

## Risk factors for new onset diabetes mellitus after liver transplantation: A meta-analysis

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Received: August 23, 2014

Peer-review started: August 23, 2014

First decision: September 23, 2014

Revised: October 16, 2014

Accepted: December 14, 2014

Article in press: December 16, 2014

Published online: May 28, 2015

diabetes mellitus (NODM) after liver transplantation by conducting a systematic review and meta-analysis.

**METHODS:** We electronically searched the databases of MEDLINE, EMBASE and the Cochrane Library from January 1980 to December 2013 to identify relevant studies reporting risk factors for NODM after liver transplantation. Two authors independently assessed the trials for inclusion and extracted the data. Discrepancies were resolved in consultation with a third reviewer. All statistical analyses were performed with the RevMan5.0 software (The Cochrane Collaboration, Oxford, United Kingdom). Pooled odds ratios (OR) or weighted mean differences (WMD) with 95% confidence intervals (CIs) were calculated using either a fixed effects or a random effects model, based on the presence ( $I^2 < 50\%$ ) or absence ( $I^2 > 50\%$ ) of significant heterogeneity.

**RESULTS:** Twenty studies with 4580 patients were included in the meta-analysis, all of which were retrospective. The meta-analysis identified the following significant risk factors: hepatitis C virus (HCV) infection (OR = 2.68; 95%CI: 1.92-3.72); a family history of diabetes (OR = 1.69, 95%CI: 1.09-2.63,  $P < 0.00001$ ); male gender (OR = 1.53; 95%CI: 1.24-1.90;  $P < 0.0001$ ); impaired fasting glucose (IFG; OR = 3.27; 95%CI: 1.84-5.81;  $P < 0.0001$ ); a family history of diabetes (OR = 1.69; 95%CI: 1.09-2.63;  $P = 0.02$ ); use of tacrolimus (OR = 1.34; 95%CI: 1.03-1.76;  $P = 0.03$ ) and body mass index (BMI)(WMD = 1.19, 95%CI: 0.69-1.68,  $P < 0.00001$ ). Other factors, such as hepatitis B virus infection and alcoholism, were not found to be associated with the incidence of NODM.

**CONCLUSION:** The study showed that HCV infection, IFG, a family history of diabetes, male gender, tacrolimus and BMI are risk factors for NODM after liver transplantation.

### Abstract

**AIM:** To determine the risk factors for new-onset

**Key words:** Diabetes mellitus; Meta-analysis; Risk

factor; Liver transplantation; Hepatitis C virus

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**Core tip:** New-onset diabetes mellitus (NODM) is a serious complication of liver transplantation (LT) that negatively affects patient and graft survival. However, the risk factors for NODM after LT have not been well elucidated. It has been reported that many factors are involved in the development of NODM. This meta-analysis demonstrated that hepatitis C virus infection, impaired fasting glucose, a family history of diabetes, male gender, tacrolimus and body mass index are risk factors for NODM after liver transplantation.

Li DW, Lu TF, Hua XW, Dai HJ, Cui XL, Zhang JJ, Xia Q. Risk factors for new onset diabetes mellitus after liver transplantation: A meta-analysis. *World J Gastroenterol* 2015; 21(20): 6329-6340 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i20/6329.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i20.6329>

## INTRODUCTION

New-onset diabetes mellitus (NODM) is a serious complication of liver transplantation (LT) that negatively affects patient and graft survival. The reported incidence of NODM after LT ranges from 9% to 63.3%<sup>[1-6]</sup>. Similar incidence rates of and risk factors for NODM have also been reported in renal transplantation<sup>[7-9]</sup>. NODM contributes to an increased risk of infections, cardiovascular disease and rejection, all of which are leading causes of mortality among LT recipients<sup>[6,10-12]</sup>. However, the mechanisms underlying NODM after LT are poorly understood.

Age, gender, body mass index (BMI), hepatitis C virus (HCV) infection, immunosuppressive regimens, and a family history of diabetes have been reported as the main risk factors for the development of NODM after LT<sup>[1,13-15]</sup>, although many controversial issues remain. For example, HCV-induced cirrhosis, one of the most studied risk factors, is the leading indication for LT<sup>[16]</sup> and has been identified as a major risk factor for the development of NODM in solid organ transplant recipients. A recent study based on the OPTN/UNOS database demonstrated that HCV infection is an independent risk factor for NODM in the liver transplant population. NODM was found to occur more frequently in HCV-positive patients (28.3% vs 23.7%, HR = 1.155), although some studies did not find any statistical association between HCV infection and post-transplant NODM<sup>[3,6,17]</sup>. However, comparing the rates of NODM between studies is often complicated by the varying definitions of NODM and differing follow-up periods.

The aim of this meta-analysis was to identify risk factors for the development of NODM after LT.

## MATERIALS AND METHODS

### Search strategy and data extraction

Two of the authors searched studies published between January 1980 and December 2013 via MEDLINE, EMBASE, and the Cochrane Library. The search strategy included the terms "diabetes mellitus", "diabetes", "liver transplantation" and related synonyms. Two authors independently screened the titles and abstracts of the retrieved papers, and full-text copies were obtained of most of the potentially relevant studies. The reference lists of the retrieved publications were also comprehensively reviewed to identify additional potentially relevant studies. Discrepancies were resolved in consultation with a third reviewer. This search was limited to human studies, without any language limitations; both case-controlled studies and observational studies were included.

### Criteria for inclusion

The studies included in the meta-analysis had to satisfy the following criteria: (1) randomized controlled trials and prospective or retrospective cohort and case-control studies investigating patients with NODM after LT; (2) adult recipients aged more than 18 years with no history of diabetes mellitus pre-transplantation; (3) follow-up period > 6 mo; and (4) description of an accurate incidence of NODM after LT that could be extracted for the meta-analysis.

### Criteria for exclusion

We excluded studies meeting the following criteria: (1) recipient age < 18 years; (2) recipients with diabetes mellitus before transplantation; (3) complete data that were unavailable for the meta-analysis; (4) use of a definition of NODM that did not meet the criteria of the 2003 International Consensus Guidelines; (5) follow-up time less than 6 mo or loss to follow-up rate greater than 10%; and (6) studies enrolling patients who had undergone multiple transplants.

### Definition

NODM was defined according to the American Diabetes Association/World Health Organization (ADA/WHO) criteria (see Table 1)<sup>[18,19]</sup>, as described in the 2003 International Consensus Guidelines for the diagnosis of post-transplantation NODM [fasting blood glucose > 126 mg/dL (7.0 mmol/L) on at least two separate occasions, and/or 2-h post-prandial blood sugar > 200 mg/dL (11.1 mmol/L)]. Alternatively, DM was defined as a requirement for glucose-lowering medications (insulin or oral hypoglycemic agents for > 1 mo)<sup>[20]</sup>.

