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ORIGINAL ARTICLE

Nonselective beta-blockers and development of portal vein thrombosis in liver cirrhosis: a systematic review and meta-analysis

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Abstract

Portal vein thrombosis (PVT), which is associated with reduced portal vein velocity, is considered to be an indicator for worse outcomes in liver cirrhosis. Nonselective beta-blockers (NSBBs), which are widely used for primary and secondary prophylaxis of esophageal variceal bleeding in liver cirrhosis, can significantly decrease the portal vein velocity. We proposed a hypothesis that the use of NSBBs might facilitate the development of PVT in cirrhotic patients. The PubMed, EMBASE, and Cochrane Library databases were searched. Major meeting abstracts and randomized-controlled trials regarding the use of NSBBs in liver cirrhosis were also hand-searched. The number of patients who developed PVT in groups treated with or without NSBBs was pooled. Odds ratios (ORs) or risk ratios (RRs) with 95% confidence intervals (CIs) were calculated. Subgroup meta-analyses were performed according to the type of studies, region, and study quality. Meta-regression and sensitivity analyses were performed to explore the source of heterogeneity. Nine of the 6416 retrieved papers were finally included. Overall, meta-analysis demonstrated that NSBBs were significantly associated with the development of PVT (OR 4.62, 95% CI 2.50–8.53; $p < 0.00001$). The heterogeneity was statistically significant ($I^2 = 80\%$; $p < 0.00001$). Subgroup meta-analyses still demonstrated a significantly positive association of NSBBs with the development of PVT in cohort studies (RR 2.57, 95% CI 1.46–4.51; $p = 0.001$) and case–control studies (OR 8.17, 95% CI 2.46–27.06; $p = 0.0006$). Sensitivity analyses based on subgroups find the source of heterogeneity. Based on the systematic review and meta-analysis, we found that the use of NSBBs increased a 4.62-fold risk of PVT in cirrhotic patients.

Keywords Nonselective beta-blockers · Portal vein thrombosis · Liver cirrhosis · Portal hypertension · Propranolol

Abbreviations

NSBBs	Nonselective beta-blockers
PVT	Portal vein thrombosis
AASLD	American Association for the Study of Liver Diseases
EASL	European Association for the Study of the Liver
EVL	Esophageal variceal ligation
DDW	Digestive Disease Week
RCT	Randomized-controlled trial
NOS	Newcastle–Ottawa Scale
OR	Odds ratio
RR	Risk ratio
MD	Mean difference
CI	Confidence interval
CP	Child–Pugh
MELD	Model for end-stage liver disease
ALT	Alanine aminotransferase
AST	Aspartate aminotransaminase
CT	Computed tomography
MRI	Magnetic resonance imaging

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Introduction

Portal vein thrombosis (PVT) is characterized by an obstruction of the blood flow by clots in the portal vein or its branches. PVT is deemed as a potential marker of decompensated cirrhosis with a prevalence of 10–25% and an incidence of

8.4–16.4% in cirrhotic patients [1]. Development of occlusive PVT may have adverse clinical consequences in patients with cirrhosis and has been associated with poor outcomes in post-liver transplant patients [2]. First, cirrhotic patients with PVT acquired longer time to achieve variceal eradication than those without PVT [3]. Second, PVT influenced the development of first bleeding or rebleeding in cirrhotic patients during short- and long-term follow-up [4]. Third, liver transplant recipients with PVT had significantly higher 30-day and 1-year mortality than those without PVT; furthermore, among the liver transplant recipients with PVT, completely occlusive PVT carried worse outcome than partially occlusive PVT [5]. Fourth, PVT was significantly related to acute kidney injury and hepatorenal syndrome in decompensated cirrhotic patients [6].

Virchow's triad is well known for the mechanism of venous thrombosis, which includes blood hypercoagulability, endothelial dysfunction, and reduced blood flow. The same mechanism is also appropriate to the development of PVT in cirrhotic patients. The well-recognized risk factors for PVT in cirrhotic patients include inherited and acquired thrombophilic disorders, inflammation, portal venous endothelial injury secondary to abdominal surgery or trauma, and decreased portal vein velocity [1, 7]. Among them, the most important risk factor of PVT in liver cirrhosis may be decreased portal vein velocity [7].

Nonselective beta-blockers (NSBBs) are recommended by the American Association for the Study of Liver Diseases (AASLD) [8], European Association for the Study of the Liver (EASL) [9], and Baveno VI consensus [10] regarding primary and secondary prophylaxis of esophageal variceal bleeding in cirrhotic patients. A recent network meta-analysis proposed that NSBBs should be superior to esophageal variceal ligation (EVL) for primary prophylaxis, because NSBBs decreased the overall mortality and led to a lower risk of serious complications than EVL [11]. Several meta-analyses confirmed the advantages of NSBBs + EVL over EVL monotherapy in decreasing the risk of variceal rebleeding, overall rebleeding, and mortality in secondary prophylaxis for esophageal variceal bleeding [12–14]. NSBBs have a two-fold mechanism: the first is to antagonize β1 receptors to decrease heart rate and cardiac output, and the second is to antagonize β2 receptors to decrease splanchnic vasodilation, thereby reducing portal blood flow.

Accordingly, we hypothesized that the use of NSBBs might facilitate the development of PVT by decreasing the portal vein velocity [15]. Herein, we conducted a meta-analysis to further clarify this hypothesis.

Methods

Registration

The registration number of PROSPERO is CRD42018096893.

Literature search

The PubMed, Cochrane library, and EMBASE databases were searched to identify all papers which reported the proportion of PVT in cirrhotic patients who received NSBBs and those who did not. Search items were "liver cirrhosis" or "cirrhotic" and "portal vein thrombosis". The last search was updated on January 24, 2019. Major meeting abstracts from the Digestive Disease Week (DDW), AASLD, and EASL were hand-searched. Randomized-controlled trials (RCTs) regarding the use of NSBBs for primary and secondary prophylaxis of variceal bleeding and management of ascites were also hand-searched.

Selection of papers

There was no language limitation. All eligible studies should compare the risk of PVT between cirrhotic patients treated with and without NSBBs. Exclusion criteria were as follows: (1) duplicate studies; (2) reviews or meta-analyses; (3) case reports; (4) correspondence; and (5) irrelevant literature.

Data extraction

The characteristics of studies were extracted as follows: first author, publication year, country, study design, type of publication, enrollment period, follow-up, target population, number of total patients, number and percentage of patients in Child–Pugh (CP) A/B + C, number of patients treated with NSBBs, type of NSBBs, and number of patients who developed and did not develop PVT in patients treated with and without NSBBs. The characteristics of patients were also extracted as follows: age, gender, etiology of cirrhosis, CP score, model for end-stage liver disease (MELD) score, portal vein velocity, ascites, esophageal varices, splenectomy, body-mass index, alanine aminotransferase (ALT), aspartate aminotransaminase (AST), bilirubin, albumin, platelet count, prothrombin time activity, and protein C.

Study quality assessment

The quality of case–control and cohort studies was evaluated using the Newcastle–Ottawa Scale (NOS) [16], which includes 8 questions. The highest NOS score should be 9 points. High quality should be considered if the NOS score is ≥ 6 points.

Endpoints

The primary endpoint was the incidence of PVT in groups treated with or without NSBBs.

Statistical analyses

Review Manager software (Version 5.3, Cochrane collaboration, the Nordic Cochrane Centre, Copenhagen) was employed for the statistical analysis. Only a random-effect model was employed. Odds ratios (ORs), risk ratios (RRs), or mean difference (MD) with 95% confidence intervals (CIs) were calculated. If only data were expressed as median with range, mean with standard deviation was estimated [17]. I^2 and p values were calculated to assess the heterogeneity among studies. $I^2 > 50\%$ and/or $p < 0.1$ were considered to have statistically significant heterogeneity. Publication bias was not performed, because the number of included studies was less than 10. Subgroup analyses were performed according to the type of studies, region, and study quality (studies with NOS ≥ 7). Stata software (Version 12.0, StataCorp, College Station, Texas, USA) was employed for the meta-regression analysis to analyze the source of heterogeneity. In the meta-regression analysis, the covariates included the publication year (before 2016 vs. after 2016), type of study design (cohort vs. case–control), sample size (> 200 vs. < 200), percentage of CP class A, percentage of decompensation events, and studies with NOS (≥ 7 vs. < 7). Sensitivity analysis was performed to explore the source of heterogeneity by omitting each included study.

Results

Study selection

Among the 6416 papers retrieved in PubMed, