

**Criteria Grid**  
**Hepatitis C Research Studies, Tools, and Surveillance Systems**

<b>Best Practice/Intervention:</b>	Wang WM. et al. (2011) Prognostic role of diabetes mellitus in hepatocellular carcinoma patients after curative treatments: a meta-analysis. <i>Hepatobiliary &amp; Pancreatic Diseases International</i> , 10(4):346-355			
<b>Date of Review:</b>	April 7, 2015			
<b>Reviewer(s):</b>	Christine Hu			
<b>Part A</b>				
<b>Category:</b>	Basic Science <input type="checkbox"/> Clinical Science <input type="checkbox"/> Public Health/Epidemiology <input type="checkbox"/> Social Science <input type="checkbox"/> Programmatic Review <input checked="" type="checkbox"/>			
<b>Best Practice/Intervention:</b>	<b>Focus:</b> Hepatitis C <input checked="" type="checkbox"/> Hepatitis C/HIV <input type="checkbox"/> Other: hepatocellular carcinoma, diabetes mellitus <b>Level:</b> Group <input checked="" type="checkbox"/> Individual <input type="checkbox"/> Other: _____ <b>Target Population:</b> hepatocellular carcinoma patients with coexisting condition of diabetes mellitus <b>Setting:</b> Health care setting/Clinic <input checked="" type="checkbox"/> Home <input type="checkbox"/> Other: _____ <b>Country of Origin:</b> China _____ <b>Language:</b> English <input checked="" type="checkbox"/> French <input type="checkbox"/> Other: _____			
<b>Part B</b>				
	<b>YES</b>	<b>NO</b>	<b>N/A</b>	<b>COMMENTS</b>
<i>Is the best practice/intervention a meta-analysis or primary research?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	meta-analysis; to clarify the effect of diabetes mellitus on hepatocellular carcinoma patients after curative treatments
<i>Has the data/information been used for decision-making (e.g. program funding developments, policies, treatment guidelines, defining research priorities and funding)?</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Information was not used for decision-making. Authors mentioned that identifying the effect of DM on prognosis of HCC can guide clinical decision-making on therapy and prevention. Future homogeneous HCC cohort studies required to estimate the precise prognostic effect of DM coexistence in HCC patients.
<i>Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Methodology clearly stated.

Are the best practices/methodology/results described applicable in developed countries?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Similar analysis can be done and the results can be extended to various countries.
	<b>YES</b>	<b>NO</b>	<b>N/A</b>	<b>COMMENTS</b>
Are the best practices/methodology/results described applicable in developing countries?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
The research study/tool/data dictionary is easily accessed/available electronically	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Full PDF available for download at <a href="http://www.hbpdint.com/EN/Y2011/V10/I4/346">http://www.hbpdint.com/EN/Y2011/V10/I4/346</a>
Is there evidence of cost effective analysis with regard to interventions, diagnosis, treatment, or surveillance methodologies? If so, what does the evidence say? <b>Please go to Comments section</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Are there increased costs (infrastructure, manpower, skills/training, analysis of data) to using the research study/tool/data dictionary?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
How is the research study/tool funded? <b>Please got to Comments section</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	This study was funded by the National Basic Research Program of China, the National Natural Science Foundation of China, the National Key Sci-Tech Special Project of Infectious Diseases, and the Shanghai Rising-Star Follow-up Program Fund
Is the best practice/intervention dependent on external funds?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Other relevant criteria: <hr/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<ul style="list-style-type: none"> <li>- Results show diabetes mellitus (DM) correlated with poor prognosis and high recurrence rate in Asian hepatocellular carcinoma (HCC) patients who underwent curative treatments</li> <li>- Patients with diabetes mellitus had shorter survival time in HCV related hepatocellular carcinoma</li> <li>- Coexisting of DM impaired overall survival of HCC patients with small tumor burden</li> </ul>

WITHIN THE SURVEILLANCE SYSTEM FOR REVIEW				
<i>Are these data regularly collected?</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Search of databases in July 2009 and repeated in March 2010.
<i>Are these data regularly collected at and/or below a national level?</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Are these data collected manually or electronically?</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Electronically: search of articles on PubMed, EMBASE, the Cochrane Library and ACP Journal Club
RESEARCH REPORTS				
<i>Has this research been published in a juried journal?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<i>Hepatobiliary &amp; Pancreatic Diseases International</i>
<i>Does the evidence utilize the existing data/surveillance information or has it generated new data and/or information?</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Existing data: 10 studies included in meta-analysis

# Prognostic role of diabetes mellitus in hepatocellular carcinoma patients after curative treatments: a meta-analysis

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**BACKGROUND:** The prognostic role of diabetes mellitus (DM) coexisting with hepatocellular carcinoma (HCC) remains controversial. To clarify its impact on survival in HCC patients after curative treatments, a meta-analysis was performed.

**DATA SOURCES:** Eligible studies were identified through multiple search strategies in the databases PubMed (MEDLINE), EMBASE, the Cochrane Library and ACP Journal Club between January 1950 and March 2010. Ten studies fulfilled the inclusion criteria, and data were aggregated comparing overall survival and recurrence-free survival in HCC patients according to DM status.

**RESULTS:** The pooled hazard ratios (HRs) estimate for overall survival was 1.34 (95% CI, 1.18-1.51;  $P < 0.0001$ ) and for recurrence-free survival was 1.48 (95% CI, 1.00-2.18;  $P < 0.0001$ ), showing a worse survival for HCC with coexisting DM. However, the patients with DM had a shorter survival time in HCV-related HCC (HR=1.71; 95% CI, 1.10-2.66;  $P = 0.016$ ), while HBV-related cases were not significantly different (HR=1.29; 95% CI, 0.69-2.40;  $P = 0.182$ ). Meanwhile, the coexistence of DM impaired overall survival in HCC patients with a small tumor burden (HR=1.63; 95% CI, 1.25-2.12;  $P < 0.0001$ ).

**CONCLUSION:** HCC patients with coexisting DM have a shorter survival time and a higher risk for tumor recurrence after curative treatments, while the precise value should be defined in more clinical trials with consistent methodology, especially prospective studies.