### Quality assessment

Study quality was evaluated using the Newcastle-Ottawa scale, which was designed especially for observational case control and cohort studies. The scale includes three separate categories, using counts

**Table 1** American Diabetes Association Criteria for diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance

Terminology		
FPG (mg/dL)	< 100	Normal
	100-125	IFG
	> 126	Diabetes mellitus
2-h glucose after 75 g oral glucose load	< 140	Normal
	140-199	IGT
	> 200	Diabetes mellitus

FPG: Fasting plasma glucose; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance.

of 1-9 as the assessment score. The total score is 9, including 4 for selection part, 2 for comparability part, and 3 for outcome part. A total score  $\geq 7$  represents high quality (see Table 2).

### Statistical analysis

The meta-analysis was performed using RevMan 5.0, according to the Cochrane Handbook for Systematic Reviews of Interventions, as recommended by the Cochrane Collaboration. Odds ratios (OR) and mean differences (MD) were calculated for each principal outcome for dichotomous and continuous variables, respectively. The 95% confidence intervals (95% CIs) were calculated for all parameters. Heterogeneity among the trials was assessed with the Cochran's  $Q$  test and  $I^2$  statistics. The meta-analysis was performed with a random-effect or fixed-effect model, based on the presence ( $I^2 < 50\%$ ) or absence ( $I^2 > 50\%$ ) of significant heterogeneity. Potential publication bias was assessed using a funnel plot, if necessary. A sensitivity analysis was also conducted by excluding individual studies in turn to evaluate the influence of a single study on the pooled estimates.

## RESULTS

### Literature review

We identified 1408 potentially relevant citations with our initial search strategy, 418 of which were excluded due to duplication. A further 941 were excluded after reviewing the titles and abstracts because they were not relevant to our analysis, and 29 more were excluded after reviewing the full articles, mainly because they did not meet the inclusion criteria. Ultimately, 19 studies involving 4580 patients were included in our meta-analysis<sup>[1-3,5,6,10,13-15,17,21-29]</sup>. The process used for article selection is presented in Figure 1. Quality assessment of the included studies was shown in Table 2, and all studies got a total score  $\geq 6$ .

### Patient characteristics

Some of the principal demographic and clinical characteristics of subjects enrolled in the included clinical trials are shown in Tables 3 and 4. Four of the

**Table 2** Newcastle-Ottawa scoring system for cohort studies

Study	Selection score	Comparability score	Outcome score	Total score
Saliba <i>et al</i> <sup>[1]</sup>	4	2	3	9
Parolin <i>et al</i> <sup>[14]</sup>	3	1	3	7
Baid <i>et al</i> <sup>[10]</sup>	3	2	3	8
Schmilovitz <i>et al</i> <sup>[21]</sup>	3	1	3	7
Moon <i>et al</i> <sup>[6]</sup>	4	1	2	7
Kishi <i>et al</i> <sup>[22]</sup>	4	2	3	9
Khalili <i>et al</i> <sup>[13]</sup>	3	2	3	7
Yoshida <i>et al</i> <sup>[15]</sup>	3	2	3	8
Gelley <i>et al</i> <sup>[23]</sup>	3	2	3	8
Dehghan <i>et al</i> <sup>[17]</sup>	4	2	2	8
Harada <i>et al</i> <sup>[24]</sup>	3	2	2	7
Anderson <i>et al</i> <sup>[25]</sup>	3	1	3	7
Ling <i>et al</i> <sup>[26]</sup>	3	2	2	7
Zhao <i>et al</i> <sup>[27]</sup>	3	2	1	6
Sánchez-Pérez <i>et al</i> <sup>[28]</sup>	3	2	3	7
Mirabella <i>et al</i> <sup>[5]</sup>	3	2	3	8
Driscoll <i>et al</i> <sup>[29]</sup>	3	1	3	7
Honda <i>et al</i> <sup>[3]</sup>	3	2	3	8
Carey <i>et al</i> <sup>[2]</sup>	4	1	3	8

studies (20%) were from Europe; eight (40%) from North or South America; and eight (40%) from Asia. The overall incidence of NODM post-LT among the included studies was 30.2% (1385/4580), ranging from 10.2%<sup>[28]</sup> to 63.3%<sup>[6]</sup>.

### Summary estimates of the outcomes

**HCV infection:** A total of 14 studies including 3362 LT recipients were included in the meta-analysis to explore the relationship between NODM and HCV infection. The incidence of NODM was 25.4% (855/3362) overall, 34.0% (372/1095) among HCV (+) recipients, and 21.3% (483/2267) among HCV (-) patients. HCV infection was associated with a statistically significantly higher incidence of NODM in a random effects model, with a pooled OR of 2.68 (95%CI: 1.92-3.72; Figure 2). This result is consistent with most previous studies. There was high heterogeneity among the studies ( $P < 0.05$ ,  $I^2 = 65\%$ ), and thus a random effects model was used.

**Hepatitis B virus infection:** Figure 3 shows the association between HBV infection and the risk of NODM after LT based on 6 studies with a total of 681 recipients. The pooled OR (OR = 1.04; 95%CI: 0.54-2.00) indicated no significant association between HBV infection and the risk of NODM after LT. A random effects model was used due to the presence of heterogeneity ( $\chi^2 = 11.60$ ;  $P = 0.04$ ,  $I^2 = 57\%$ ).

### Gender

Eleven studies were included to analyze the association between gender and NODM after LT (2033 recipients). The results of the meta-analysis are shown in Figure 4. The pooled OR for male vs female gender was 1.53 (95%CI: 1.24-1.90), indicating a mild association between male gender and an increased risk of NODM

