes. Sensitivity analysis further demonstrated the credibility of the original pooling result (Supplemental Table S2). The pooled RR of HCC was 1.59 (95% CI 1.07–2.36) among studies diagnosing diabetes only by the medical records. Moreover, the impact of diabetes on HCC occurrence appeared to be affected by the length of follow-up in the subgroup analysis (Table 2). The funnel plot (Fig. 3), Begg's test ($p = 0.161$), and Egger's test ($p = 0.222$) revealed a low likelihood of publication bias.

3.3. Association of diabetes with the occurrence of HCC in HBV-related cirrhosis

The association of diabetes with HCC occurrence in HBV-related cirrhotic patients was reported in five studies [21,23,27]. Considering no significant heterogeneity between studies ($I^2 = 36.9\%$, $p = 0.175$), we therefore selected a fixed-effect model. Patients with diabetes had a high risk of HCC occurrence (RR 2.67; 95% CI 2.03–3.51; Fig. 4) compared with patients without diabetes. Sensitivity analysis confirmed the robustness of the original pooling result (Supplemental Table S3).

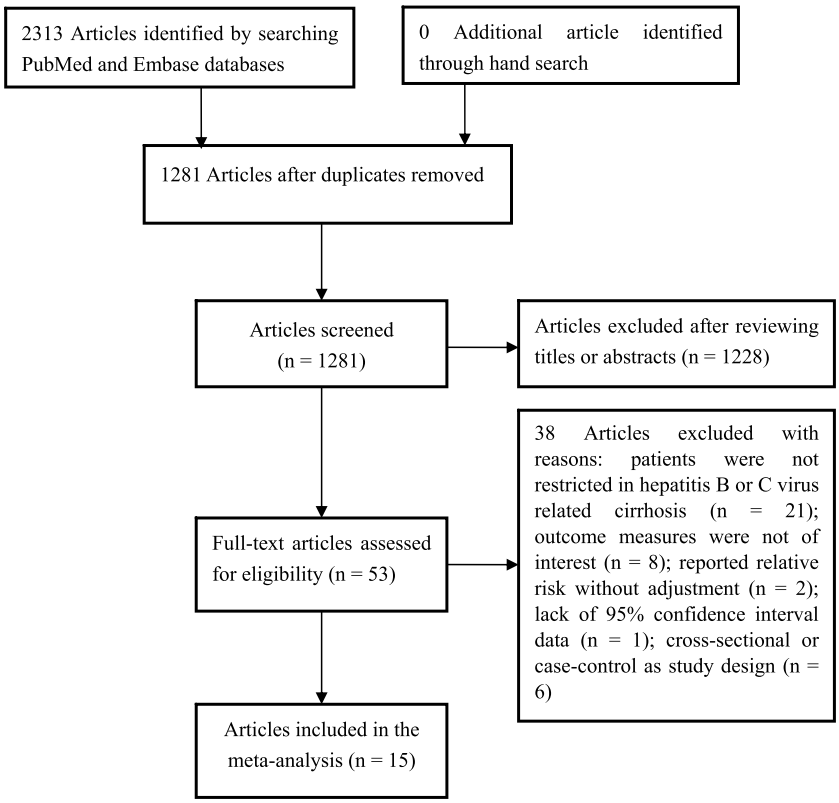

Fig. 1. Flow chart showing the process of study selection.

Table 1
Baseline characteristic of the included studies.