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**KEY WORDS:** hepatocellular carcinoma; diabetes mellitus; prognostic factors; survival; meta-analysis

## Introduction

Hepatocellular carcinoma (HCC) is the fifth most frequent malignant neoplasm, and its incidence and mortality rates have increased in recent years.<sup>[1]</sup> Although the survival of patients with HCC has been improved by advances in surgical techniques and perioperative management, long-term survival remains unsatisfactory owing to the high rate of recurrence and metastasis.<sup>[2,3]</sup> The dismal clinical outcome of HCC leads to an urgent need for in-depth understanding of the relevant factors affecting HCC prognosis after treatment. These may serve to guide decision-making for therapeutic strategies for HCC patients and improve their prognosis.

Diabetes mellitus (DM) is positively associated with risks of several common human malignancies, including cancers of the colon, breast, endometrium, pancreas and liver.<sup>[4]</sup> Compared with their non-diabetic counterparts, patients with pre-existing DM have a higher risk for developing HCC, and it has been suggested as a potential risk factor for HCC.<sup>[5-8]</sup> Given the higher risk of HCC in patients with DM, investigation of how pre-existing DM may influence the prognosis of HCC after treatment is critical to decide the proper care of these patients. Recent researches have focused on the effects of comorbid conditions on the prognosis of HCC patients after treatment.<sup>[9-11]</sup> But potential interactions between DM and HCC are so complex that a conclusion remains controversial.<sup>[12-14]</sup>

To clarify a more precise effect of DM on HCC patients after curative treatments, we conducted a systematic review and meta-analysis to test the hypothesis that preexisting DM has an adverse effect on prognosis in

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patients with HCC after curative treatments. Ten studies which fulfilled the selection criteria were included in a standard meta-analysis. Using this strategy to clarify the potential connection between DM and the prognosis of HCC patients may be helpful to clinical practice and enrichment of our knowledge.

### Methods

#### Eligibility criteria

Studies must have evaluated the correlation of DM status with survival of HCC patients, and only trials providing information about overall survival (OS) and/or recurrence-free survival (RFS) were included. Studies not directly reporting hazard ratios (HRs) were allowed only if data were available for statistical estimation as described below. If the same patient populations were reported in several publications, only the most recent and/or complete one was included in the analysis to avoid overlap between cohorts. The criteria of DM diagnosis were based on the definitions described by the World Health Organization<sup>[15]</sup> or the American Diabetes Association.<sup>[16]</sup>

#### Identification of studies

Articles were identified by an electronic search of PubMed (MEDLINE), EMBASE, the Cochrane Library and ACP Journal Club in July 2009 and then repeated in March 2010. The key words included terms for diabetes mellitus (e.g., diabetes, glucose intolerance, insulin resistance, hyperglycemia, hyperinsulinemia), hepatocellular carcinoma (e.g., liver cancer, liver neoplasm, liver malignant neoplasm), and prognosis (e.g., overall survival, disease-free survival, outcome, mortality, recurrence). The language was restricted to English, and studies were only on humans. Only full papers and published studies in the medical literature were included. Data from abstracts, review articles, editorials, case reports, and letters were not included. Characteristics of the studies were extracted from published articles and summarized in a uniform manner to aid comparison. All candidate articles were read independently by 4 reviewers (Wang WM, Xu Y, Yang XR and Fan J) and scored according to NOQAS.<sup>[17]</sup> This scoring system is described in a recent systematic review.<sup>[17]</sup> We only changed the contents of "comparability (1) a" to "study controls for tumor grade". When necessary, authors were contacted. Any discrepancies were resolved by a consensus in regular meetings attended by at least three-quarters of the investigators.

#### Statistical analysis

The association between DM status, OS and RFS was

derived by summarizing the  $\log_e$  (HRi) (LnHRi) from the eligible studies with inverse variance weights. The LnHRi and the corresponding standard error [SE(LnHRi)] were used as data points for the meta-analysis. LnHRi was estimated from the presented parameters (O-E statistic and its variance, HR point estimate or its CI, events in each arm or total events, numbers randomized on each arm, *P* value, numbers at risk in each group) using the methods described by Parmar et al.<sup>[18]</sup> If no numerical data for the estimation of summary statistics were given, data were extracted manually from Kaplan-Meier survival curves to reconstruct the HR estimate. The rate of patients censored was presumed constant during the study follow-up.<sup>[18]</sup> When censoring data were presented, censored subjects were allocated to the appropriate time interval. Survival curves were read by Engauge Digitizer 4.1 software (<http://digitizer.sourceforge.net/>) after magnification to improve the accuracy. In the study by Nagasue et al,<sup>[19]</sup> insufficient data were presented to extract data of OS/RFS by any of the methods described above. No significant difference was reported in survival outcome between the coexistence of DM and without DM in HCC.

For the meta-analysis, the HR was assigned to be 1.00, and a variance of LnHRi was assumed for similar sized studies (Kawamura et al<sup>[12]</sup>) to avoid selection bias.<sup>[20]</sup> *P* values quoted less than the specified threshold were assumed to be at the threshold, resulting in a conservative estimate of significance level.<sup>[21]</sup>

The combined HR was displayed in Forest plots. And  $I^2$  and *Q* estimates were performed in statistical assessment. If the  $I^2$  value was >50% or the *P* value was less than 0.1, representing significant heterogeneity, a Der Simonian-Laird random-effects model (D+L) was used. Otherwise, an inverse variance fixed-effects model (I-V) was selected.<sup>[22]</sup> Assessment of publication bias was performed using the Begg's/Egger's bias indicator test.<sup>[23]</sup> For all tests, a *P* value was two-sided and less than 0.05 was considered statistically significant unless specially described.

All statistical analyses were conducted using the HR calculations spreadsheet in Microsoft Excel<sup>[24]</sup> and Stata 11.0 statistical software (Stata Corp, College Station, TX, USA).