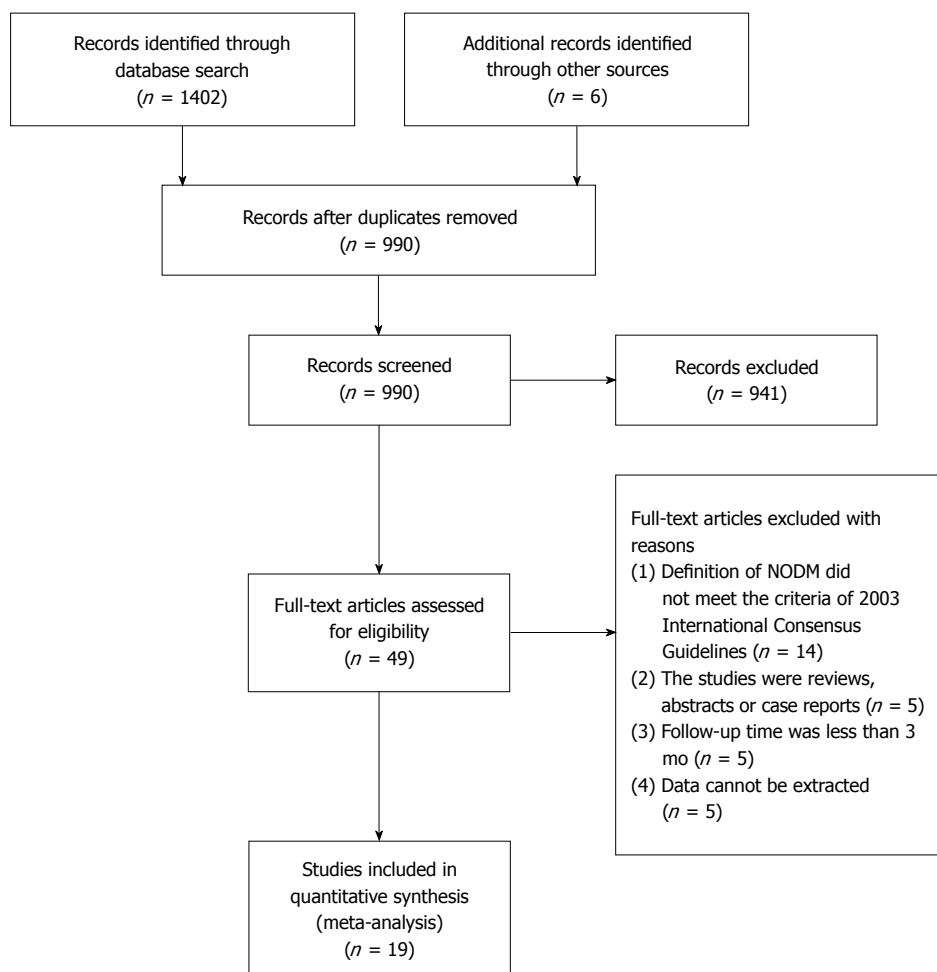


Figure 1 Flow diagram of the study selection.

Table 3 Baseline characteristics of the included studies

Ref.	Year	Country	Total number	NODM	Follow-up	Reference number
Saliba <i>et al</i> <sup>[1]</sup>	2007	France	211	48	6-24 mo	1
Parolin <i>et al</i> <sup>[14]</sup>	2004	Brazil	82	15	≥ 1 yr	14
Baid <i>et al</i> <sup>[10]</sup>	2001	United States	136	52	> 6 mo	10
Schmilovitz <i>et al</i> <sup>[21]</sup>	2003	Israel	91	27	> 6 mo	21
Moon <i>et al</i> <sup>[6]</sup>	2006	United States	619	392	6-122 mo	6
Kishi <i>et al</i> <sup>[22]</sup>	2006	Japan	205	71	> 6 mo	22
Khalili <i>et al</i> <sup>[13]</sup>	2004	United States	555	209	1.6-6.8 yr	13
Yoshida <i>et al</i> <sup>[15]</sup>	2013	Canada	280	89	> 6 mo	15
Gelley <i>et al</i> <sup>[23]</sup>	2011	Hungary	206	63	> 6 mo	23
Dehghan <i>et al</i> <sup>[17]</sup>	2008	Iran	170	44	6-156 > 6 mo	17
Harada <i>et al</i> <sup>[24]</sup>	2013	Japan	331	128	3.8-11.2 yr	24
Anderson <i>et al</i> <sup>[25]</sup>	2009	United States	45	11	6 mo	25
Ling <i>et al</i> <sup>[26]</sup>	2013	China	125	25	6-61 mo	26
Zhao <i>et al</i> <sup>[27]</sup>	2009	China	66	11	3-38 mo	27
Sánchez-Pérez <i>et al</i> <sup>[28]</sup>	2008	Spain	127	13	> 6 mo	28
Mirabella <i>et al</i> <sup>[5]</sup>	2005	India	830	90	> 10 mo	5
Driscoll <i>et al</i> <sup>[29]</sup>	2006	United States	115	36	12 mo	29
Honda <i>et al</i> <sup>[3]</sup>	2013	Japan	161	22	> 3 mo	3
Carey <i>et al</i> <sup>[2]</sup>	2012	United States	225	39	≥ 1 yr	2

NODM: New-onset diabetes mellitus.

after LT. As no heterogeneity was found across the studies ( $P = 0.71$ ,  $I^2 = 0\%$ ), we used a fixed effects model (Figure 4).

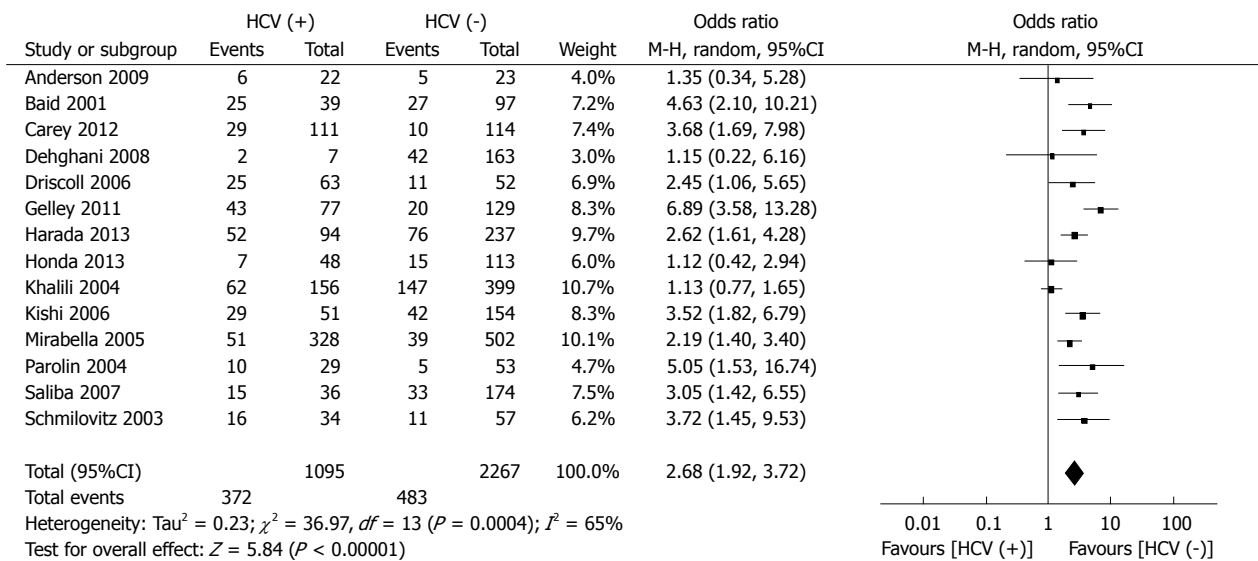
### Pre-transplant impaired fasting glucose