Author/year	Region	Study design	Patients (% men)	Age (years)	DM definition/prevalence	Incidence of HCC	Relative risk	Follow-up	Maximum adjusted variables
Veldt 2008 [13]	Europe, Canada	Prospective	HCV cirrhosis 303 (68)#	50 (44–57)	Fasting glucose, GTT, antidiabetic agents (19.1%)	NP	3.28 (1.35–7.97)	4.0 years	Age, sex, BMI, platelet count, bilirubin, albumin
Di Costanzo 2008 [14]	Italy	Retrospective	HCV cirrhosis 138 (52.2)	63.3 ± 8.1	Medical records (29.7%)	46%	1.41 (0.83–2.39)	7 years	Age, sex, cigarette smoking, alcohol intake, interferon
Ziol 2010 [31]	France	Prospective	HCV cirrhosis 150 (52.2)	57 ± 13	Fasting glucose, antidiabetic agents (36.3%)	24%	3.20 (1.62–6.31)	4.9 years	Age, sex, smoking, alcohol use, BMI, biological and histologic data
Hsu 2014 [21]	Taiwan	Retrospective	HBV cirrhosis 210 (73.3)	52.8 (46–60)	Medical records (23.3%)	16.7%	3.49 (1.54–7.91)	25.2 months	Age, sex. MELD score, use of metformin
Elkrief 2014 [22]	France	Retrospective	HCV cirrhosis 348 (68)	59 (51–71)	Medical records (40%)	29%	1.94 (1.13–3.33)	55 months	Age, sex, MELD score, alcohol abuse, HIV coinfection, HBV coinfection
Hsiang 2015 [23]	New Zealand	Retrospective	HBV cirrhosis 223 (66.8)	51 ± 12	Fasting glucose, GTT, active diabetes follow-up (22.4%)	16.1%	2.36 (1.14–4.85)	5.0 years	Age, sex, antiviral therapy, sustained viral suppression, MELD score
Yang (a) 2016 [15]	USA	Retrospective	HCV cirrhosis 154 (NP)	57.7 ± 12.3	Fasting glucose, HbA1C, antidiabetic agents (34%)	NP	0.6 (0.2–1.3)	38 months	Age, sex, race, albumin
Yang (b) 2016 [15]	USA	Retrospective	HCV cirrhosis 410 (72.7)	50.4 ± 7.0	Medical records (20%)	11%	0.7 (0.3–1.4)	6 years	Age, albumin
Hedenstierna 2016 [24]	Sweden	Retrospective	HCV cirrhosis 180 (69)	54 (26–72)	Medical records (18%)	7.8%	6.26 (1.70–23.1)	7.8 years	Age at sustained virologic response, sex, albumin
Hallager 2017 [16]	Denmark	Prospective	HCV cirrhosis 1038 (69)	51.9 (26–86)	Medical records (12.2%)	11.6%	1.29 (0.89–1.88)	3.8 years	Age, sex, genotype, alcohol overuse
Degasperi 2019 [25]	Italy	Retrospective	HCV cirrhosis 505 (60)	63 (28–87)	Medical records (19%)	5.5%	2.52 (1.08–5.87)	25 months	Male gender, γ-glutamyl transferase, CPT score, fibrosis-4 score, α-fetoprotein, LSM, LSPS
Abe 2020 [26]	Japan	Retrospective	HCV cirrhosis 188 (48)	70 (61–77)	DM history, fasting glucose, HbA1C, antidiabetic agents (23%)	4.0%	3.80 (1.35–10.65)	4 years	Age, albumin-bilirubin score, platelet count
Tang 2021 [27]	China	Prospective	HBV cirrhosis 467 (86.3)	48.1 ± 9.4	Medical records (43.5%)	34%	2.09 (1.42–3.10)	4.4 years	Age, family history of liver cancer, anti-virial treatment, low density lipoprotein cholesterol, triglyceride, TC
Rodríguez-Escaja 2021 [28]	Spain	Prospective	HCV cirrhosis 379 (78.7)	54 (48.7–61)	Fasting glucose, antidiabetic agents (27.2%)	17.9%	1.17 (0.63–2.19)	49.5 months	Age, sex, alanine transaminase, aspartate transaminase, γ-glutamyl transferase, platelet count, prior decompensation
Cheng 2022 [29]	China	Retrospective	HBV cirrhosis 252 (77.3)	52.1 ± 10.2	Medical records (NP)	19.0%	3.06 (1.54–6.08)	57 months	Age, alcohol drinking, international normalized ratio, alpha-fetoprotein
Li 2023 [30]	China	Retrospective	HBV cirrhosis 412 (65.8)	49–62	Medical records (47.6%)	NP	6.73 (2.77–16.5)	30 months	Age, sex, α-fetoprotein, hepatitis B surface antigen, alcohol abuse, antiviral treatment