### Results

#### Eligible studies

Eighty-two potential articles were included through the search strategy. After viewing the contexts, 29 candidate studies were identified according to the requirements. Upon further analysis, 3 were about

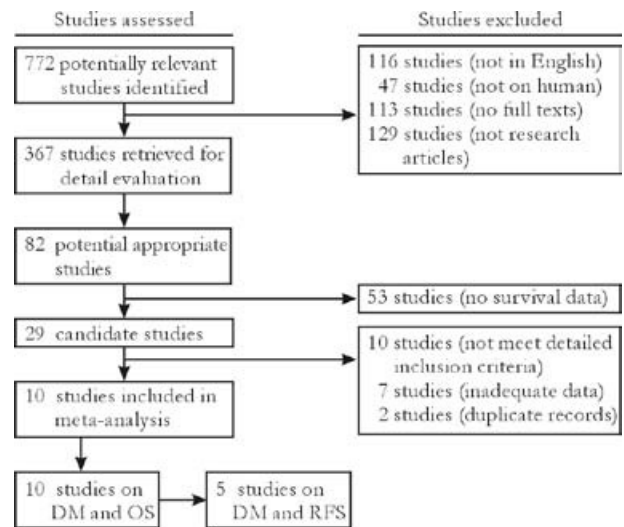
liver transplantation,<sup>[25-27]</sup> 2 just reflected that DM is a risk factor for hepatic decompensation,<sup>[28, 29]</sup> 1 showed that DM is linked with acute renal failure, which is a poor predictor for HCC,<sup>[30]</sup> 1 identified the risk factors predicting major postoperative complications,<sup>[31]</sup> 3 were about glucose intolerance and insulin resistance,<sup>[32-34]</sup> and 19 related to survival/mortality stratified by DM status. Among the 19 potential studies, 9 were eliminated due to inadequate data<sup>[35-43]</sup> and duplicate records for analysis<sup>[13, 44]</sup> (Fig. 1). While the duplicate study separately analyzed the impact of DM on the OS and recurrence of HBV- or HCV-related HCC undergoing resection,<sup>[44]</sup> we selected it for the survival analysis of DM and the interaction with viral factors. Finally, 10 eligible studies were included in this meta-analysis.<sup>[9-14, 19, 45, 46]</sup> All 4081 patients (sample size range 40-1713) in this study came from Asia. The mean age of most patients was 52.4-67.4 years (range 33.0-79.0), and 85% were male. The research period was from 1985 to 2008, and the median follow-up time was explicitly stated in 7 studies (range 18-54 months; median 33 months). Five trials (containing 1275 patients) analyzed the relationship of DM and RFS, and the other 5 studies were about the cumulative recurrence rate (RR). The characteristics of these studies are summarized in Table 1.

**Survival analysis**

Of the 10 eligible studies for pooling of OS/RFS data, none provided data for a direct estimation of LnHRi. In the analysis of the impact of DM status on OS of HCC patients, 8 HRi values were above 1.00, indicating that HCC patients with DM had a worse prognosis. Of these patients, 4 had a lower 95% CI above 1.00, suggesting a significant effect.

The forest plot in Fig. 2A shows the HRi and 95% CI for all studies in OS, and a pooled HR of 1.34 (95%

CI, 1.18-1.51;  $P < 0.0001$ ) using a fixed-effects analysis, and of 1.37 (95% CI, 1.17-1.60;  $P < 0.0001$ ) in a random-effects analysis. DM was confirmed as a poor prognostic factor of HCC in OS. No evidence of heterogeneity was found between studies ( $Q = 10.78$ ,  $I^2 = 16.5\%$ ,  $P = 0.291$ ), and the result of the fixed-effects model was accepted preferentially. To assess the effect of assuming an HRi of 1.00 for OS, it<sup>[19]</sup> was excluded and reanalyzed. It remained unchanged in the pooled HR=1.35 (95% CI, 1.19-1.53,  $P < 0.0001$ ;  $Q = 10.20$ ,  $I^2 = 21.6\%$ ,  $P = 0.251$ ). One study<sup>[19]</sup> with the largest weights was excluded, and HR was 1.46 (95% CI, 1.23-1.74,  $P < 0.0001$ ;  $Q = 8.74$ ,  $I^2 = 8.4\%$ ,  $P = 0.365$ ). Similarly, the overall effect remained virtually unchanged (HR=1.32, 95% CI, 1.16-1.50,  $P < 0.0001$ ;  $Q = 9.81$ ,  $I^2 = 18.4\%$ ,  $P = 0.279$ ) after removal of the lower



**Fig. 1.** Flowchart of study identification, rejection and selection in the meta-analysis.

**Table 1.** Individual studies in meta-analysis

Authors	Study design	Country/Region	Period (yr)	Patient (male %)	DM (n, %)	DM cut-off (mg/dL)	Quality points	Treatment type	Child grade A/B/C	HBV/HCV-related (n, %)	Cirrhosis (n, %)	Survival analysis
Ikeda et al	Unclear	Japan	1985-1995	342 (80.4)	87 (25.4)	140	6	S	NR	B64 (18.7)/C144 (42.1)	NR	OS, RFS
Nagasue et al	R	Japan	1986-1996	63 (73.0)	45 (71.4)	140	5	S	0/46/17	B16 (25.4)/C29 (39.7)	55 (87.3)	OS, RFS
Toyoda et al	R	Japan	1990-1999	581 (73.1)	92 (15.8)	144 <sup>†</sup>	7	S, NS, NT	313/204/64	B103 (17.7)/C422 (72.6)	520 (89.5)	OS, RR
Poon et al	P	Hong Kong, China	1989-1999	525 (81.3)	62 (11.8)	140	6	S	503/22/0	B437 (83.2)/C16 (3.0)	251 (47.8)	OS, RFS, RR
Huo et al	C, R	Taiwan, China	1996-1999	239 (87.9)	39 (16.3)	126	6	S	NR	B162 (67.8)/C41 (17.2)	108 (45.2)	OS
Huo et al a	P	Taiwan, China	1996-2001	255 (86.3)	41 (16.1)	126	5	S	255/0/0	B189 (74.1)/CNR	120 (47.1)	OS, RFS, RR
Huo et al b	P	Taiwan, China	1996-2001	312 (81.1)	79 (25.3)	126	5	NS	222/90/0	B184 (59.0)/CNR	NR	OS
Komura et al	R	Japan	1987-2004	90 (83.3)	30 (33.3)	126	6	S	77/13/0	B25 (27.8)/C62 (68.9)	NR	OS, RFS, RR
Amarpurkar et al	C, P	India	1997-2006	160 (84.4)	46 (28.8)	126	4	S, NS	*-/ */107	B57 (35.7)/C19 (11.9)	NR	OS
Kawamura et al	C, R	Japan	1980-2006	40 (87.5)	18 (45.0)	126	6	S, NS	NR	B0/C0	29 (72.5)	OS, RR
Huo et al	P	Taiwan, China	2002-2008	1713 (76.6)	392 (22.9)	126	5	S, NS	1281/339/93	B943 (55.0)/C538 (31.4)	Re	OS

