Metabolic Disorders and Risk of Portal Vein Thrombosis in Liver Cirrhosis: A Systematic Review and Meta-Analysis

Jiao Li, Qiong Wang, Mei Yang, Xiaobin Sun

Department of Gastroenterology, The Third People's Hospital of Chendu, Affiliated Hospital of Southwest Jiaotong University, Chengdu, Sichuan, China

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ABSTRACT

Portal vein thrombosis is considered to be an indicator of worse outcomes in patients with hepatic cirrhosis. More and more evidence shows that metabolic disorders are noticeable pro-thrombotic factors. However, whether or not metabolic disorders increase the risk of cirrhotic portal vein thrombosis is controversial. We aim to quantify the magnitude of the association between metabolic disorders and the risk of cirrhotic portal vein thrombosis. Databases were searched for papers to identify studies in which metabolic disorders were compared in liver cirrhosis with or without portal vein thrombosis. Based on data from the eligible studies, metabolic disorders related to portal vein thrombosis included diabetes mellitus, nonalcoholic fatty liver disease, hypercholesterolemia, and body mass index. Pooled adjusted odds ratios with 95% CIs were calculated. Data for 22 studies with a total of 57 371 portal vein thrombosis cases and 3 979 015 participants were included. Statistically significant pooled odds ratios for portal vein thrombosis were obtained for diabetes mellitus (odds ratio 1.80, 95% CI 1.42-2.28), nonalcoholic fatty liver disease (odds ratio 1.61, 95% CI 1.34-1.95), and hypercholesterolemia (odds ratio 3.59, 95% CI 1.83-7.03). Body mass index was likely irrelevant with cirrhotic portal vein thrombosis (odds ratio 1.01, 95% CI 0.87-1.17), both in overall and subgroup meta-analyses. Significant heterogeneities among studies were observed, except for the hypercholesterolemia group. Metabolic disorders, such as diabetes mellitus, nonalcoholic fatty liver disease, and hypercholesterolemia, increased the risk of portal vein thrombosis in cirrhotic patients by 1.80-fold, 1.61-fold, and 3.59-fold, respectively. Body mass index did not appear to be a risk predictor of cirrhotic portal vein thrombosis. Further, well-designed clinical and mechanistic studies are required to strengthen the arguments, especially in obese patients.

Keywords: *Body mass index, diabetes mellitus, hypercholesterolemia, non-alcoholic fatty liver disease, portal vein thrombosis*

INTRODUCTION

Portal vein thrombosis (PVT) is defined as the presence of blood clots in the portal vein trunk or its branches, sometimes extending to the splenic or superior mesenteric vein. The majority of PVT occurs in patients with underlying cirrhosis and the incidence of PVT increases along with the severity of liver dysfunction, evaluated at about 1% in compensated cirrhosis and 2%–23% in liver transplantation (LT) candidates, according to a systematic review.[1] Clinical outcomes of PVT in cirrhosis vary from usually asymptomatic to life-threatening situations, including variceal bleeding, refractory ascites, hepatic encephalopathy, hepatic and intestinal ischemia.[2,3] To date, the contribution of PVT in cirrhosis to hepatic decompensation and overall mortality remains controversial.[2,4,5] Yet, a recent meta-analysis including 16 studies suggested that PVT might affect short-term prognosis (less than 1 year) other than long-term prognosis in cirrhotic patients.[5]

In cirrhotic patients, the development of PVT is usually silent and PVT is most often detected incidentally by imaging examinations.[2] Consequently, how to identify the high-risk population of PVT is becoming particularly important. All components of Virchow's triad for the mechanism of venous thrombosis, including reduced blood flow, endothelial dysfunction, and blood hypercoagulability, similarly apply to interpret the development of cirrhotic PVT.[2] Accumulating evidence shows that the dominant risk for cirrhosis PVT is static portal blood flow, secondary to portal hypertension (PH).[6] A matched case–control study confirmed that PV velocity <15 cm/s was the strongest independent risk factor predicting cirrhotic PVT.[6] Previous decompensation of cirrhosis and

Jiao Li and Qiong Wang have equally contributed to the work.

Corresponding author: ***Xiaobin Sun****, e-mail:* ***xb_sun2021@163.com***
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thrombocytopenia have also been identified as predictors of cirrhotic PVT, indirectly reflecting the pathophysiologic role of the severity of PH in the development of PVT.[7] Meanwhile, endothelial dysfunction, which is mainly due to intra-abdominal surgery in cirrhotic patients, also contributes to PVT development. It was reported that splenectomy accounted for at least a 10-fold increased risk of PVT, independent of liver dysfunction in China.[8] Likewise, hypercoagulability due to inherited or acquired thrombophilic disorders in patients with hepatic cirrhosis could enhance the PVT risk.[2]

Liver cirrhosis gains a delicate hemostatic rebalance, which is both pro- and anti-hemostatic, resulting in either clotting or bleeding.[9] Concurrently, obesity and metabolic disorders, such as diabetes mellitus (DM), nonalcoholic fatty liver disease (NAFLD), or dyslipidemia, are all considered as noticeable pro-thrombotic factors.[10-13] Compelling evidence confirmed the actually increased rates of venous thromboembolism (VTE) like deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with the metabolic disorders mentioned above.[14,15] A meta-analysis including 21 studies reported that the risk of VTE was 2.33-fold for obesity, 1.42-fold for DM, and 1.16-fold for hypercholestero lemia.[14] A case–control study highlighted that VET was 2.46-fold greater in nonalcoholic steatohepatitis compared with all other etiologies of liver disease.[15] In turn, it was assumed that the hypercoagulability in metabolic disorders may easily break the hemostatic balance within cirrhosis to predispose to PVT. Unfortunately, to date, the impact of metabolic disorders on cirrhotic PVT events is unsettled and controversial, particularly in obese patients. Current studies suggest that a higher body mass index (BMI) is inversely,[6] irrelevantly,[3] or significantly[16,17] related to cirrhotic PVT on different BMI thresholds. Due to an increase in the prevalence of obesity and co-existing metabolic disorders have become a global phenomenon and NAFLD has emerged as one of the faster-growing risk of liver cirrhosis, it is necessary to understand the exact correlation between metabolic disorders and cirrhotic PVT. In this context, the purpose of the present study is to estimate the quantitative association between metabolic disorders and the development of cirrhotic PVT by using a meta-analysis of case-control and cohort studies.

Main Points

- *Metabolic disorders such as diabetes mellitus, nonalcoholic fatty liver disease, and hypercholesterolemia increased the risk of portal vein thrombosis (PVT) in cirrhotic patients by 1.80-fold, 1.61- fold, and 3.59-fold, respectively.*
- *Body mass index did not appear to be a risk predictor of cirrhotic PVT.*

MATERIALS AND METHODS

The registration number of PROSPERO is CRD420212 59259. There was no interaction with patients directly, as we acquired data from already published articles. Our institutional review board waived patient approval, and informed consent was not required for this study.

Literature Search Strategy

A comprehensive electronic literature search was performed by 2 authors in the PubMed, Cochrane library, EMBASE databases, Web of Science, China national knowledge infrastructure, China Biology Medicine, Wan Fang Databases, and Wei Pu Databases to identify studies in which metabolic disorders were compared in liver cirrhosis with or without PVT by April 22, 2021. Search items were "liver cirrhosis" AND ("portal vein thrombosis" OR "portal cavernoma" OR "mesenteric vein thrombosis" OR "splenic vein thrombosis" OR "abdominal venous thrombosis") AND "risk factor," combined with both MeSH terms and free-text terms (search strategy in PubMed showed in Supplementary Table 1). Further correlative studies were identified through the reference lists of the included studies.

Inclusion and Exclusion Criteria

All included studies should evaluate the association between metabolic disorders (e.g., obesity, DM, dyslipidemia, and NAFLD) and PVT risk in patients with hepatic cirrhosis or LT candidates. The following manuscripts were excluded: (1) animal trails, (2) correspondence or editorial, (3) case reports, (4) reviews or meta-analyses, (5) irrelevant literatures, (6) inadequate data on the outcomes of interest (e.g., adjusted odds ratio (OR) and/or 95% CI), (7) number of studies related to each metabolic disorder $\leq$2.

Study Quality Assessment

Two authors assessed the risk of bias independently. Any discrepancies were discussed with a third author by a joint revaluation of the original article. The quality of case–control and cohort studies was evaluated using the Newcastle–Ottawa Scale (NOS), which includes eight questions. The highest NOS score should be 9 points, and studies with a 6 or higher score were defined as high-quality studies.

Data Extraction

Data from retrieved studies were independently extracted by 2 authors and checked by the other author. For all studies, we extracted information on the first author, publication year, country, study design, enrollment period, data source of patients, target population, number of patients with PVT, number of total patients, measurement of PVT and metabolic disorders, outcomes of interests (adjusted OR, relative risk or hazard ratio [HR] with 95% CI for metabolic disorders and PVT risk). The characteristics of patients were also extracted as follows: age, gender, etiology of cirrhosis, Child-Pugh (CP) score, or model for end-stage liver disease score.

Statistical Analysis

The meta-analysis was performed using Review Manager Version 5.3 software provided by the Cochrane Collaboration (RevMan; The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) and Stata software (Version 14.0, StataCorp, College Station, TX, USA). This meta-analysis pooled the adjusted ORs or HRs and their 95% CIs, with the hypothesis that these were comparable measurements of relationship, given that PVT events were rare in patients with hepatic cirrhosis.[18] We used a fixed-effects model to calculate the pooled effect sizes if the data were not significantly heterogeneous. Otherwise, a random-effects model was used. Heterogeneity was evaluated by I^2 statistics and Cochrane Q test. $I^2 > 50\%$ or $P < .05$ was considered as a statistically significant heterogeneity. Sensitivity analysis was used by omitting each included study, and Galbraith plot analysis was performed to find studies as the main source of heterogeneity. If possible, the sources of heterogeneity were further explored by using meta-regression and subgroup analysis, which were performed on the type of geography region, target population, quality of the study, study design, and sample size. Publication bias was evaluated using the funnel plot and Egger's test with 9 or more studies. We further conducted a Trim-and-Fill analysis if statistically significant publication bias was considered.

RESULTS

Study Identification and Literature Characteristics

The search strategy retrieved 2654 potentially relevant studies, in which 2606 articles were excluded after scanning titles and abstracts, leaving 48 articles for further evaluation (Figure 1). Two papers that extracted data from the National Inpatient Sample database were both involved because they focused on different metabolic disorders as outcomes (i.e., studies by Zakko et al[3] and Fan et al[19]). Meanwhile, there were a total of 9 studies focused on LT candidates from the same database named nationwide United Network for Organ Sharing/Organ Procurement and Transplantation Network database. These studies adopted in part overlapping enrollment period or patient inclusion criteria but with similar conclusions, and the most comprehensive study on metabolic disorders by Ghabril[20] was finally selected in this meta-analysis (Supplementary Table 2). For other published articles of overlapping cohorts, we chose the articles with the largest and most updated data. Simultaneously, 12 studies that were unable to provide sufficient information for data extraction were excluded. In addition, only one study related to "visceral fat(VT)[21]" or "hypertriglyceridemia[22]" was retrieved, respectively, which was further excluded for meta-analysis (Supplementary Table 3). Thus, 22 studies were finally included in the meta-analysis (Figure 1), in which a study included stratified data of NAFLD-related cirrhosis added with or without cryptogenic cirrhosis.[20]

Information regarding the included 22 studies has been provided in Table 1. Of these, 14 were in case–control design[6,17,23-34] and 8 were in cohort design,[3,16,19,20,35-38] 21 were retrospective studies except 1 prospective study;[36] 13 of them came from China;[23-30,32-35,37] 4 from the United States;[3,6,19,20] 2 from Spain;[16,17] 1 from Iran;[31] 1 from Belgium;[38] and 1 from Egypt.[36]

Study Quality

Among the included studies, 8 studies had a score of 8 points, 11 had a score of 7 points, 3 had a score of 6 points, and 2 had a score of 5 points, which was indicated by the low-quality of the studies (Supplementary Tables 4 and 5).

Patient Characteristics

Overall, 3 979 015 liver cirrhotic patients and 57 371 PVT cases in the 22 selected studies were selected, under the condition that the number of PVT cases in non-obese cirrhotic group was unknown in study by Zakko et al.[3] Most of these studies included middle-aged patients, predominantly male. Target population included 98.7% (3 928 380/3 979 015) of liver cirrhosis[3,6,19,23-30,32-37] and 0.13% (50 635/3 979 015) of LT candidates.[16,17,20,31,38] Diagnostic methods of PVT were unclear in 9 studies,[3,16,17,19,23,26,29,32,34] ultrasound alone in 1 study,[27] computed tomography (CT) alone in

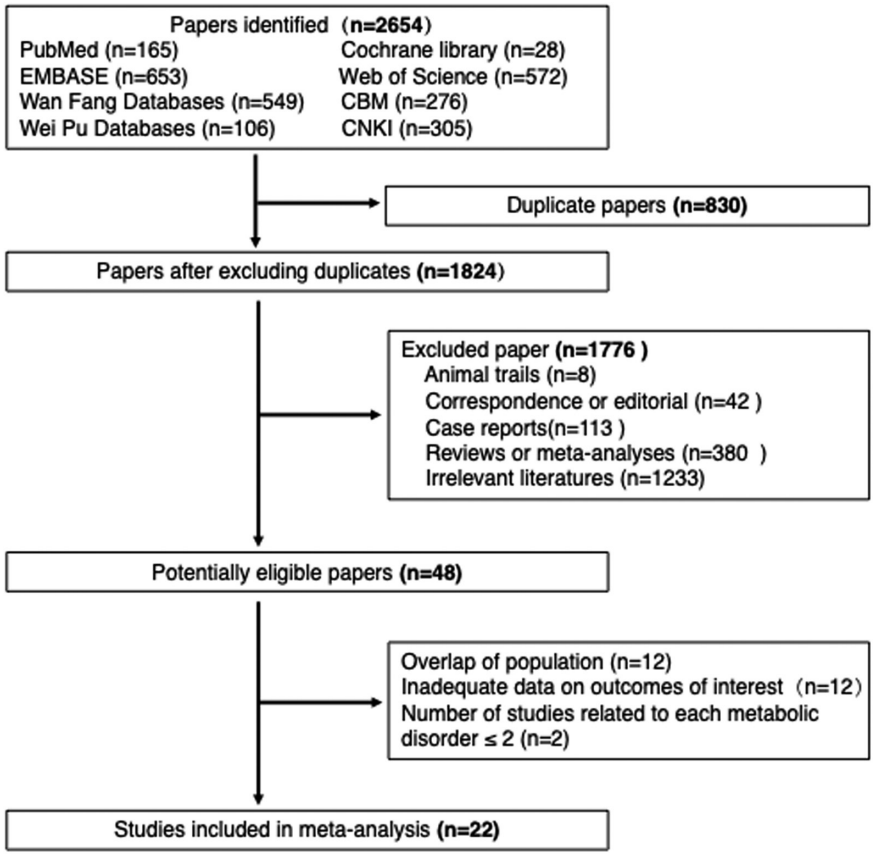

Figure 1. Flowchart of study selection. CBM, China Biology Medicine; CNKI, China national knowledge infrastructure.

1 study,[25] intraoperative findings alone in 1 study,[31] imaging data or intraoperative findings in 1 study,[20] ultrasound or CT or magnetic resonance imaging (MRI) in 5 studies,[24,28,30,33,38] and ultrasound followed by a confirmation with CT or MRI in 4 studies.[6,35-37] The commonly reported metabolic disorders associated with PVT risk were DM in 12 studies,[20,24,26-34,36] NAFLD-related cirrhosis in 4 studies,[6,19,20,31] hypercholesterolemia in 3 studies,[23,29,35] and BMI in 9 studies.[3,6,16,17,20,25,29,37,38] Of these, BMI defined as obese (≥ 30 kg/m^2) in 3 studies,[3,16,20] overweight and obese (≥25 kg/m^2) in 3 studies,[17,25,29] and BMI increased in 3 studies.[6,37,38]

Diabetes Mellitus and Risk of Portal Vein Thrombosis Event

Meta-analysis including 12 studies (N = 51 302 patients) demonstrated a positive association of DM with the PVT risk (random OR 1.80, 95% CI 1.42-2.28; P <.00001), with statistically significant between-study heterogeneity (I^2 = 68%; P = .0003) (Figure 2A). And then eliminating each of the included studies from the analysis did not significantly alter the overall risk of PVT events with the pooled ORs (range 1.67-1.93) (Supplementary Table 6). Galbraith plot analysis identified 4 studies by Ghabril et al,[20] Qiu et al,[27] Zhang et al,[28] and Chen et al[30] as the major sources of heterogeneity (Supplementary Figure 1). Significant heterogeneity was not found (I^2 = 0, P = .8), and a significant correlation (fixed OR 1.71, 95% CI 1.46-2.00; P < .00001) was still noted after eliminating the 4 studies above (Supplementary Figure 2). Subsequently, among the meta-regression, heterogeneity was not related to the geographical region (Asian vs no-Asian) (P =.443), target population (liver cirrhosis vs LT candidates) (P = .328), type of study design (case–control study vs cohort study) (P = .443), study quality (NOS ≥ 7 vs < 7) (P = .799), and sample size (N > 200 vs ≤ 200) (P = .511) (Supplementary Table 7). The meta-analysis of the Asia subgroup demonstrated a significant association of DM with PVT development (random OR 1.92, 95% CI 1.46-2.52) in a lower heterogeneity (I^2 = 51%), similar to the

Table 1. Study Characteristics of Included Studies

First Author (Year)	Country	Study Design	Enrollment Period	Data Source	Target Patients	Age (Year Mean ± SD or Rang)	Male (%)	No. Pts. With PVT/Total No. Pts (n)	No. Pts. with Child-Pugh A/B/C(n) or Mean ± SD	Metabolic Factors, and Adjusted OR or HR (±95% CI) for PVT	NOS Score
Fan TY[23] (2007)	China	Case–control	2000-2006	Single-center	LC	NA	57.63	11/59	NA	HC (OR 5.44, 1.072-27.581)	6
Ayala, R[16] (2012)	Spain	Cohort	2001-2006	Single-center	LT	NA	66.84	62/380	NA	BMI>30 kg/m^2 (HR 13.161, 1.324-130)	7
Lu X[35] (2013)	China	Cohort	2008-2010	Single-center	LC	36-68	68.97	15/87	NA	HC (OR 5.888, 1.369-25.322)	8
Abdel-Razik, A[36] (2015)	Egypt	Cohort	2012-2014	Single-center	LC	58.5 ± 9.5	67.50	17/120	18/64/38	DM (OR 2.15, 1.315-6.013)	8
Ghabril, M[20] (2016)	USA	Cohort	2003-2013	OPTN/UNOS	LT	54.8 ± 4.2	67.93	3321/48570	NA	BMI>30 kg/m^2 (OR 1.13, 1.03-1.23) DM (OR 1.23, 1.11-1.36) NAFLD (OR 1.42, 1.20-1.70) Cryptogenic disease (OR 1.5, 1.30-1.80) NAFLD + Cryptogenic disease (OR 1.5, 1.33-1.71)	7
Liu JZ[24] (2016)	China	Case–control	2008-2014	Single-center	LC	57.6 ± 12.3	58.29	99/199	46/101/52	DM (OR 2.244, 1.043-4.828)	7
Xiong J[25] (2016)	China	Case–control	2003-2013	Single-center	LC	53.8 ± 12.9	68.01	78/722	NA	BMI ≥ 25 kg/m^2 (OR 0.174, 0.04-0.755)	7
Wang SH[26] (2017)	China	Case-control	2015-2016	Single-center	LC	51.7 ± 7.6	60.00	53/125	9.58 ± 2.78	DM (OR 1.683, 0.897-3.158)	7
Eshraghian, A[31] (2018)	Iran	Case-control	2013-2015	Single-center	LT	42.0 ± 13.4	NA	174/1007	20.89 ± 6.02[†]	NAFLD + cryptogenic disease (OR 1.36, 1.08-1.72) DM (OR 2.03, 1.13-3.64)	8
Mou SY[37] (2018)	China	Cohort	2012-2016	Single-center	LC	49.6 ± 9.3	50.41	37/123	99/24/0	BMI increased (OR 0.859, 0.75-0.983)	8
Qiu T[27] (2018)	China	Case–control	2012-2016	Single-center	LC	57.0 ± 10.8	51.58	44/444	6.24 ± 1.92	DM (OR 4.189, 2.067-6.231)	7
Stine, J.G[6] (2018)	USA	Case–control	2005-2015	Single-center	LC	53.8 ± 13.1	64.00	50/100	22/54/24	NAFLD (HR 5.34, 1.53-18.66) BMI increased (0.86, 0.79-0.95)	6
Zakko, A[3] (2018)	USA	Cohort	2013	NIS	LC	59.0[‡]	65.0[‡]	Total: 589 420 1125/69934[‡]	NA	BMI ≥ 30 kg/m^2 (OR 0.87, 0.75-1.0)	5

(*Continued*)

Table 1. Study Characteristics of Included Studies (*Continued*)

First Author (Year)	Country	Study Design	Enrollment Period	Data Source	Target Patients	Age (Year Mean ± SD or Rang)	Male (%)	No. Pts. With PVT/Total No. Pts (n)	No. Pts. with Child-Pugh A/B/C(n) or Mean ± SD	Metabolic Factors, and Adjusted OR or HR (±95% CI) for PVT	NOS Score
Zhang Y[28] (2018)	China	Case–control	2013-2016	Single-center	LC	51.6 ± 10.6	74.26	68/136	6.24 ± 1.92	DM (OR 4.323, 1.625-5.899)	7
Zeng CM[29] (2019)	China	Case–control	2015-2019	Single-center	LC	57.3 ± 13.9	62.07	58/116	NA	BMI ≥ 25 kg/m^2 (OR 2.019, 1.025-3.973) DM (OR 2.308, 1.211-3.859) HC (OR 2.696, 1.145-3.352)	5
Chen YJ[30] (2019)	China	Case–control	2012-2012	Single-center	LC	49.7 ± 10.3 (24-76)	77.41	33/239	127/92/20	DM (OR 0.404, 0.124-1.32)	8
Liu JJ[32] (2019)	China	Case–control	2012-2016	Single-center	LC	51.6 ± 10.6	58.14	16/86	44/34/8	DM (OR 1.69, 0.94-3.13)	7
Reyes, L[17] (2019)	Spain	Case–control	2000-2015	Single-center	LT	57.8 ± 9.6	83.33	46/288	74/139/73	BMI ≥ 25 kg/m^2 (OR 2.4, 1.1-5.4)	8
Bert, J[38] (2020)	Belgium	Cohort	2006-2016	Single-center	LT	57.4 ± 16.5	66.92	40/390	14.31 ± 15.45†	BMI increased (OR 1.1, 1.028-1.777)	8
Fan, X. W[19] (2020)	USA	Cohort	2000-2014	NIS	LC	57.9 ± 111.4	62.40	51 924/3 336 144	NA	NAFLD (OR 1.82, 1.64-2.03)	7
Rinat·Kdrim[33] (2020)	China	Case–control	2015-2019	Single-center	LC	56.8±11.4 (42-68)	68.13	80/160	NA	DM (OR 1.5, 1.2-2.0)	7
Zhu YB[34] (2020)	China	Case-control	2018-2019	Single-center	LC	53.3±7.9 (39-74)	55.00	20/100	51/39/10	DM (OR 1.7,0.95-3.14)	6

SD, standard deviation; Pts, patients; PVT, portal vein thrombosis; OR, odds ratio; HR, hazard ratio; NOS, Newcastle–Ottawa Scale; LC, liver cirrhosis; NA, not available; HC, hypercholesterolemia; LT, liver transplantation; BMI, body mass index; DM, diabetes mellitus; OPTN/UNOS, Organ Procurement and Transplantation Network Database/Nationwide United Network for Organ Sharing; NAFLD, nonalcoholic fatty liver disease; NIS, National Inpatient Sample.
†Model for end-stage liver disease (MELD) score. ‡Obese-cirrhotic group only.

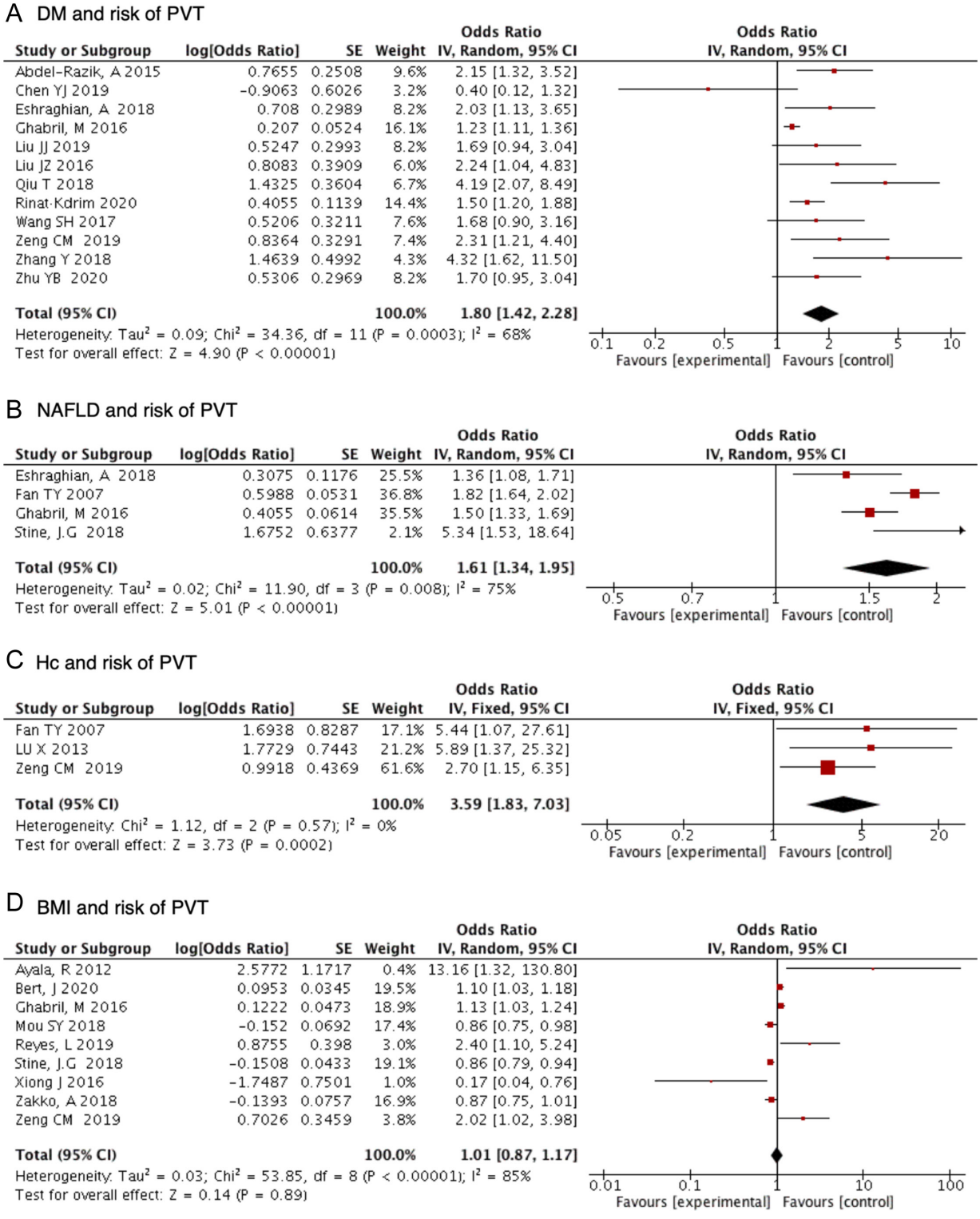

Figure 2. Meta-analysis regarding the metabolic disorders and risk of portal vein thrombosis (PVT). (A) Diabetes mellitus (DM) and risk of PVT. (B) Nonalcoholic fatty liver disease (NAFLD) and risk of PVT. (C) Hypercholesterolemia (HC) and risk of PVT. (D) Body mass index (BMI) and risk of PVT.

America and Africa subgroups. The association was slightly higher in the subgroup of NOS < 7 (fixed OR 1.95, 95% CI 1.27-3.00) than the NOS ≥ 7 subgroup (random OR 1.78, 95% CI 1.37-2.32). Information above indicated the geographical region and quality of study did not affect the overall pooled results. In the subgroup analysis of target population, the type of study design, and sample size, significant association was only demonstrated in liver cirrhosis (random OR 1.93, 95% CI 1.47-2.53), case–control studies (random OR 1.92, 95% CI 1.46-2.52), and sample size ≤200 (fixed OR 1.73, 95% CI 1.47-2.03). However, DM did not affect the PVT development in the subgroup of LT candidates, cohort studies, and sample size > 200. These results are shown in Table 2.

Egger's test showed statistically significant asymmetry of the funnel plot (P = .014), thus suggesting the presence of publication bias among studies. However, the further Trim-and-Fill analysis added with one imputed study showed that the pooled OR before and after trimming was 1.80 (95% CI 1.42-2.28) and 1.73 (95% CI 1.38-2.19), showing that the publication bias had little impact on the interpretation of the results (Figure 3).

Nonalcoholic Fatty Liver Disease and Risk of Portal Vein Thrombosis Event

Given that most cases of cryptogenic cirrhosis were likely related to fatty liver, we roughly regard cryptogenic cirrhosis as NAFLD-related cirrhosis.[20,31] A pooled analysis of 4 studies (n = 3 385 821 patients) showed a significant positive association of NAFLD in the development of PVT, with pooled random OR 1.61 (95% CI 1.34-1.95) (Figure 2B). In this analysis, statistically significant between-study heterogeneity was observed (I^2 = 75%, P = .008). Sensitivity analysis failed to demonstrate any source of heterogeneity with the pooled ORs (range 1.51-1.71) (Supplementary Table 8). Subsequently, we found a similar risk of PVT in the confirmed only-NAFLD population (random OR 1.71, 95% CI 1.3-2.25, P < .0001, I^2 = 83%) with 3 studies[6,20,23] and the NAFLD added with cryptogenic cirrhosis (fixed OR 1.47, 95% CI 1.32-1.63, P < .00001, I^2 = 0) with 2 studies[20,31] (Supplementary Figure 3).

Hypercholesterolemia and Risk of Portal Vein Thrombosis Event

Three studies (n = 262 participants) assessed the adjusted OR of hypercholesterolemia and PVT risk, and

Table 2. Subgroup Analyses of Diabetes Mellitus and Risk of Portal Vein Thrombosis

Variable	No. of Studies	No. of Cases	Adjusted OR (with 95%CI)	*P*	I^2 Values (with *P* values)
Geographical region					
Studies in Asia	10	2612	1.92 (1.46-2.52)	*P* < .0001	51% (*P* = .03)
Studies in America	1	48 570	1.23 (1.11-1.36)	*P* < .0001	/
Studies in Africa	1	120	2.15 (1.32-3.52)	*P* = .02	/
Target population					
Liver cirrhosis	10	1725	1.93 (1.47-2.53)	*P* < .0001	52% (*P* = .03)
LT candidates	2	49 577	1.45 (0.91-2.30)	*P* = .11	63% (*P* = .10)
Quality of study					
NOS≥7	10	51 086	1.78 (1.37-2.32)	*P* < .0001	71% (*P* = .0003)
NOS<7	2	216	1.95 (1.27-3.00)	*P* = .02	0% (*P* = .49)
Type of study design				0.48	
Case-control studies	10	2612	1.92 (1.46-2.52)	*P* < .0001	51% (*P* = .03)
Cohort studies	2	48 690	1.54 (0.9-2.64)	*P* = .11	79% (*P* = .03)
Sample size					
N≤200	8	1042	1.73 (1.47,2.03)	*P* < .0001	0% (*P* = .44)
N>200	4	50 260	1.58 (0.81-3.07)	*P* = .18	83% (*P* = .0006)

OR, odds ratio; LT, liver transplantation; NOS, Newcastle–Ottawa Scale.

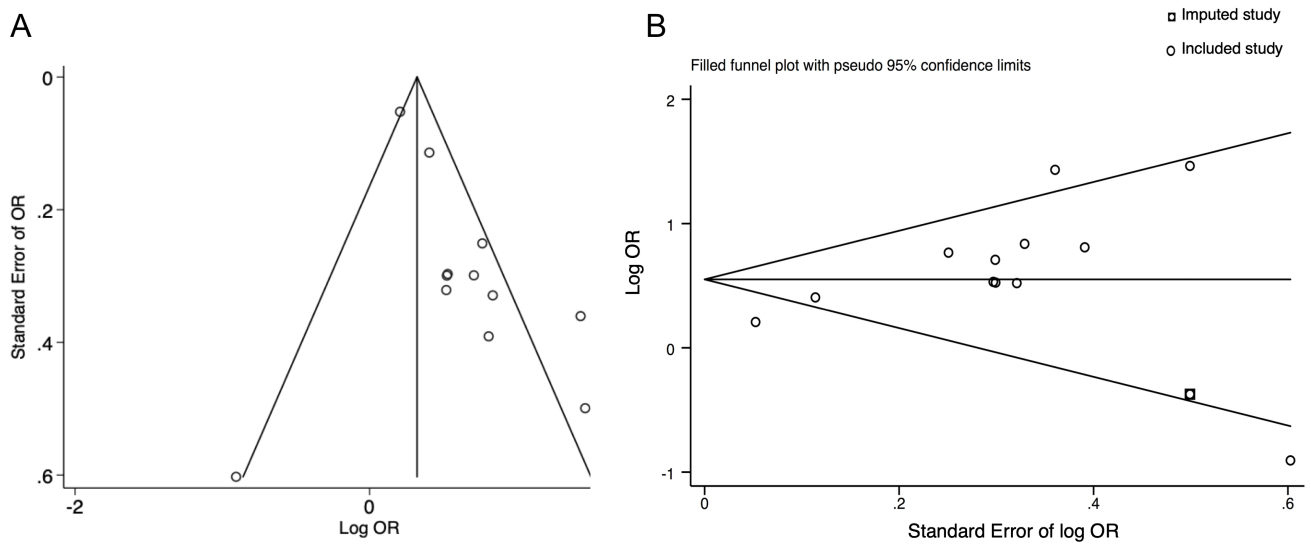

Figure 3. Publication bias assessment in studies on diabetes mellitus and portal vein thrombosis. (A) Funnel plot demonstrating visible asymmetry suggesting publication bias after plotting included studies. (B) Adjusted funnel plot using the "Trim and Fill test" without significantly altering the outcomes (hollow square represented the imputed study).

meta-analysis showed that hypercholesterolemia had a high risk of PVT (fixed OR 3.59, 95% CI 1.83-7.03, P = .0002), with no significant heterogeneity among the studies (I^2 = 0%, P = .57) (Figure 2C).

Body Mass Index and Risk of Portal Vein Thrombosis Event

Nine studies (n = 640 109) provided data suitable for pooling primary analysis of BMI and the PVT risk. Body mass index did not contribute to PVT risk in those studies (random OR 1.01, 95% CI 0.87-1.17, P = .89, I^2 = 85%) (Figure 2D). Sensitivity analysis did not disclose any source of heterogeneity (Supplementary Table 9). Subsequently, among the meta-regression, heterogeneity was not related to geographical region (Asian vs no-Asian) (P = .722), study quality (NOS ≥ 7 vs < 7) (P = .736), type of study design (case-control study vs cohort study) (P = .813), and sample size (> 200 vs ≤200) (P = .574), but except for target population (liver cirrhosis vs LT candidates) (P = .028) (Supplementary Table 10). And then, BMI did not contribute to PVT risk in all the subgroup of studies in Europe, America, or Asia, liver cirrhosis or LT candidates, NOS ≥ 7 or NOS < 7, cohort or case–control studies, sample size ≤200 or >200. We also conducted a stratified analysis based on different BMI thresholds (≥30 kg/m^2, ≥25 kg/m^2, and BMI increased) with a similar result. The heterogeneities were statistically significant in all the subgroup analysis and stratified analysis. These results are shown in Table 3. Finally, the funnel plot and Egger's test did not reveal significant publication bias (Egger's test: P for bias = .783) (Supplementary Figure 4).

DISCUSSION

Major Findings

Portal Vein Thrombosis is an important and often overlooked complication of cirrhosis. Our meta-analysis is hitherto the first study focused on metabolic disorders and risk of cirrhotic PVT. We were not only able to confirm that metabolic disorders such DM, NAFLD, and hypercholesterolemia were significantly associated with a 1.80-fold, 1.61-fold and 3.59-fold increased risk of PVT but also demonstrated comprehensively that BMI did not appear to be a risk predictor of cirrhotic PVT. The estimated ORs for these variables may be less robust than the established major risk factors for PVT, such as decreased PV velocity and splenectomy.[6,8] However, metabolic disorders were more widespread and often coexist, and their coexistence was likely associated with an enhancement effect.[39] Given the multifactorial nature of PVT, our findings highlighted that the concomitant action of metabolic disorders is responsible partly for the pathogenesis of cirrhotic PVT.

Biological Plausibility

According to Virchow's triad, the hypercoagulable milieu within metabolic disorders may predispose cirrhotic patients to develop PVT events. The aforementioned metabolic disorders such as DM, NAFLD, hyperlipidemia,

Table 3. Subgroup Analyses Body Mass Index and Risk of Portal Vein Thrombosis

Variable	No. of Studies	No. of Cases	Adjusted OR (with 95% CI)	*P*	I^2 Values (with *P* Values)
Geographical region					
Studies in Europe	3	1058	2.0 (0.79-5.09)	.14	76% (*P* = .02)
Studies in Asia	3	961	0.85 (0.35-2.03)	.71	81% (*P* = .005)
Studies in America	3	638 090	0.95 (0.78-1.15)	.59	90% (*P* < .00001)
Target population					
liver cirrhosis	5	590 481	0.88 (0.76-1.01)	.07	62% (*P* = .04)
LT candidates	4	49 628	1.15 (1.0-1.33)	.05	64% (*P* = .03)
Quality of study					
NOS≥7	6	50 473	1.06 (0.88-1.27)	.54	81% (*P* < .00001)
NOS<7	3	589 636	0.91 (0.76-1.09)	.89	67% (*P* = 0.05)
Type of study design					
Cohort studies	5	638 883	1.0 (0.87-1.16)	.98	83% (*P* = .0001)
Case–control studies	4	1126	1.10 (0.52-2.34)	.81	82% (*P* = .0007)
Sample size					
N≤200	6	639 770	1.06 (0.89-1.27)	.49	79% (*P* = .0002)
N>200	2	339	0.90 (0.76-1.07)	.24	67% (*P* = .05)
BMI threshold					
BMI ≥30 kg/m^2	3	638 370	1.04 (0.77-1.41)	.80	85% (*P* = .001)
BMI ≥25 kg/m^2	3	1126	1.14 (0.35-3.74)	.83	80% (*P* = .006)
BMI increased	2	613	0.94 (0.78-1.13)	.49	92% (*P* < .00001)

OR, odds ratio; LT, liver transplantation; NOS, Newcastle–Ottawa Scale; BMI body mass index.

and obesity disturb the physiological balance across all the 3 stages of hemostasis, leading to a prothrombotic state hallmarked with platelet hypersensitivity, coagulation factor disorders, and hypofibrinolysis.[10-13,40] In the primary hemostasis, most metabolic disorders increased the level of von Willebrand factor and decreased the level of ADAMTS13, which contributed to platelet hypersensitivity.[12,40,41] Besides, hyperglycemia and insulin resistance in DM also enhanced the number of platelets.[42] In the secondary hemostasis, liver cirrhosis with hepatic insufficiency showed a decreasing trend of factors II, V, VII, IX, X, XI, and fibrinogen,[2] while metabolic disorders showed the opposite characteristics.[11-13,43] Meanwhile, increased levels of FVIII and decreased levels of protein C, protein S, and antithrombin, both in cirrhotic patients and metabolic disorders, might predispose patients to hypercoagulable state.[2,12] And hypo-fibrinolysis was a cardinal abnormality in the tertiary hemostasis, such as the elevation of plasminogen activator inhibitor-1 and thrombin-activator fibrinolysis inhibitor along with the decrease of tissue plasminogen activator and tissue activating factor antigen.[11,12,44] However, few researchers had formally assessed the hemostasis system in the context of cirrhosis coexisting with metabolic disorders. Further mechanistic research is needed imperatively.

Obesity and Portal Vein Thrombosis

Until now, obesity is a well-established risk factor for VTE and non-cirrhotic PVT according to epidemiological studies in the general population.[45,46] Interestingly, in the context of liver cirrhosis, overall and subgroup meta-analysis showed no difference in cirrhotic PVT between normal BMI and above-normal BMI. Similarly, the lack of association between BMI and VTE complications in LT candidates corroborated our finding.[47] But the reasons for it were unclear, and possible explanations currently under discussion are summarized as follows.

First, BMI had some limitations and was probably not the best index to evaluate "obesity" in the context of liver cirrhosis. As we know, BMI was a marker of excess body fat content in adults, but it failed to consider the distribution of such body fat. Body fat distribution, like central obesity measured by waist circumference (WC) due

to visceral fat accumulation, was the best indicator of VET.[48,49] Meanwhile, the presence of ascites and edema among patients with hepatic cirrhosis affects the accuracy of BMI and then overestimating the true incidence of obesity.[6] It was reported that correcting for ascites volume resulted in 11%-20% of patients moving into a lower BMI classification.[50] A striking study concluded that VF is an independent risk factor for cirrhotic PVT regardless of BMI and WC, further strengthening our findings.[21] Second, another potential explanation was probable: the underestimation of true PVT incidence, due to limited accuracy of ultrasonography in severe obesity with larger amounts of subcutaneous fat or end-stage cirrhosis with mass ascites.[3] Taken together, these measurement biases may attenuate the risk estimates of the association of obesity and cirrhotic PVT. Additionally, the potential pro-thromboembolic effect of obesity might be partly attenuated due to the impaired synthetic capacity in patients with hepatic cirrhosis.[12,51] Then, obesity might not impact cirrhotic PVT as much as other associated comorbidities, such as DM, NAFLD, and hypercholesterolemia. Further prospective studies are needed to confirm such association and to give a more mechanistic insight.

Clinical Relevance

Portal Vein Thrombosis cannot be overlooked as patients with cirrhosis have a poor prognosis, especially for LT candidates. Accordingly, the clinical implication of identifying high-risk groups for PVT was extremely important. We might encounter more cirrhotic patients with PVT soon along with the rapid increase of metabolic disorders. Indeed, in contrast to hereditary thrombophilias, these risk factors could be ameliorated with appropriate therapy and lifestyle change. Metabolic optimizations like glucose control, lipid-lowering, regular exercise, and weight loss can alleviate the pro-thrombotic state.[11,52] Hence, it is plausible to hypothesize that appropriate metabolic optimizations will be of benefit to relieve the risk of cirrhotic PVT. Our study suggested a possible method to stratify patients with higher risk of cirrhotic PVT and further stresses the need for routine evaluation and management of metabolic disorders for prevention of PVT.

Study Limitations

Our study had several limitations. First, the heterogeneity among most of the studies was significant. A meta-analysis has inherent weaknesses in terms of combining heterogeneous data sets, especially for the utilization of non-randomized studies containing multiple confounding variables. Second, more clinical trials with the link between metabolic disorders and cirrhotic PVT are further needed to supplement and consolidate our conclusions. In the DM group, the outcomes of subgroup analysis of LT candidates, cohort studies, and sample size >200 were opposite to the overall analysis and the reason was unclear. Concurrently, the limited availability of included studies restricted us to conduct further subgroup analyses for the NAFLD group. We also had no power of drawing accurate conclusions because only one study related to visceral fat[21] or hypertriglyceridemia[22] was included. Third, because a majority of the included studies were case–control studies, we could not fully determine the cause–effect relationship between metabolic disorders and PVT development. Fourth, a major portion of patients in the DM and BMI group has been conducted in the LT population. It is particularly important to consider cohort characteristics in these studies, as a few LT candidates were not indicated for end-stage cirrhosis but non-cirrhotic causes, such as acute liver failure. Although the target population was not the source of heterogeneity in the BMI group, the inconsistent conclusions in the DM group between liver cirrhosis and LT candidates needed to be further verified.

In conclusion, metabolic disorders, such as DM, NAFLD, and hypercholesterolemia, are significantly associated with an increased risk of PVT in patients with hepatic cirrhosis, but BMI does not appear to be a risk predictor of cirrhotic PVT. High-quality clinical and mechanistic studies are needed for further verification, especially in obese patients. Furthermore, we also stress the importance of the routine evaluation and management of metabolic disorders for the prevention of PVT in patients with hepatic cirrhosis.

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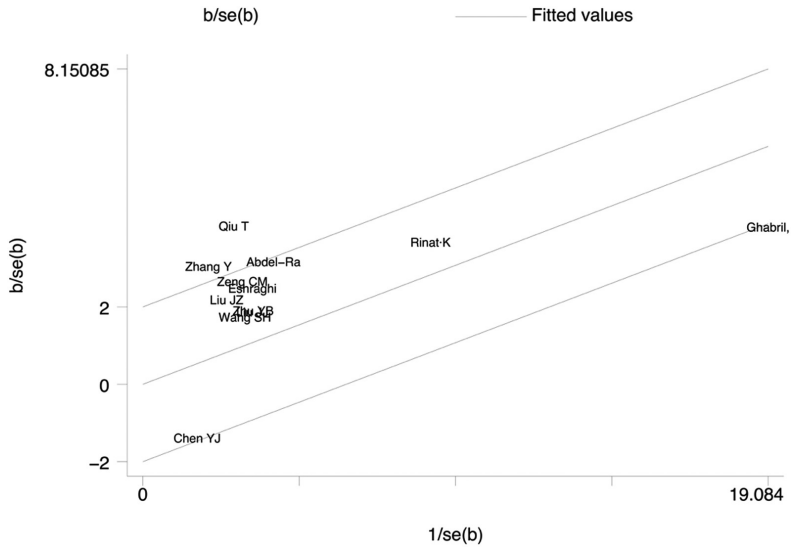
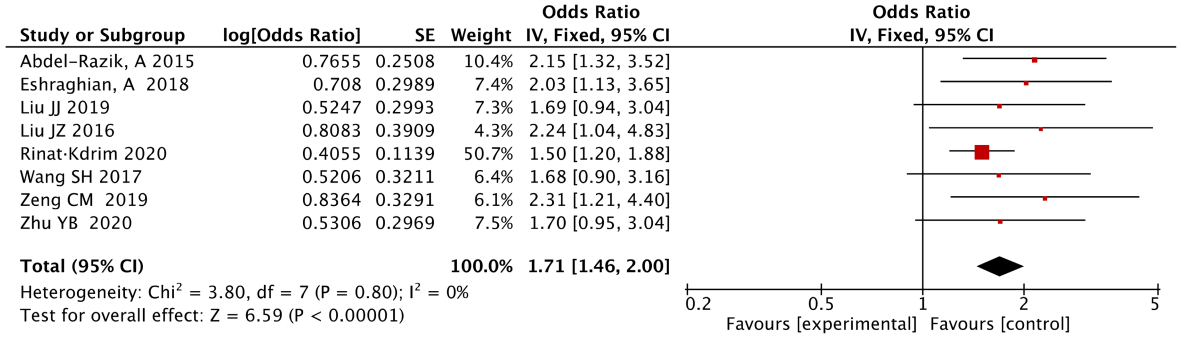
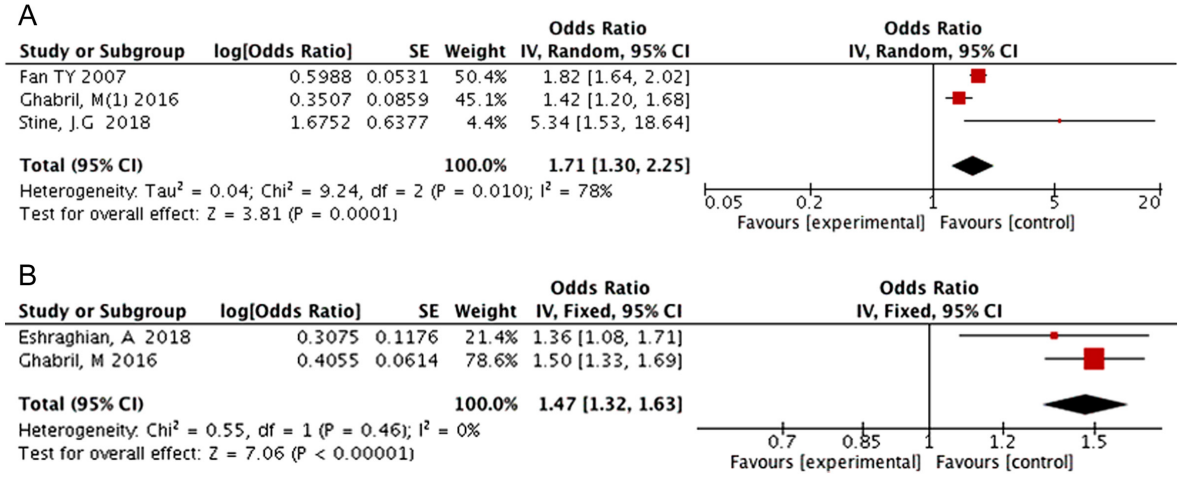


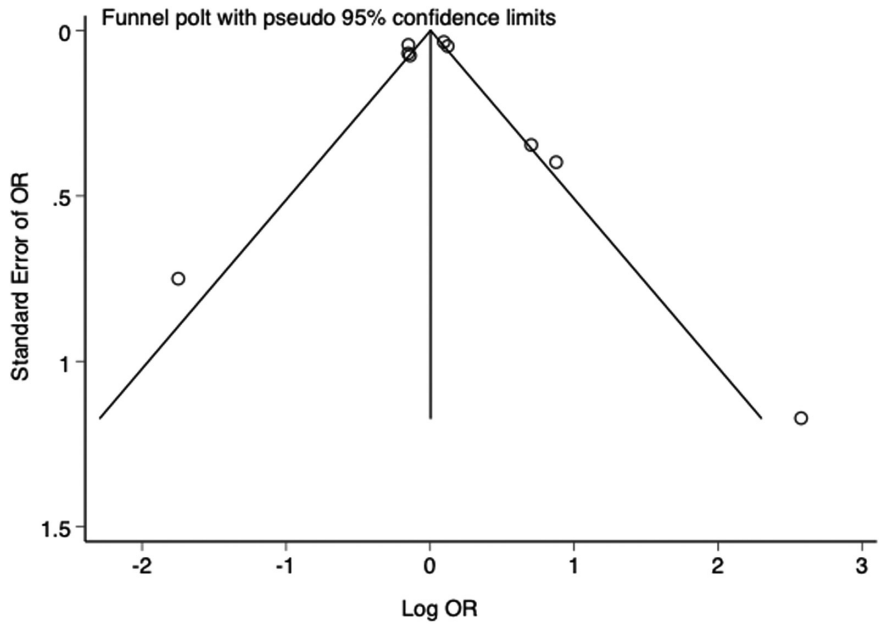
Supplementary Figure 1. Galbraith plot analysis regarding diabetes mellitus and risk of portal vein thrombosis. The analysis identified 4 studies by Ghabrill, M, Qiu T, Zhang Y, and Chen YJ as the major sources of heterogeneity.



Supplementary Figure 2. Meta-analysis regarding diabetes mellitus and risk of portal vein thrombosis after eliminating the major sources of heterogeneity, which included studies of Ghabrill, M, Qiu T, Zhang Y, and Chen YJ.



Supplementary Figure 3. Stratified meta-analyses regarding nonalcoholic fatty liver (NAFLD) and risk of portal vein thrombosis (PVT). Panel A: Only- NAFLD population and risk of PVT; Panel B: NAFLD added with cryptogenic cirrhosis and risk of PVT.



Supplementary Figure 4. Funnel plot regarding body mass index and risk of portal vein thrombosis. And the funnel plot is symmetry according to Egger's test (*P* = .783).

Supplementary Table 1. Search Strategy in PubMed

Date base	Search Strategy	Result
PubMed	1# "Liver Cirrhosis" [Mesh]	91 679
	2# (Hepatic Cirrhosis [Title/Abstract]) *OR* (Cirrhosis, Hepatic [Title/Abstract]) *OR* (Cirrhosis, Liver [Title/Abstract]) *OR* (Fibrosis, Liver [Title/Abstract]) *OR* (Liver Fibrosis [Title/Abstract])	22 191
	3# 1 *OR* 2	100 463
	4# (portal vein thrombosis[Title/Abstract]) *OR* (portal venous thrombosis[Title/Abstract]) *OR* (portal vein thrombus[Title/Abstract]) *OR* (portal venous thrombus[Title/Abstract]) *OR* (portal vein obstruction[Title/Abstract]) *OR* (portal venous obstruction[Title/Abstract]) *OR* (portal vein occlusion[Title/Abstract]) *OR* (portal venous occlusion[Title/Abstract]) *OR* (thrombotic portal vein[Title/Abstract]) *OR* (thrombosed portal vein[Title/Abstract]) *OR* (occluded portal vein[Title/Abstract]) *OR* (occlusive portal vein[Title/Abstract]) *OR* (obstructed portal vein[Title/Abstract]) *OR* (obstructive portal vein[Title/Abstract]) *OR* (portal cavernoma[Title/Abstract]) *OR* (cavernous transformation of portal vein[Title/Abstract]) *OR* (mesenteric vein thrombosis[Title/Abstract]) *OR* (mesenteric venous thrombosis[Title/Abstract]) *OR* (mesenteric vein obstruction[Title/Abstract]) *OR* (mesenteric venous obstruction[Title/Abstract]) *OR* (mesenteric vein occlusion[Title/Abstract]) *OR* (mesenteric venous occlusion[Title/Abstract]) *OR* (splenic vein thrombosis[Title/Abstract]) *OR* (splenic venous thrombosis[Title/Abstract]) *OR* (splenic vein obstruction[Title/Abstract]) *OR* (splenic venous obstruction[Title/Abstract]) *OR* (splenic vein occlusion[Title/Abstract]) *OR* (splenic venous occlusion[Title/Abstract]) *OR* (splanchnic vein thrombosis[Title/Abstract]) *OR* (splanchnic venous thrombosis[Title/Abstract]) *OR* (splanchnic vein obstruction[Title/Abstract]) *OR* (splanchnic venous obstruction[Title/Abstract]) *OR* (splanchnic vein occlusion[Title/Abstract]) *OR* (splanchnic venous occlusion[Title/Abstract]) *OR* (abdominal vein thrombosis[Title/Abstract]) *OR* (abdominal venous thrombosis[Title/Abstract]) *OR* (abdominal vein obstruction[Title/Abstract]) *OR* (abdominal venous obstruction[Title/Abstract]) *OR* (abdominal vein occlusion[Title/Abstract]) *OR* (abdominal venous occlusion[Title/Abstract])	9990
	5# 3# AND 4#	1142
	6# "Risk Factors" [Mesh]	862 150
	7# (Factor, Risk [Title/Abstract]) *OR* (Factors, Risk [Title/Abstract]) *OR* (Risk Factor [Title/Abstract])	223 483
	8# 6 *OR* 7	986 098
	9# 5 *AND* 8	165

Supplementary Table 2. Characteristics of Studies Focused on Liver Transplantation Candidates from UNOS/OPTN

First Author (Year)	Country	Study Design	Enrollment Period	Target Patients	Age (Year Mean ± SD)	Male (%)	No. Pts. with PVT/Total No. Pts (n)	MELD Score (Mean ± SD)	Metabolic Factors, and Adjusted OR or HR (±95% CI) for PVT
Stine JG(1) (2014)	USA	Case–control	Jan 2003-Dec 2012	LT	NA	NA	3503/50 468	NA	NAFLD + Cryptogenic disease (OR 1.45, 1.298-1.622) BMI increased (OR 1.01, 1.0-1.01)
Stine JG(2) (2015)	USA	Case–control	Jan 2003-Dec 2012	LT	52.68 ± 9.91	66.70	2096/33 368	22.68 ± 9.89	NAFLD (OR 1.55, 1.33-1.81) BMI increased (OR 1.00, 0.99-1.01)
Bezinover, D(3) (2016)	USA	Case–control	2000-2012	LT	Mean 52.51	70.22	4247/65 646	NA	BMI ≥40 kg/m^2(OR 1.19, 1.08-1.31 BMI ≥25 kg/m^2(OR 1.05, 0.96-1.38) BMI≤18.5 kg/m^2(OR 1.04, 0.79-1.38) DM (OR 1.22, 1.01-1.26)
Ghabril, M(4) (2016)	USA	Case–control	2003-September 2013	LT	54.8 ± 4.2	67.93	3321/48 570	NA	BMI>30 kg/m^2 (OR 1.13, 1.03-1.23) DM (OR 1.23, 1.11-1.36) NAFLD (OR 1.42, 1.20-1.70) Cryptogenic disease (OR 1.5, 1.30-1.80) NAFLD + cryptogenic disease (OR 1.5, 1.33-1.71)
Stine JG(5) (2016)	USA	Case–control	~ Sep 2014	LT	NA	NA	2626/35 959	19.64	HR-NASH (OR 2.05, 1.57-2.67) LR-NASH (OR 1.72, 1.49-1.97)
Stine JG(6) (2017)	USA	Case–control	Feb 2002-Sep 2014	LT	53.20 ± 9.20	67.99	2626/35 072	22.86 ± 9.07	HR-NASH (OR 2.11, 1.60-2.76) LR-NASH (OR 1.71, 1.49-1.96)
Montenovo, M(7)(2018)	USA	Case–control	Jan 2002-Jun 2014	LT	53.1 ± 10.26	67.00	3612/61 557	18.94 ± 9.53	NAFLD (OR 1.34, 1.22-1.48) BMI increased (OR 1.14, 1.08-1.2) DM (OR 1.22, 1.13-1.32)
Bezinover, D(8) (2019)	USA	Case–control	2000-2012	LT	53.50±10.20	65.39	4414/49 155	23.98 ± 14.73	BMI increased (OR 1.02, P = .008) DM (OR 1.31, $P < 0.001$)
Gaballa, D(9) (2019)	USA	Case–control	Feb 2002-Sep 2016	LT	54.15 ± 9.38	68.27	4311/66 568	18.06 ± 9.37	NAFLD + cryptogenic disease (HR 1.29, 1.08-1.54)

OPTN/UNOS, Organ Procurement and Transplantation Network database/Nationwide United Network for Organ Sharing; SD, standard deviation; Pts, patients; PVT, portal vein thrombosis; MELD, model for end-stage liver disease; NA, not available; OR odds ratio; HR, hazard ratio; LT, liver transplantation; NA, not available; NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; DM, diabetes mellitus; HR-NASH, high-risk non-alcoholic steatohepatitis; LR-NASH, low-risk non-alcoholic steatohepatitis,

Supplementary Table 3. Characteristics of Studies Regarding Visceral Fat, Hypertriglyceridemia, and Risk of Portal Vein Thrombosis

First Author (Year)	Country	Study Design	Enrollment Period	Data Source	Target Patients	Age (Year Mean ± SD or Range)	Male (%)	No. Pts. With PVT/ Total No. Pts (n)	No. Pts. with Child-Pugh A/B/C (n) or Mean ± SD	Metabolic factors, and Adjusted OR or HR (±95% CI) for PVT
Hernández-Conde, M(10) (2019)	Spain	Case–control	2016-2018	Single-center	LC	63.0 ±10.1	70.09	16/214	160/39/12	VF increased (OR 1.2, 1.03-1.3)
Zuo HW (11) (2021)	China	Case–control	2013-2018	Single-center	LC	54.8 ± 10.9	61.48	119/283	144/115/24	TG increased (OR 0.411, 0.19-0.889)

SD, standard deviation; PVT, portal vein thrombosis; OR, odds ratio; HR, hazard ratio; LC, liver cirrhosis; VF, visceral fat; TG, hypertriglyceridemia.

Supplementary Table 4. Methodological Quality of Case–Control Studies

	Selection			Comparability		Outcome			
Author(Year)	Adequate Definition of Cases	Representativeness of Cases	Selection of Controls	Definition of Controls	Control for Important Factors†	Exposure Ascertainment	Same Method of Ascertainment for All Subjects	NonResponse Rate	Total Quality Scores
Fan TY (2007)	⋆	0	0	⋆	⋆	⋆	⋆	⋆⋆	6
Liu JZ (2016)	⋆	0	0	⋆	⋆⋆	⋆	⋆	⋆⋆	7
Xiong J (2016)	⋆	0	0	⋆	⋆⋆⋆	⋆	⋆	⋆	7
Wang SH (2017)	⋆	0	0	⋆	⋆⋆	⋆	⋆	⋆	7
Eshraghian, A (2018)	⋆	⋆	0	⋆	⋆⋆	⋆	⋆	⋆	8
Qiu T (2018)	⋆	0	0	⋆	⋆⋆	⋆	⋆	⋆	7
Stine,J.G (2018)	⋆	0	0	⋆	⋆⋆	0	⋆	⋆	6
Zhang Y(2018)	⋆	0	0	⋆	⋆⋆	⋆	⋆	⋆	7
Zeng CM (2019)	⋆	0	0	⋆	⋆	0	⋆	⋆	5
Chen YJ (2019)	⋆	⋆⋆	0	⋆	⋆⋆	⋆	⋆	⋆	8
Liu JJ (2019)	⋆	0	0	⋆⋆	⋆⋆	⋆	⋆	⋆	7
Reyes, L (2019)	⋆	⋆	0	⋆	⋆⋆	⋆	⋆	⋆	8
Rinat·Kdrim (2020)	⋆	⋆	0	⋆	⋆	⋆	⋆	⋆	7
Zhu YB (2020)	0	⋆	0	⋆	⋆⋆	0	⋆	⋆	6

†A maximum of 2 stars could be awarded for this item. Studies that controlled for age and/or sex received one star, whereas studies that controlled for liver function (e.g., Child-Pugh score, model for end-stage liver disease (MELD) score, or etiology of liver cirrhosis received an additional star.

Supplementary Table 5. Methodological Quality of Cohort Studies

	Selection			Comparability		Outcome			
Author (Year)	Representativeness of the Exposed Cohort	Selection of the Non-exposed Cohort	Ascertainment of Exposure	Outcome of Interest not Present at Start of Study	Control for Important Factors[†]	Assessment of Outcome	Follow-Up Long Enough for Outcomes to Occur[‡]	Adequacy of Follow-Up of Cohorts[c]	Total Quality Scores
Ayala, R (2012)	⋆	⋆	⋆	0	⋆⋆	0	⋆	⋆	7
Lu X (2013)	⋆	⋆	⋆	⋆	⋆⋆	⋆	0	⋆	8
Abdel-Razik, A (2015)	⋆	⋆	⋆	⋆	⋆⋆	⋆	⋆	0	8
Ghabril, M (2016)	⋆	⋆	0	⋆	⋆⋆	⋆	0	⋆	7
Mou SY (2018)	⋆	⋆	⋆	⋆	⋆⋆	⋆	0	⋆	8
Zakko, A (2018)	⋆	⋆⋆	⋆⋆	0	⋆⋆	0	0	0	5
Bert, J (2020)	⋆	⋆	⋆	0	⋆⋆	⋆	⋆	⋆	8
Fan, X. W (2020)	⋆	⋆	⋆	0	⋆⋆	⋆	0	⋆	7

[†]A maximum of 2 stars could be awarded for this item. Studies that controlled for age and/or sex received one star, whereas studies that controlled for traditional risk factors of PVT (e.g., Child-Pugh score, model for end-stage liver disease(MELD) score, or etiology of liver cirrhosis or comorbidities) received an additional star.
[‡]A cohort study with a follow-up time > 12 months (median or mean) was assigned one star.
[c]A cohort study with a follow-up rate > 80% was assigned one star.

Supplementary Table 6. Sensitivity Analysis Regarding Diabetes Mellitus and Risk of Portal Vein Thrombosis

Study Omitted	No. of Studies	No. of Cases	Pooled ORs (with 95% CI)	*P*	I^2 Values (with *P* Values)
Abdel-Razik, A (2015)	11	51 182	1.77 (1.38-2.27)	*P* < .00001	68% (*P* =.0006)
Chen YJ (2019)	11	51 063	1.88 (1.49-2.37)	*P* < .00001	67% (*P* =.0008)
Eshraghian, A (2018)	11	50 295	1.79 (1.39-2.29)	*P* < .00001	69% (*P* =.0003)
Ghabril, M (2016)	11	2732	1.93 (1.51-2.47)	*P* < .00001	47% (*P* =.04)
Liu JJ (2019)	11	51 216	1.82 (1.41-2.34)	*P* < .00001	70% (*P* =.0002)
Liu JZ (2016)	11	51 103	1.78 (1.39-2.27)	*P* < .00001	70% (*P* =.0003)
Qiu T (2018)	11	50 858	1.67 (1.35-2.08)	*P* < .00001	60% (*P* =.06)
Rinat·Kdrim (2020)	11	51 142	1.89 (1.40-2.55)	*P* < .0001	70% (*P* =.0002)
Wang SH (2017)	11	51 177	1.82 (1.42-2.34)	*P* <.00001	71% (*P* =.0002)
Zeng CM (2019)	11	51 186	1.77 (1.38-2.26)	*P* < .00001	69% (*P* =.0004)
Zhang Y (2018)	11	51 166	1.72 (1.37-2.17)	*P* < .00001	66% (*P* =.001)
Zhu YB (2020)	11	51 202	1.82 (1.41-2.34)	*P* < .00001	70% (*P* = .0002)

OR, odds ratio.

Supplementary Table 7. Meta-Regression Regarding Diabetes Mellitus and Risk of Portal Vein Thrombosis

Variable	Tau2	I^2 _regression	Adjust R^2	OR (with 95% CI)	*P*
Target population (Asian vs. no-Asian)	0.074	56.60%	5.17%	1.27 (0.65 to 2.47)	.443
Type of study design (liver cirrhosis vs. LT candidates)	0.060	53.36%	23.62%	0.74 (0.39 to 1.41)	.3288
Study design (case-control study vs. cohort study)	0.074	56.60%	5.17%	1.27 (0.65 to 2.47)	.443
Study quality (NOS ≥ 7 vs. < 7)	0.090	68.55%	-15.90%	0.91 (−.39 to 2.12)	.799
Sample size (N> 200 vs. ≤200)	0.085	58.89%	-9.31%	0.82 (0.44 to 1.56)	.511

OR, odds ratio; LT, liver transplantation; NOS, Newcastle–Ottawa Scale.

Supplementary Table 8. Sensitivity Analysis Regarding Nonalcoholic Fatty Liver and Risk of Portal Vein Thrombosis

Study Omitted	No. of Studies	No. of Cases	Pooled ORs (with 95% CIP	*P*	I^2 Values (with *P* Values)
Eshraghian, A (2018)	3	3 384 814	1.71 (1.37-2.13)	*P* <.00001	78% (*P* =.01)
Fan, X. W (2020)	3	49 677	1.51 (1.19-1.91)	*P* = .0007	57% (*P* =.10)
Ghabril, M (2016)	3	3 337 251	1.71 (1.24-2.37)	*P* = .001	76% (*P* =.02)
Stine, J.G (2018)	3	3 385 721	1.58 (1.33-1.87)	*P* < .00001	76% (*P* = .01)

OR, odds ratio.

Supplementary Table 9. Sensitivity Analysis Regarding Body Mass Index and Risk of Portal Vein Thrombosis

Study omitted	No. of studies	No. of cases	Pooled OR (with 95%CI)	*P*	I^2 values (with P values)
Ayala, R (2012)	8	639729	1.00 (0.87-1.15)	*P*=.98	86% (*P*<.00001)
Bert, J (2020)	8	639719	1.00 (0.83-1.20)	*P*=.99	84% (*P*<.00001)
Ghabril, M (2016)	8	591539	0.99 (0.83-1.18)	*P*=.99	85% (*P*<.00001)
Mou SY (2018)	8	639986	1.05 (0.89-1.24)	*P*=.58	85% (*P*<.00001)
Reyes, L (2019)	8	639821	0.98 (0.85-1.14)	*P*=.81	86% (*P*<.00001)
Stine, J.G (2018)	8	640009	1.05 (0.89-1.23)	*P*=.57	81% (*P*<.00001)
Xiong J (2016)	8	639387	1.02 (0.89-1.18)	*P*=.75	86% (*P*<.00001)
Zakko, A (2018)	8	50689	1.04 (0.88-1.23)	*P*=.61	86% (*P*<.00001)
Zeng CM (2019)	8	639993	0.98 (0.85-1.14)	*P*=.81	86% (*P*<.00001)

Supplementary Table 10. Meta-Regression Regarding Body Mass Index and Risk of Portal Vein Thrombosis

Variable	Tau2	I^2_regression (%)	Adjust R^2 (%)	OR (with 95%CI)	*P*
Target population (Asian vs. no-Asian)	0.097	85.82	−204.75	1.17 (0.43-3.19)	.722
Type of study design (liver cirrhosis vs. LT candidates)	0.002	63.14	95.06	1.29 (1.038-1.6144)	.028
Study design (case-control study vs. cohort study)	0.077	82.73	−143.31	1.09 (0.45-2.67)	.813
Study quality (NOS ≥ 7 vs < 7)	0.045	78.52	−40.89	1.11 (0.55-2.26)	.736
Sample size (N> 200 vs ≤200)	0.023	76.58	27.97	1.15 (0.65-2.03)	.574

OR, odds ratio.

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