Abbreviations: HR, hazard ratio; CI, confidence interval; NP, not provided; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency; GTT, glucose tolerance test; MELD, Model for End-Stage Liver Disease; BMI, body mass index; HbA1C, glycosylated hemoglobin; TC, total cholesterol.
Results from the Ishak fibrosis score 6 subgroup.

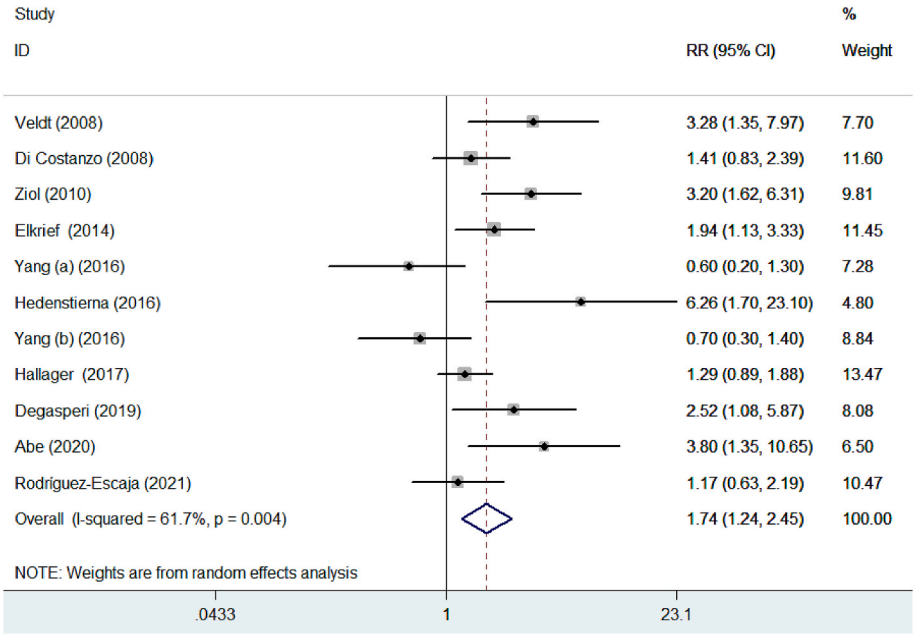

Fig. 2. Pooled risk ratio with 95% confidence intervals of hepatocellular carcinoma for hepatitis C virus-related cirrhotic patients with diabetes versus those without.

Table 2
Subgroup analysis for the impact of diabetes on hepatocellular carcinoma occurrence.

Subgroup	Study number	Pooled risk ratio	95% confidence intervals	Heterogeneity between studies
Study design	4	1.85	1.10–3.12	$p = 0.033$; $I^2 = 65.7\%$
Retrospective	7	1.68	1.01–2.80	$p = 0.008$; $I^2 = 65.4\%$
Prospective				
Sample size	6	1.53	1.06–2.21	$p = 0.068$; $I^2 = 51.3\%$
≥300	5	2.15	1.06–4.34	$p = 0.007$; $I^2 = 71.9\%$
<300				
Length of follow-up	8	1.98	1.30–3.02	$p = 0.010$; $I^2 = 62.2\%$
≥48 months	3	1.28	0.68–2.43	$p = 0.083$; $I^2 = 59.8\%$
<48 months				
Median/mean age	3	2.09	1.17–3.74	$p = 0.185$; $I^2 = 40.8\%$
≥60 years	8	1.62	1.05–2.49	$p = 0.003$; $I^2 = 68.0\%$
<60 years				

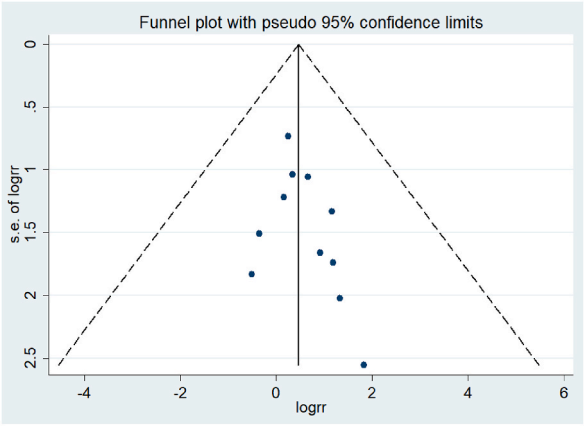

Fig. 3. Funnel plot of studies evaluating the association of diabetes with hepatocellular carcinoma occurrence in hepatitis C virus-related cirrhosis.

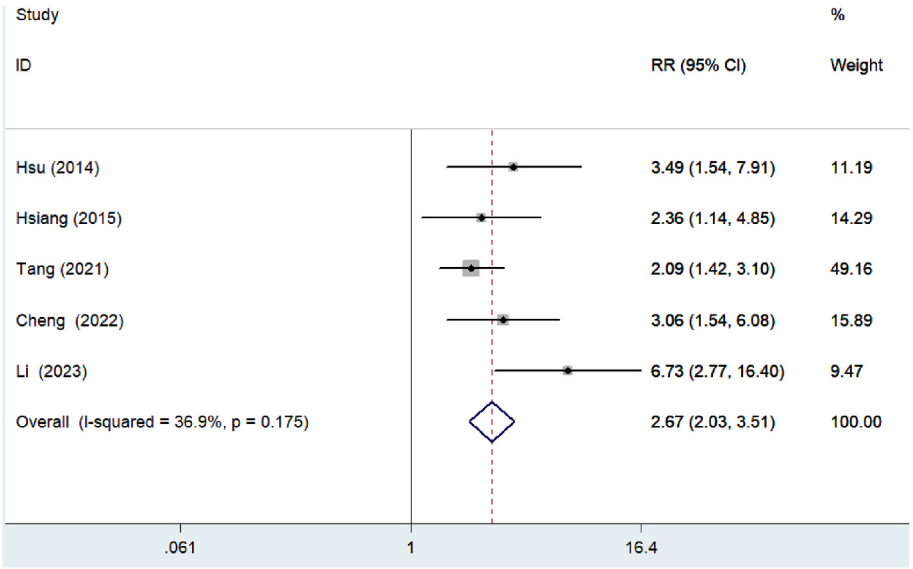

Fig. 4. Pooled risk ratio with 95% confidence intervals of hepatocellular carcinoma for hepatitis B virus-related cirrhotic patients with diabetes versus those without.

4. Discussion

The current meta-analysis firstly addressed the association of diabetes with the HCC occurrence among patients with HBV or HCV-related cirrhosis. The principal finding of this meta-analysis confirmed that diabetes was independently associated with higher risk of HCC in these populations. When compared with these nondiabetic counterparts, HBV and HCV-related cirrhotic patients with diabetes had a 2.67-fold and 1.74-fold additional increased risk of HCC. These findings indicate that the presence of diabetes mellitus in HBV and HCV-related cirrhotic patients heightens HCC risk. However, the significant association of diabetes with HCC appeared to be affected by the length of follow-up among patients with HCV-related cirrhosis.

An early meta-analysis [32] concluded that diabetes was associated with approximately 1.93-fold higher risk of HCC in cirrhotic patients. When restricted to two studies enrolling patients with HCV-related cirrhosis, the pooled relative risk was 1.90 for the diabetic individuals. However, this well-designed meta-analysis enrolled the diverse types of cirrhotic patients rather than focused on the HBV or HCV-related cirrhosis. By contrast, our meta-analysis enrolled a larger number of studies compared with the previous meta-analysis, presenting somewhat lower risk of HCC among cirrhotic patients with HCV infection. Furthermore, we analyzed the relationship of diabetes with HCC risk among cirrhotic patients with HBV infection, which not summarized in the previous meta-analysis.

The relationship between diabetes and HCC occurrence in cirrhotic patients may confound by use of metformin. A meta-analysis using of case-control studies showed that metformin use was associated with a 53.2% reduced risk of HCC in diabetic patients [33]. Therefore, lack of adjustment of antidiabetic medications particularly metformin may have affected the prognostic role of diabetes in the current meta-analysis. Moreover, duration of follow-up may be another factor that biased the predictive value of diabetes. Our subgroup analysis indicated that the impact of diabetes on HCC occurrence enhanced with the lengthening of follow-up duration. This result may be explained by the severity of insulin resistance and diabetes increases with the progression of cirrhosis [34,35]. In addition, the age of the patients should consider as a confounding factor, as the effect of diabetes on HCC occurrence was stronger among the elderly (age $\geq$60 years) subgroup.

Our meta-analysis showed that the pooled risk estimate of HCC for diabetes was higher in cirrhotic patients with HBV infection than those with HCV infection. This finding may be in part due to higher ratio of HCC incidence for HBV (8.73-fold) compared with HCV (7.07-fold) in the cirrhotic stage/non-cirrhotic stage [4]. However, future studies are needed to investigate why the impact of diabetes on developing HCC differs in diverse types of cirrhosis.

Although the mechanisms underlying the association between diabetes and HCC in cirrhotic patients are not fully elucidated, several hypotheses have been proposed [36]. First, oxidative stress from diabetes and hyperinsulinemia/insulin resistance can produce reactive oxygen species and proinflammatory cytokines, contributing to hepatocarcinogenesis. Second, activation of insulin-like growth factor signaling pathways may participate in initiation and progression of HCC. Third, HCV or HBV infection itself also increases the development of HCC. On the other hand, hepatogenous diabetes induced by the liver insufficiency and portal hypertension is accelerated in patients with cirrhosis, which is associated with a higher risk of developing [37].

In our analyzed studies, diabetes was observed in up to 46% and 34% among HCV and HBV-related cirrhotic patients. The concomitant presence of diabetes would heighten the HCC risk among HBV and HCV-related cirrhotic patients. Therefore, screening for diabetes should be recommended for all cirrhotic patients. Intensive glycemic control and regularly ultrasonography surveillance are warranted for cirrhotic patients with the concomitant presence of diabetes. However, whether the degree of glycemic control can

reduce HCC occurrence in these patients requires further study.

Several limitations should be noted in the current meta-analysis. First, most of included studies were retrospective designs and these studies used various criteria for diagnosis of liver cirrhosis, which may have led to potential selection bias. Second, lack of clearly reported in the definition of diabetes in most of the studies was another important limitation. Third, significant heterogeneity existed in cirrhotic patients with HCV infection. Difference in the definitions of cirrhosis, methods of determining diabetes, adjustment for confounders, and length of follow-up may be partly explained the heterogeneity. Finally, antidiabetic agents such as metformin could modify the development of HCC among diabetic patients [33,38]. Lack of adjustment for antidiabetic agents may have biased the pooling risk summary.

5. Conclusion

Diabetes was significantly associated with higher risk of developing HCC among cirrhotic patients with HBV or HCV infection. Measurement of blood glucose level may improve risk classification of HCC in these cirrhotic patients.

Author contribution statement

Yu Fan: Conceived and designed the analysis; Analyzed and interpreted the data; Wrote the paper.
Xiaomeng Jiang: Conceived and designed the analysis; Analyzed and interpreted the data.
Ye Zang; Wei Xu: Performed the experiments; Contributed materials, analysis tools or data; Wrote the paper.
Yue Qiu: Analyzed and interpreted the data.

Data availability statement

Data included in article/supp. material/referenced in article.

Additional information

Supplementary content related to this article has been publish online at [URL].

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e18425.

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