Study design is described as consecutive patients (C), prospective (P), or retrospective (R). Treatment describes whether the patients received curative surgical resection (S). NS: non-surgical treatment (e.g., PAI or PEI, RFA, TACE, or medical management); or NT: no treatment. DM cut-off: all were fasting plasma glucose level except #. NR: not related; Re: related but the contents was not described. Incomplete data are indicated with an asterisk (\*). Study quality is listed using the results of the NOQAS; and total scores are 9.

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quality point study.<sup>[10]</sup> Integrating the HRi of 6 studies with curative treatments,<sup>[11-14, 19, 45]</sup> HR was 1.43 (95% CI, 1.18-1.75,  $P<0.0001$ ;  $Q=8.18$ ,  $I^2=38.9\%$ ,  $P=0.147$ ) shown by fixed-effects analysis (Table 2, Fig. 3).

Limiting analysis to the 5 studies<sup>[11, 12, 19, 45, 46]</sup> assessing DM coexisting in Japanese HCC patients revealed the pooled HR to be 1.60 (Table 2). Four studies estimated this in a Chinese population,<sup>[9, 13, 14]</sup> and the summary HR was 1.21 (Table 2, Fig. 4).

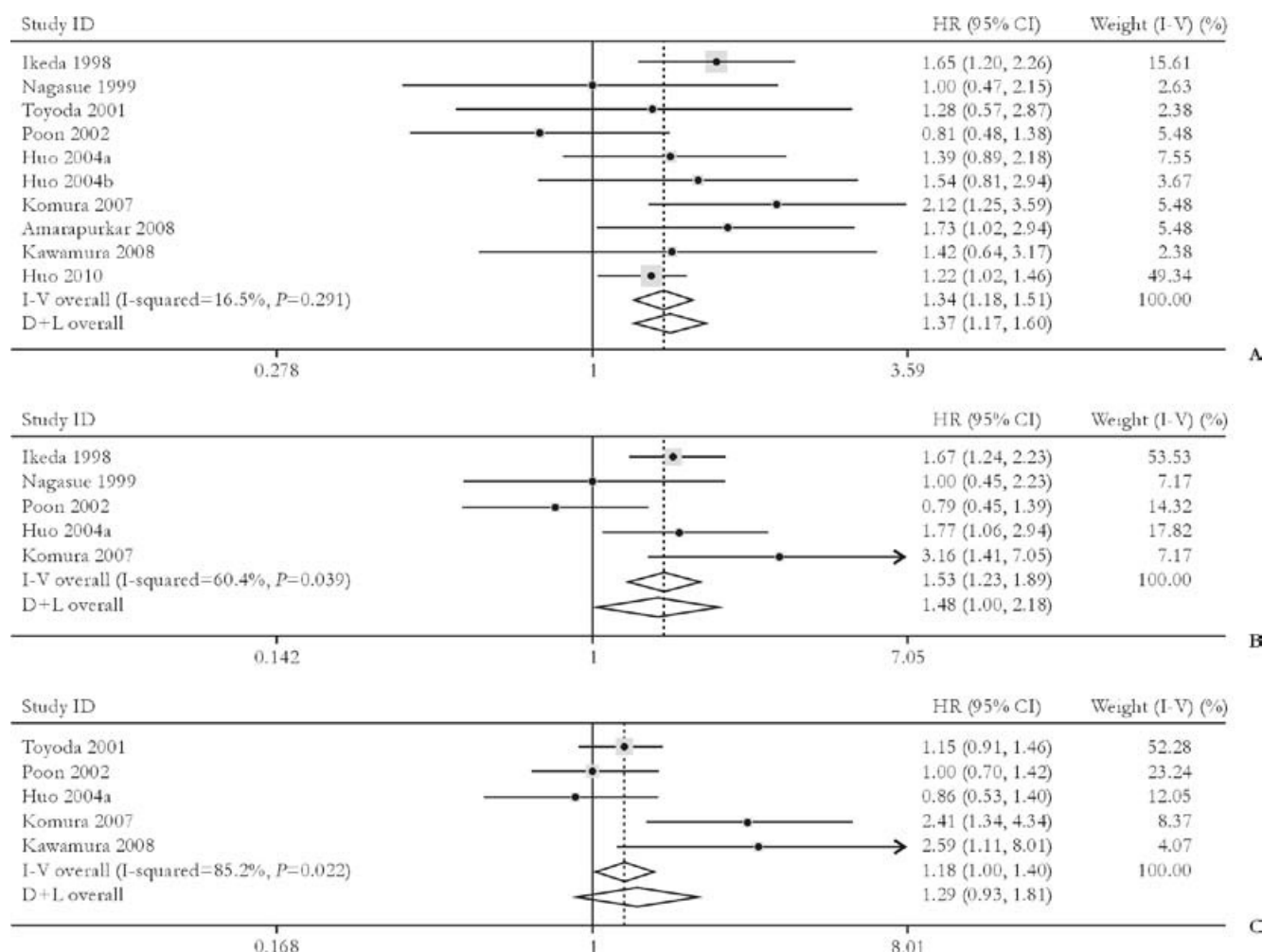
Prognostic significance of DM only occurred in HCV-related HCC patients ( $P=0.016$ ). HR was 1.29 in HBV-related HCCs, with evidence of study heterogeneity, while the HR was 1.71 in the HCV-related HCCs (Table 2,

Fig. 5).