Three studies investigated the association between pre-transplant impaired fasting glucose (IFG) and

**Table 4** Baseline characteristics of the included studies

Ref.	Study year	Study design	Risk factors
Saliba <i>et al</i> <sup>[1]</sup>	2003.10-2004.6	Retrospective	BMI, HCV, IFG, immunosuppression
Parolin <i>et al</i> <sup>[14]</sup>	2004.1-2004.6	Retrospective	Gender, BMI, HCV, a family history of diabetes, alcohol
Baid <i>et al</i> <sup>[10]</sup>	1991.1-1998.10	Retrospective	HCV
Schmilovitz <i>et al</i> <sup>[21]</sup>	1992-2002	Retrospective	Gender, HCV, alcohol, immunosuppression, HBV
Moon <i>et al</i> <sup>[6]</sup>	1996.1-2004.10	Retrospective	Gender, HCV
Kishi <i>et al</i> <sup>[22]</sup>	1996.1-2005.1	Retrospective	HCV
Khalili <i>et al</i> <sup>[13]</sup>	1990-1994	Retrospective	HCV
Yoshida <i>et al</i> <sup>[15]</sup>	1996.1-2006.10	Retrospective	Immunosuppression
Gelley <i>et al</i> <sup>[23]</sup>	1995-2009	Retrospective	HCV
Dehghan <i>et al</i> <sup>[17]</sup>	1994-2006	Retrospective	Gender, HCV, BMI, immunosuppression, HBV
Harada <i>et al</i> <sup>[24]</sup>	1996.1-2011.1	Retrospective	Gender, HCV, alcohol, HBV
Anderson <i>et al</i> <sup>[25]</sup>	2004.1-2005.10	Retrospective	Gender, HCV, BMI, a family history of diabetes, alcohol, HBV
Ling <i>et al</i> <sup>[26]</sup>	2006.11-2009.7	Retrospective	Gender, BMI, HBV
Zhao <i>et al</i> <sup>[27]</sup>	2001-2008.3	Retrospective	Gender, IFG, a family history of diabetes, immunosuppression, HBV
Sánchez-Pérez <i>et al</i> <sup>[28]</sup>	1997.3-2001.10	Retrospective	Immunosuppression
Mirabella <i>et al</i> <sup>[5]</sup>	NR	Retrospective	HCV
Driscoll <i>et al</i> <sup>[29]</sup>	1998.1-2001.8	Retrospective	CMV, gender, BMI, HCV, a family history of diabetes, immunosuppression
Honda <i>et al</i> <sup>[3]</sup>	1998.12-2011.10	Retrospective	CMV, gender, HCV, BMI, a family history of diabetes
Carey <i>et al</i> <sup>[2]</sup>	1999.6-2008.2	Retrospective	Gender, BMI, HCV, IFG, a family history of diabetes, alcohol, immunosuppression

NR: Not reported; HCV: Hepatitis C virus; IFG: Impaired fasting glucose; HBV: Hepatitis B virus; CMV: Cytomegalovirus; BMI: Body mass index.



**Figure 2** Forest plot of studies finding an association between hepatitis C virus infection and new onset diabetes mellitus. There was significant heterogeneity in the results of the meta-analysis. The pooled OR (OR = 2.68; 95%CI: 1.92-3.72) indicated a significant association between hepatitis C virus infection and the risk of new-onset diabetes mellitus after liver transplantation.

NODM after LT. The meta-analysis revealed that pre-transplant IFG was associated with a significantly higher rate of NODM than normal blood glucose (pooled OR = 3.27; 95%CI 1.84-5.81), with no evidence of heterogeneity ( $P = 0.68$ ,  $I^2 = 0\%$ ; Figure 5).

### Family history

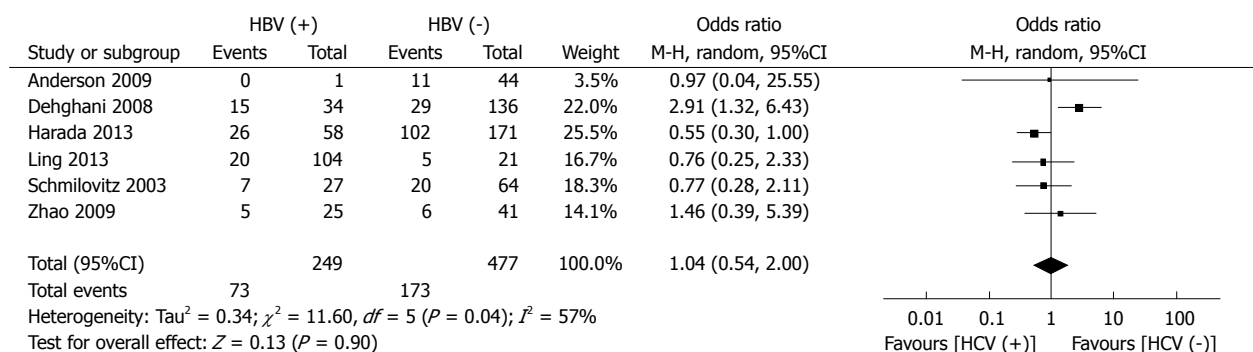
Six studies investigated the association between family history and NODM. The pooled OR was 1.69 (95%CI 1.09-2.63;  $P = 0.025$ ,  $I^2 = 24\%$ ; Figure 6), indicating that there was a significant association between a

family history of DM and the risk of NODM after LT.