According to tumor size, the pooled HR was 1.63 and 0.67 in the groups with tumor diameter  $\leq 5$  cm and  $>5$  cm respectively (Table 2).<sup>[13, 14, 46]</sup> DM coexistence impaired OS (HR=1.63,  $P<0.0001$ ) in HCC patients with tumor diameter  $\leq 5$  cm (Fig. 6).

### Impact of DM on RFS and RR

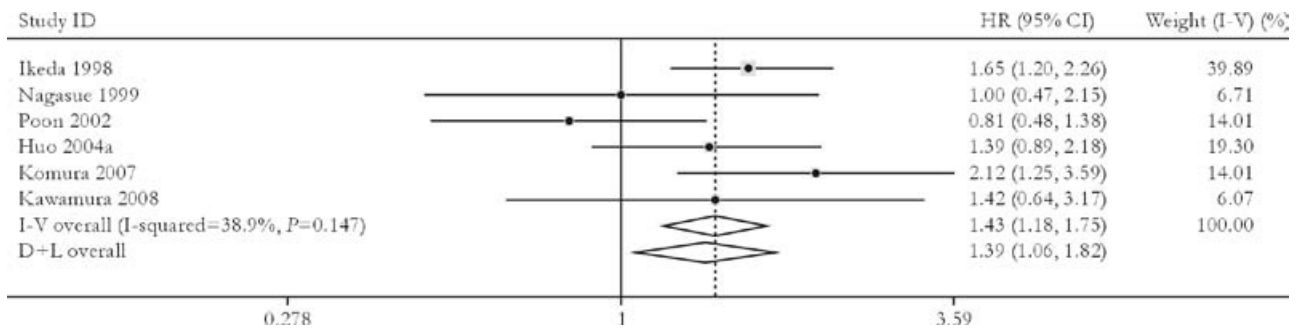
For RFS, 3 lower 95% CI of the HRi values were above 1.00.<sup>[11, 13, 45]</sup> For RR, 2 stated lower 95% CI  $>1.00$  and DM worsened the RR.<sup>[11, 12]</sup> HRi values were recorded for the included studies using available data and the techniques described above.



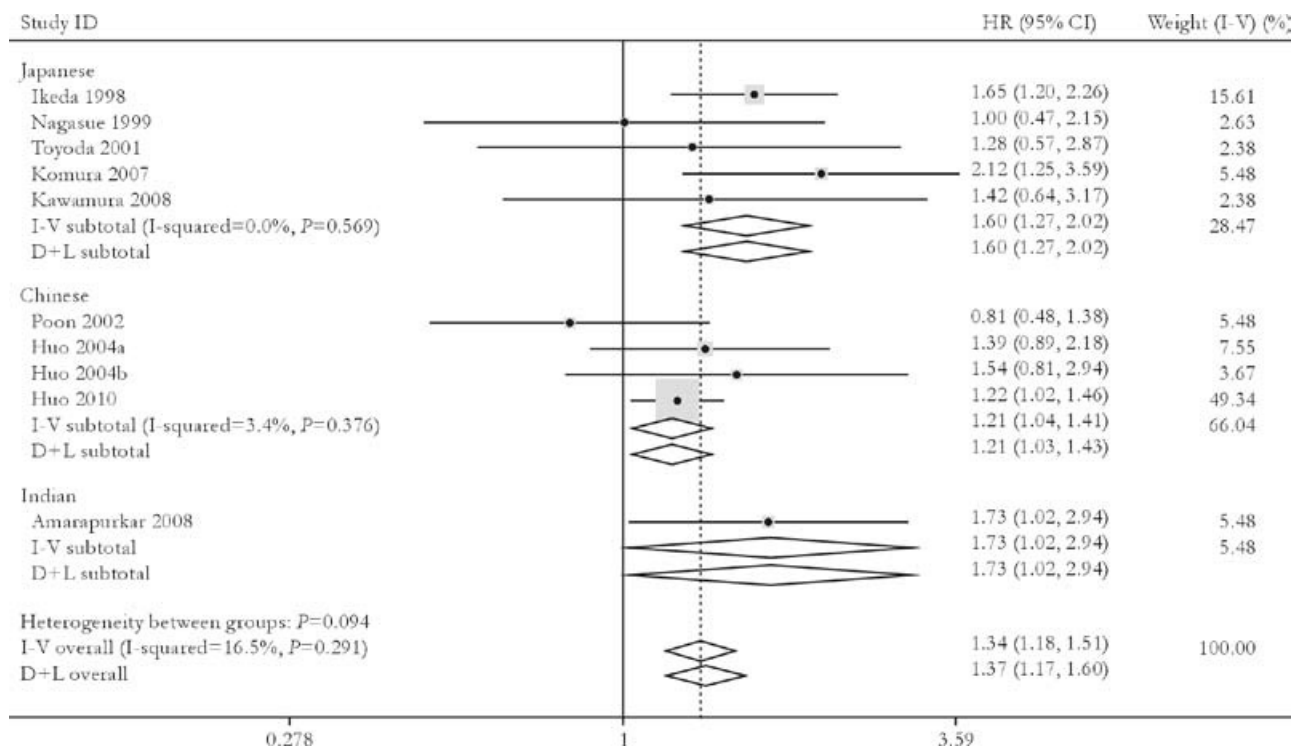
**Fig. 2. A:** Forest plot of HR for OS from HCC associated with coexisting DM status. DM coexistence was a predictor of worse survival of OS in HCC (HR=1.34,  $P<0.0001$ ). **B:** Forest plot of HR for RFS from HCC associated with DM status in 5 studies. The summary HR value (HR=1.48,  $P<0.0001$ ) implies a worse RR for the group with DM. **C:** Forest plot of HR for RR from HCC associated with DM status in 5 studies. The summary HR value (HR=1.29,  $P=0.022$ ) implies a worse RR for the group with DM. It includes combined HR calculated using both the general inverse variance fixed effects (I-V) and Der Simonian-Laird random effects models (D+L) as well as the evaluation for heterogeneity ( $I^2$ ). Horizontal lines represent 95% CI. Black boxes indicate the HRi point estimate, and their areas are proportional to the weights of the studies. The broken line and diamond represent the summary estimate. The unbroken vertical line is at the null value (HR=1.0).

**Table 2.** Results of meta-analysis

	Study (n)	HR value (summary measure)	95% CI	P value (overall effect)	Q estimates	I <sup>2</sup> value (%)	P value (test for heterogeneity)	Effects model selected
OS	10	1.34	1.18-1.51	<0.0001	10.78	16.5	0.291	Fixed
Japanese	5	1.60	1.27-2.02	<0.0001	2.94	0.0	0.569	Fixed
Chinese	4	1.21	1.04-1.41	0.013	3.10	3.4	0.376	Fixed
HBV-related	3	1.29	0.69-2.40	0.182	5.25	61.9	0.072	Random
HCV-related	3	1.71	1.10-2.66	0.016	2.87	30.3	0.238	Fixed
Diameter ≤5 cm	3	1.63	1.25-2.12	<0.0001	0.56	0.0	0.754	Fixed
Diameter >5 cm	2	0.67	0.39-1.15	0.145	0.71	0.0	0.398	Fixed
Curative treatments	6	1.43	1.18-1.75	<0.0001	8.18	38.9	0.147	Fixed
RFS	5	1.48	1.00-2.18	<0.0001	10.09	60.4	0.039	Random
RR	5	1.29	0.93-1.81	0.045	11.48	65.2	0.022	Random



**Fig. 3.** Forest plot of the HR of OS on subgroup analysis of those undergoing curative treatments. HCC patients with DM had a poor OS (pool HR=1.43, P<0.0001).



**Fig. 4.** Forest plot of the HR of OS on subgroup analysis based on genetic backgrounds.



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In Fig. 2B, the forest plot displays the HRi and 95% CI for 5 studies in RFS, and the summary HR was 1.48 (Table 2) using a random-effects analysis. The heterogeneity was discovered using a restrictive  $I^2$  test.<sup>[14]</sup> Omitting this study gave a similar result (HR=1.70, 95% CI, 1.35-2.15,  $P<0.0001$ ;  $Q=4.00$ ,  $I^2=25.0\%$ ,  $P=0.262$ ), except there was nearly no heterogeneity. The pooled HR was 1.58 (95% CI, 1.02-2.45,  $P<0.0001$ ;  $Q=8.95$ ,  $I^2=66.5\%$ ,  $P=0.030$ ) after excluding the study and assuming HR of 1.00.<sup>[19]</sup> If one study with the largest weights<sup>[45]</sup> was excluded, HR was 1.42 (95% CI, 1.80-2.53,  $P=0.046$ ;  $Q=9.36$ ,  $I^2=68.0\%$ ,  $P=0.025$ ). Similarly, the overall effect remained virtually unchanged (HR=1.54,

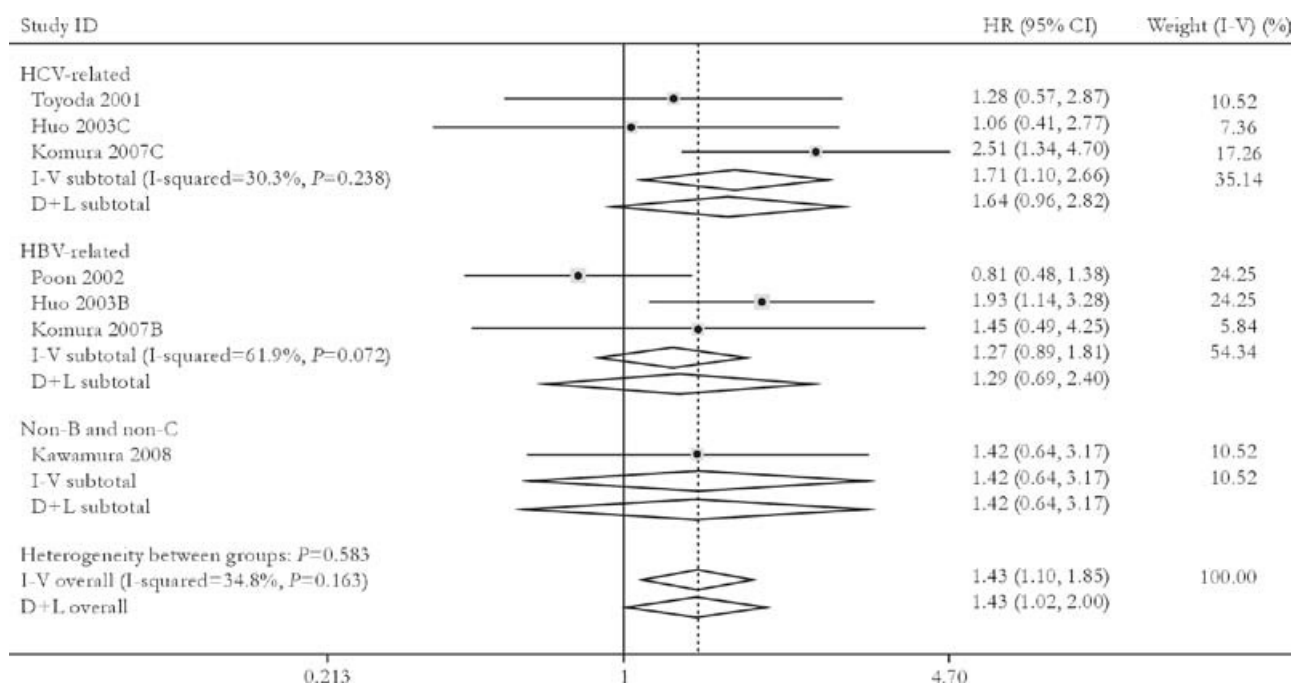
95% CI, 0.81-2.93,  $P=0.001$ ;  $Q=8.71$ ,  $I^2=77.0\%$ ,  $P=0.013$ ) when the lower quality point studies were removed.<sup>[13,19]</sup>

The forest plot in Fig. 2C displays the HRi and 95% CI for 5 studies in RR;<sup>[11-14,46]</sup> the pooled HR was 1.29 (Table 2).

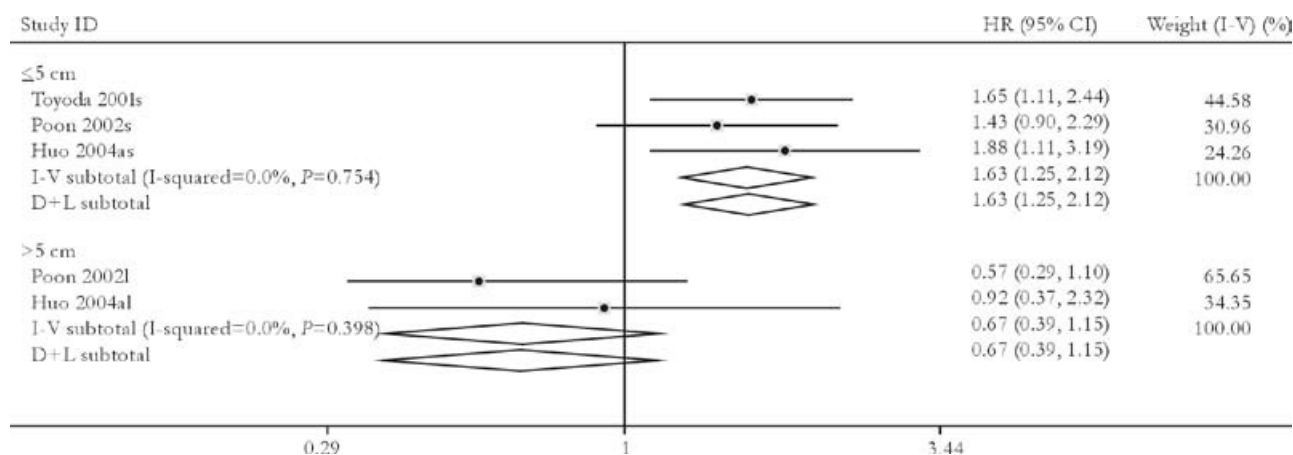
All of these results indicated that DM was an important predictor for HCC patients after curative treatments.

### Assessment of publication bias

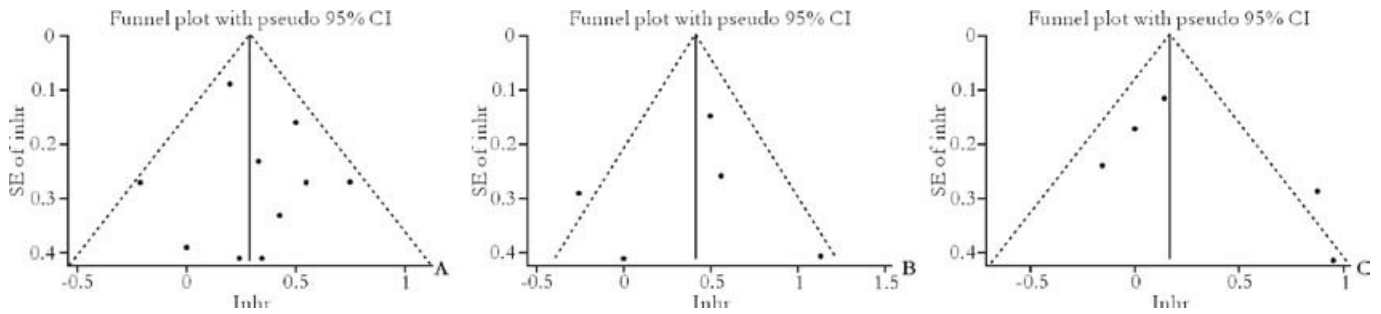
No evidence of overt publication bias was found in these studies by using visual assessment of the funnel plot (Fig. 7A), or formal evaluation using Begg's ( $P=0.916$ ) and Egger's tests ( $P=0.748$ ) (Fig. 8A).



**Fig. 5.** Forest plot of the HR of OS on subgroup analysis based on viral status. HCC patients with DM and HCV had a poor OS (pool HR=1.71,  $P=0.016$ ).



**Fig. 6.** Forest plot of the HR of OS on subgroup analysis based on tumor diameter. HCC patients with DM had a poor OS if diameter ≤5 cm (pooled HR=1.63,  $P<0.0001$ ).



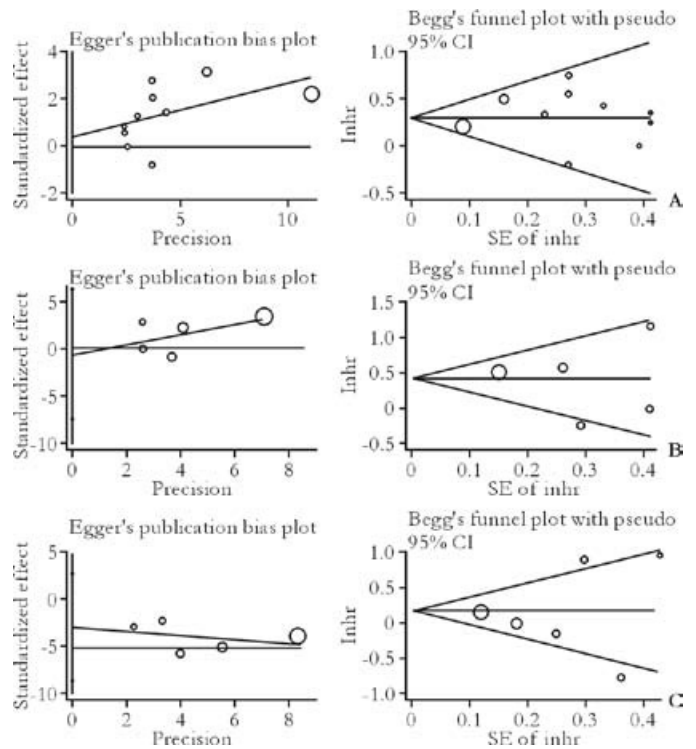
**Fig. 7.** Funnel plot of the HR of OS (A), RFS (B), and RR (C) from HCCs associated with DM status in the studies. It displays HR on a log scale against its standard error (SE) for each study included in the meta-analysis. The vertical line indicates the pooled estimate of the LnHR, with the sloping lines representing the expected 95% CI for a given SE. Under the assumption of no heterogeneity between studies, 95% of studies lie between or on these two lines.

Similarly, there was no significant publication bias in the RFS and RR studies ( $P=1.000, 0.816$  and  $0.734, =0.389$ , respectively) (Fig. 8B, C) although one study was outside the pseudo 95% CI line in the funnel plot (Fig. 7B, C).

**Discussion**

DM is a global problem with devastating human, social and economic impact. Its prevalence has reached epidemic proportions.<sup>[47]</sup> Growing evidence shows that DM is an independent risk for several common human malignancies, including HCC.<sup>[4]</sup> Meanwhile, HCC patients, commonly with chronic liver disease and a cirrhosis background, are predisposed to DM. As a result, identifying the effect of DM on the prognosis of HCC can guide clinical decision-making on therapy and prevention.

In this study, we used meta-analysis to investigate the effect of DM as a coexisting condition on the long-term outcome of HCC patients based on 10 eligible published studies. Pooled estimates showed that DM as a concomitant disease correlated with poor prognosis and high RR in Asian HCC patients who underwent curative treatments. Many published studies have investigated possible mechanisms of the influence of DM on HCC. First, patients with DM always have insulin resistance which can cause compensatory hyperinsulinemia. It has been reported that hyperinsulinemia is associated with an increasing growth rate of HCC.<sup>[48]</sup> Meanwhile, Dellon et al<sup>[49]</sup> reported that hyperinsulinemia can promote the phosphorylation and activation of AKT and ERK pathways via interaction with the insulin receptor, which may play important roles in tumor development and progress. Furthermore, diabetics have a disorder in insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-1 (IGFBP-1) levels.<sup>[50]</sup> Once they are combined, this induces a conformational change which results in autophosphorylation to convert



**Fig. 8.** Detecting publication bias on OS (A), RFS (B), and RR (C) using the Egger's and Begg's funnel plot.

to the active form.<sup>[51]</sup> This event triggers the initiation of multiple downstream signaling pathways, including the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) signaling cascades, which results in cellular proliferation and inhibition of apoptosis.<sup>[51-53]</sup> Finally, as a result of hyperglycemia, oxidative stress is a key in the pathogenesis and complications of DM.<sup>[54]</sup> Free radicals caused by oxidative stress mediate endothelial cell dysfunction, which plays an important role in the various stages of tumor progression and metastasis.<sup>[55]</sup>

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Further, we explored the prognostic role of DM in HCC subgroups with different virus infection backgrounds, and found that patients with DM had a shorter survival time in HCV-related HCC, while HBV-related cases were not significantly different. This may be related to different modes of pathogenesis of HBV- and HCV-related HCC. The prevalence of DM and insulin resistance is higher in patients with HCV infection than in those with HBV.<sup>[56]</sup> Chronic inflammation and oxidative stress are closely associated with the death and regeneration of hepatocytes in HCV-related HCC.<sup>[57]</sup> Patients with DM in these cohorts may have a worse progression of liver fibrosis and an increase in the development of HCC in HCV-related liver disease.<sup>[58]</sup> Moreover, a series of hepatic molecules regulating glucose metabolism are modulated by HCV infection. HCV core-induced suppressor of cytokine signaling 3 promotes proteosomal degradation of insulin receptor substrate (IRS) 1 and 2 through ubiquitination; then the disruption of IRS1 and IRS2, respectively results in insulin resistance and DM.<sup>[59]</sup> While in HBV-related liver disease, integration of the viral genome into the host DNA appears to induce HCC<sup>[60]</sup> and the coexistence of DM may have little synergistic effect on such a mechanism. In HBV carriers, chronic HBV infection seems not to be related to insulin resistance or hepatic steatosis.<sup>[61]</sup> But these results also should be interpreted with prudence considering the small number of included studies.

We also found that coexisting DM impaired OS of HCC patients with a small tumor burden, which implied that close surveillance and controlling the level of blood glucose may improve the prognosis of these patients. However, the results still need to be interpreted with caution due to the heterogeneity and poor representation of contributing studies. For RFS and RR, the prognostic role of DM in subgroups with different virus infection backgrounds and tumor diameter could not be analyzed owing to an absence of adequate data.

Many other factors, such as tumor stage, liver function and degree of liver fibrosis may affect the survival of patients with DM. Unfortunately these data were not explicitly reported in the studies. Furthermore, meta-regression should be carried out to reveal any significant associations between the most important factors (study size, year of publication, length of follow-up, type of DM, method of data presentation and extraction) with outcome. However, this was not performed owing to a small number of studies included in the analysis. Several studies noted that anti-diabetic therapies can affect the survival of HCC patients, but no abundant data were received for meta-analysis. An Italian

study indicated that patients with DM, particularly males and treated with insulin, had an increased frequency of HCC.<sup>[62]</sup> In a population-based cohort study, diabetics exposed to sulfonylureas and insulin had a significantly increased risk of cancer-related mortality compared to those exposed to metformin.<sup>[63]</sup> The former anti-diabetic drugs might facilitate tumor development by increasing circulating insulin levels, but metformin as an insulin-sensitizer against hyperinsulinemia may reduce the risk of cancer.<sup>[64]</sup>

Heterogeneity or publication bias between studies should be noted in assessing the validity of clinical research studies because it detects potentially important differences using a small number of primary studies analyzed in each group. No evidence of significant heterogeneity was found in OS and RFS analysis. To lower or even avoid bias, we identified all the key published analyses and used rigid inclusion criteria in selecting studies. Some potential sources of heterogeneity or bias in this meta-analysis may be attributed to therapies for DM and HCC, tumor stage, inadequate blinding of survival data from assessors, estimate of HR, ethnic background and language.

In summary, the meta-analysis results support the hypothesis that coexisting DM status is a prognostic factor for a poor outcome in HCC patients, especially those with HCV infection. However, studies that are better designed, especially homogeneous HCC cohorts analyzed prospectively, are required to unequivocally estimate the precise prognostic effect of DM coexistence in HCC patients. Moreover, the underlying mechanism of the effect of DM on the prognosis of HCC should be elucidated clearly so that an effective strategy can be identified to reduce the negative impact after operation.

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