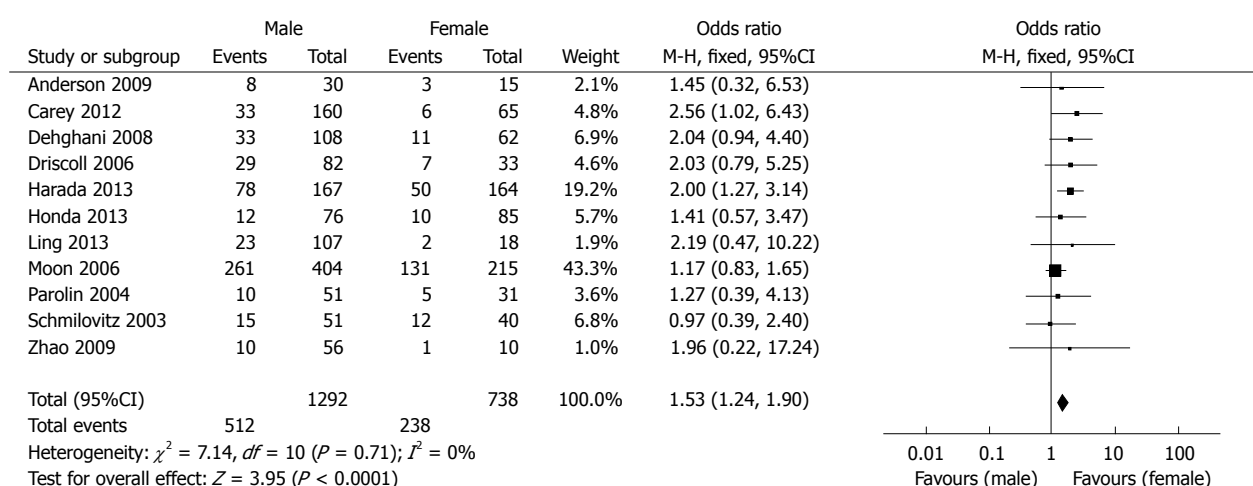
### Immunosuppressive therapy

Tacrolimus-based immunosuppressive therapy has been reported to be an independent risk factor for NODM after LT in many clinical studies, in comparison with cyclosporine. Ten retrospective studies were included in the meta-analysis. The pooled OR (OR = 1.34; 95%CI: 1.03-1.76) showed that tacrolimus was associated with an increased risk of NODM in liver transplant recipients, with moderate heterogeneity

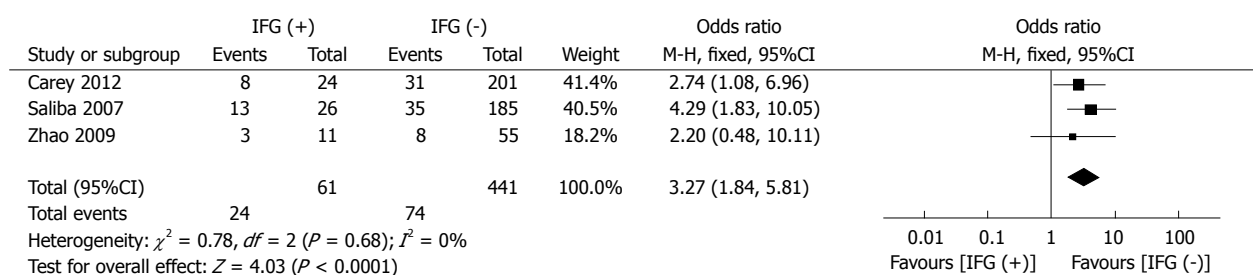




**Figure 3 Forest plot of studies finding an association between hepatitis B virus infection and new onset diabetes mellitus.** There was significant heterogeneity in the results of the meta-analysis. The pooled OR (OR = 1.04; 95%CI: 0.54-2.00) indicated a significant association between hepatitis B virus infection and the risk of new-onset diabetes mellitus after liver transplantation.



**Figure 4 Forest plot of studies finding an association between gender and new onset diabetes mellitus.** There was no significant heterogeneity in the results of the meta-analysis. The pooled OR (OR = 1.53; 95%CI: 1.24-1.90) indicated a significant association between male gender and the risk of new-onset diabetes mellitus after liver transplantation.



**Figure 5 Forest plot of studies finding an association between impaired fasting glucose and new-onset diabetes mellitus.** There was no heterogeneity in the results of the meta-analysis. The pooled OR (OR = 3.27; 95%CI: 1.84-5.81) indicated a significant association between pre-transplant impaired fasting glucose and the risk of new-onset diabetes mellitus after liver transplantation.

across the studies ( $P = 0.15$ ,  $I^2 = 33\%$ ; Figure 7).

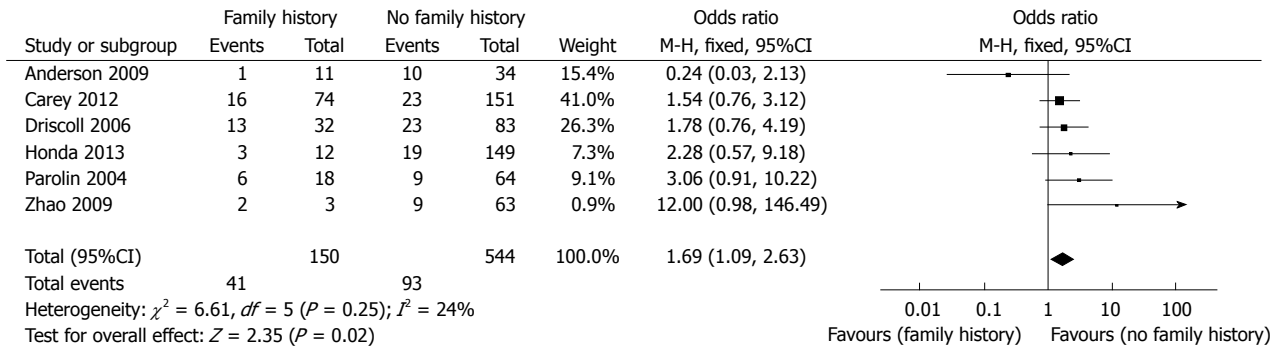
### Alcoholism and BMI

Five studies provided data on the relationship between alcoholic cirrhosis and NODM after LT, and the pooled OR was 0.71 (95%CI: 0.36-1.37;  $P = 0.14$ ,  $I^2 = 43\%$ ; Figure 8). Seven studies (1046 participants) reported explicit pre-transplant BMI values and NODM rates for LT recipients. The results of the meta-analysis

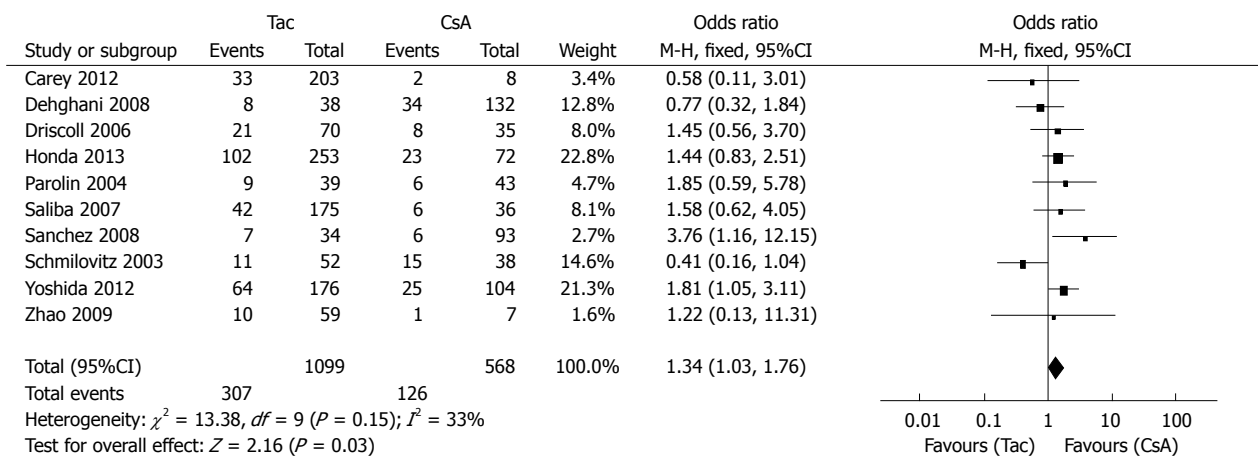
demonstrate that the pre-transplant BMI of recipients with NODM was significantly higher than that of recipients who did not develop NODM (WMD=1.19, 95%CI: 0.69-1.68;  $P = 0.15$ ,  $I^2 = 37\%$ ; Figure 9).

### Subgroup analysis

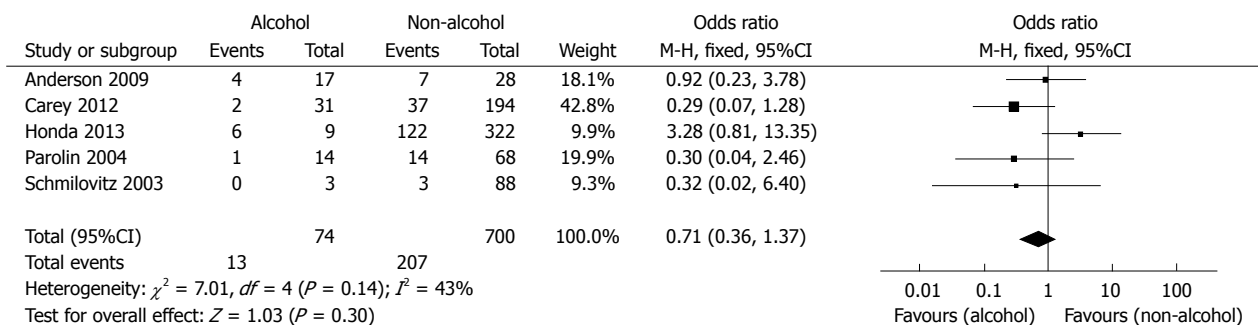
To investigate any confounding factors that might be related to heterogeneity among studies, we performed a subgroup analysis upon the analyses that



**Figure 6 Forest plot of studies finding an association between a family history of diabetes and new-onset diabetes mellitus.** There was no significant heterogeneity in the results of the meta-analysis. The pooled OR (OR = 1.69; 95%CI: 1.09-2.63) indicated a significant association between a family history of diabetes and the risk of new-onset diabetes mellitus after liver transplantation.



**Figure 7 Forest plot of studies finding an association between immunosuppression and new-onset diabetes mellitus.** There was no significant heterogeneity in the results of the meta-analysis. The pooled OR (OR = 1.34; 95%CI: 1.03-1.76) indicated a significant association between tacrolimus and the risk of new-onset diabetes mellitus after liver transplantation.



**Figure 8 Forest plot of studies finding an association between alcohol-related cirrhosis and new-onset diabetes mellitus.** There was no significant heterogeneity in the results of the meta-analysis. The pooled OR (OR = 0.71; 95%CI: 0.36-1.37) indicated no significant association between alcohol-related cirrhosis and the risk of new-onset diabetes mellitus after liver transplantation.

revealed significant heterogeneity (HCV infection and HBV infection), stratifying the studies according to transplant country (United States or other countries) and publication year (before or after 2010; Table 5). In the subgroup analysis for HCV infection, we found that the heterogeneity among the studies increased ( $P = 0.004$ ,  $I^2 = 74\%$ ) when studies were restricted to the US and decreased ( $P = 0.06$ ,  $I^2 = 46\%$ ) when studies were restricted to other countries. As for the subgroup

analysis of HBV infection, heterogeneity among the studies decreased greatly when the syntheses were stratified by the year of publication. All results from the subgroup analysis were consistent with the results of the overall analysis.

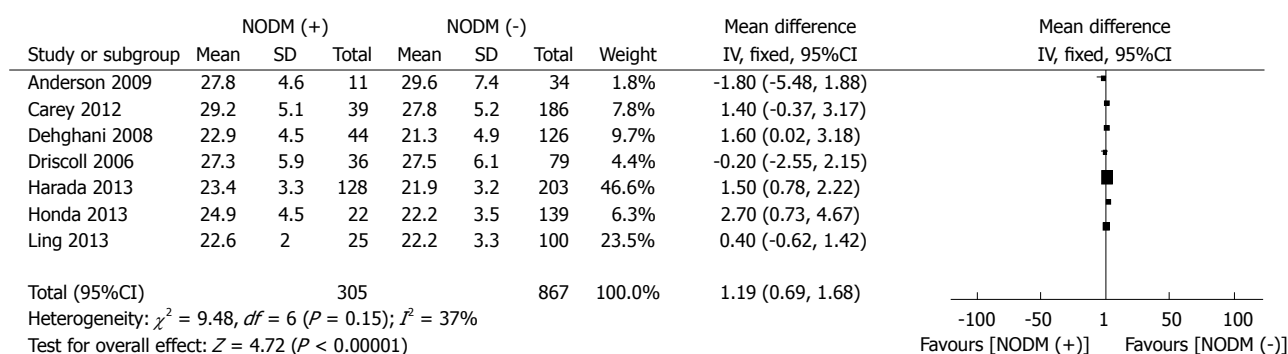
#### Publication bias assessment and sensitivity analysis

We assessed the publication bias with funnel plots for the studies involving HCV, gender, and

**Table 5** Subgroup analysis

Risk factor	Subgroup	Studies, <i>n</i>	Effect estimate (95%CI)	<i>P</i> value	Heterogeneity
HCV	United States	5	2.29 (1.19-4.41)	< 0.01	$P = 0.004$ , $I^2 = 74\%$
	Other	9	2.96 (2.11-4.15)	< 0.01	$P = 0.06$ , $I^2 = 46\%$
	Overall	14	2.68 (1.92-3.72)	< 0.01	$P = 0.004$ , $I^2 = 65\%$
HBV	Published before 2010	4	1.61 (0.94-2.78)	0.08	$P = 0.23$ , $I^2 = 30\%$
	Published after 2010	2	0.59 (0.35-1.00)	0.05	$P = 0.61$ , $I^2 = 0\%$
	Overall	6	1.04 (0.54-2.00)	0.9	$P = 0.04$ , $I^2 = 57\%$

HCV: Hepatitis C virus; HBV: Hepatitis B virus.



**Figure 9** Forest plot of studies finding an association between body mass index and new-onset diabetes mellitus. There was no significant heterogeneity in the results of the meta-analysis. The WMD (WMD = 1.19, 95%CI: 0.69-1.68) indicated a significant association between body mass index and the risk of new-onset diabetes mellitus after liver transplantation.

immunosuppression. The funnel plots for HCV showed slight asymmetry, suggesting possible publication bias. The funnel plots for gender and immunosuppression were both generally symmetrical and suggested a lack of significant publication bias (Figure 10). In the sensitivity analysis, the removal of any study from the analysis did not significantly alter the overall results.

## DISCUSSION

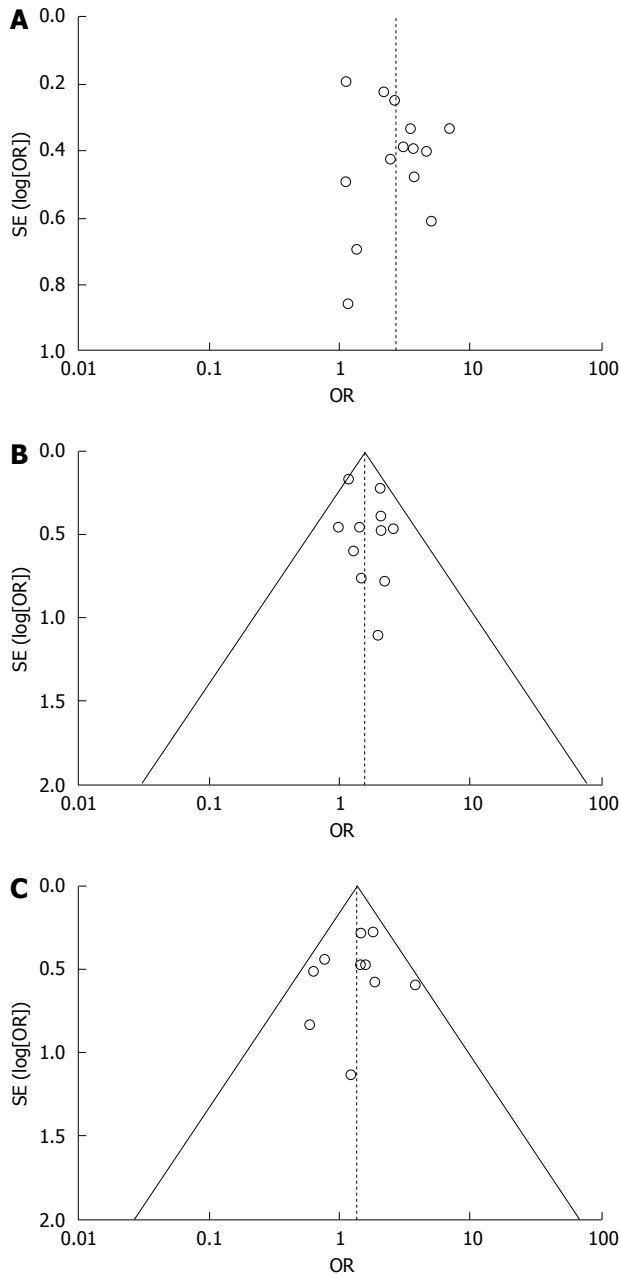
NODM is a common complication of LT, with an incidence of 9% to 63.3%, and is associated with impaired long-term liver allograft function and patient survival. The overall incidence of post-LTNODM in the included studies was 30.2% (1385/4580). A number of risk factors for NODM after LT have been reported, including HCV infection, age, race, ethnicity, family history, BMI, acute rejection and type of immunosuppressive agents, but controversy persists regarding risk factors for NODM in LT recipients. The aim of the present study was to determine the risk factors for NODM using meta-analysis.

HCV infection is the leading cause of end-stage liver disease in the United States<sup>[4]</sup>. Epidemiological studies have shown a significant association between HCV and NODM after solid organ transplantation<sup>[7,30]</sup>, but several studies have also reported a negative relationship between NODM and HCV<sup>[22,31]</sup>. This controversy may result from the relatively small number of cases and from discrepancies in the studies' follow-up periods and choices of diagnostic

criteria for NODM. The present meta-analysis provides retrospective evidence of a 2.68-fold increased risk of NODM among patients with HCV infection compared with HCV-negative recipients. The explicit mechanism between the development of NODM and HCV has yet to be fully elucidated. Chronic HCV infection can impair glucose metabolism in the liver by destroying hepatocytes<sup>[32]</sup>. Several possible mechanisms for HCV-induced insulin resistance have been proposed. It has been widely reported recently that in addition to causing liver injury, HCV is detrimental to other organs and tissues<sup>[33]</sup>. A post-mortem study proved that HCV is able to replicate in the pancreas before causing a failure of compensatory hyperinsulinemia by damaging  $\beta$ -cells via cytokine-mediated tissue damage<sup>[33-36]</sup>. The current meta-analysis confirms an association between HCV and NODM post-LT; the potential cause of the increased risk of NODM in HCV-infected LT recipients therefore requires further investigation.

The risk factors for developing NODM have previously been shown to differ between genders<sup>[22,24,37-39]</sup>. Male gender was identified as an independent risk factor for the presence of post-transplant diabetes in many studies<sup>[22]</sup>. Saab *et al.*<sup>[37]</sup> reported that males are more likely to have NODM, which is consistent with the results of Stockmann *et al.*<sup>[38]</sup> and Dehghani *et al.*<sup>[40]</sup>. However, other studies have found no relationship between NODM and gender. The current meta-analysis indicated that males were at a significantly greater risk of developing NODM than females, based on a pooled OR of 1.53 (95%CI: 1.24-1.90). This finding is consistent





**Figure 10** Funnel plots of studies conducted on new-onset diabetes mellitus and the risk factors of hepatitis C virus infection (A), gender (B) and immunosuppression (C).

with a number of studies suggesting that gender is an independent risk factor for NODM. This difference may be a consequence of differences in lifestyles, dietary habits and other social factors between female and male recipients.

The non-modifiable risk factor of a family history of diabetes mellitus was reported to have a positive but non-significant association with NODM after LT in many studies. The results of the pooled OR in the present study suggest that a family history of diabetes mellitus can slightly increase the incidence of NODM after LT, similar to the results found in the general population. IFG prior to transplantation has been shown to be a risk factor for NODM after LT in many studies.

Pre-transplant IFG has also been shown to predict NODM in renal transplant recipients<sup>[41]</sup>. In the general population, fasting plasma glucose is significantly associated with the incidence of type 2 diabetes mellitus<sup>[42]</sup>. Approximately 70% of individuals with abnormal blood glucose, defined as impaired glucose tolerance or IFG, may ultimately develop diabetes mellitus<sup>[43]</sup>. In cirrhotic patients, the prevalence of impaired glucose tolerance has been estimated to be approximately 60% to 80%. The current meta-analysis showed a significant relationship between pre-transplant IFG and NODM after LT. Thus, we speculated that pre-transplant IFG has similar effects in transplant recipients and the ordinary population, although further research is required to determine whether the pathogenetic mechanism is the same in the two populations.

The reported incidence of NODM after solid organ transplantation was significantly higher among recipients receiving tacrolimus than cyclosporine; this pattern has been observed in liver, renal, heart and lung transplants<sup>[44,45]</sup>. Despite its adverse impact on glucose metabolism, tacrolimus significantly reduced the risks of acute rejection, patient death and graft loss after liver transplantation compared with cyclosporin<sup>[45]</sup>. Sánchez-Pérez *et al.*<sup>[28]</sup> reported that patients treated with tacrolimus were 4 times more likely to develop NODM or IFG post-LT than those treated with cyclosporine, similar to previously reported results in the literature<sup>[39,46]</sup>. However, discrepancies were still observed among studies<sup>[2,17,21,47]</sup>, perhaps due to the differing definitions of NODM<sup>[48]</sup>. In the current meta-analysis, the type of immunosuppressant (tacrolimus vs cyclosporine A) was found to be an independent risk factor for NODM after LT. The additional risk factors evaluated in this meta-analysis, including HBV infection and alcohol-related cirrhosis before transplantation, were not found to correlate with NODM after LT.

HBV is a leading cause of end-stage liver diseases, such as cirrhosis and hepatocellular carcinoma, in Asia<sup>[49]</sup>. The relationship between HBV infection and NODM after LT has been investigated in many studies recently, and a study from Iran reported that HBV infection was an independent risk factor for NODM. Still, other studies have found no consistent association. The number of the cases included in these studies is limited, and so more investigations from larger centers are needed to determine the impact of HBV infection on NODM after LT. Alcohol-related cirrhosis was not found to be significantly associated with the risk of NODM post-LT in the current study. One of the potential reasons for this finding is that these factors are significantly modified by transplantation, which could result in a moderate effect on glucose metabolism after LT.

The present meta-analysis has some limitations. First, a major limitation was publication bias. Most of the cases represent Western populations. Studies with statistically significant results are more likely to

be published than those with non-significant results, whereas studies with small sample sizes might be published in a journal from the author's native country; both of these factors might have distorted the results of the meta-analysis. To minimize such bias, we included studies from as many sources as possible. An American study using the Organ Procurement and Transplant Network/United Network for Organ Sharing (OPTN/UNOS) liver transplant database was identified and found to include 15463 recipients between July 2004 and December 2008<sup>[4]</sup>. Several independent risk factors for NODM were identified by the study, including recipient age, race, BMI, HCV, recipient cirrhosis history, tacrolimus, and diabetic donors. We excluded this study because it did not provide an explicit definition of NODM, sufficient follow-up or sufficiently detailed information for the meta-analysis. Several other studies were also excluded for similar reasons. Next, we tried to contact the authors of these papers. Some of them very kindly replied to us and supplied us with a great deal of useful data; however, these studies did not meet the criteria for inclusion.

Second, heterogeneity was inevitable due to methodological differences among the studies. The calculated  $I^2$  was as high as 76% when assessing the association between HCV infection and NODM, which may be related to differences in the length of follow-up, sample size, race and age. To reduce the effect of high heterogeneity, a random effects model was used when  $I^2$  was greater than 50%.

Third, the current meta-analysis did not distinguish between the subtypes of NODM. NODM can be classified into two subtypes according to the period of persistence: transient-NODM (T-NODM, *i.e.*, NODM that is temporarily present for 1-6 mo after LT) and persistent-NODM (P-NODM, *i.e.*, NODM that is sustained for  $\geq 6$  mo after LT)<sup>[6]</sup>; however, such definitions were applied inconsistently among the studies<sup>[13,22]</sup>. The two types of NODM were found to be significantly different in terms of risk factors, post-transplant complications, and patient outcomes. Unfortunately, we were unable to pursue any further analysis of the risk factors for T-NODM and P-NODM due to the variable definitions and the limited number of related studies. Fourth, all of the studies included in the meta-analysis were retrospective clinical trials, which are not considered as reliable as prospective studies. No prospective clinical trials were identified. Most of the studies in this meta-analysis did not adjust for potential confounders, including gender, age, BMI, *etc.*, and so the potential effect of other confounders on the pooled results could not be excluded. Therefore, further prospective clinical trials are needed to better understand risk factors for NODM.

In conclusion, this meta-analysis found that HCV infection, IFG, a family history of diabetes, male gender, and tacrolimus use are all significantly associated with an increased risk of developing NODM after LT.

The mechanism by which these risk factors influence the development of NODM remains unclear. Some of the identified factors are potentially modifiable, including HCV infection and tacrolimus-based immunosuppression. Well-designed prospective clinical trials that are designed to investigate the risk factors for NODM are needed to further confirm our findings.

## COMMENTS

### Background

New-onset diabetes mellitus (NODM) is a common complication after liver transplantation and is associated with increased rates of rejection, infection, cardiovascular disease, and with decreased survival. To date, information regarding incidence, risk factors, and clinical consequences of NODM in liver transplant recipients has been limited. Most of the published data are from single center studies with relatively small sample sizes, so the authors performed the meta-analysis to analyze the risk factors for NODM in liver transplant recipients.

### Research frontiers

Due to the significantly negative impact of NODM on the long term outcome of liver transplantation, the study about NODM has been becoming a new hotspot. In order to identify the risk factors, the meta-analysis included many potential factors which have been frequently reported, including hepatitis C virus (HCV) infection, hepatitis B virus infection, impaired fasting glucose (IFG), a family history of diabetes, male gender, tacrolimus, BMI and alcoholism.

### Innovations and breakthroughs

In 2009, a meta-analysis was conducted to analyze the connection between HCV infection and NODM after liver transplantation. However, the number of included studies was limited and many others potential factors were missed to be evaluated. Therefore, firm conclusions could not be drawn. Many high-quality studies with large sample sizes have been published recently. Therefore, it is important to conduct this comprehensive meta-analysis. Except for HCV infection, this study also identified HCV infection, IFG, a family history of diabetes, male gender, tacrolimus and body mass index (BMI) as risk factors for NODM after liver transplantation.

### Applications

Some of the identified factors are potentially modifiable, including pre-transplant BMI and tacrolimus-based immunosuppression, and large-scale prospective clinical trials are needed to assess whether modifying these modifiable risk factors will indeed prevent NODM after liver transplantation.

### Terminology

NODM after liver transplantation is an incompletely understood phenomenon estimated to occur in 9%-63.3% of recipients who were not diabetic prior to transplant.

### Peer-review

The authors have made a systematic review and meta-analysis of risk factors for new onset diabetes mellitus post liver transplantation (LT). The focus of the study is very important as in the Western world almost 1/3 of patients develop diabetes mellitus post LT. Although there is no novel finding in the study, it is nicely performed and written. The results are in congruence with earlier meta-analyses.

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ISSN 1007-9327



9 771007 932045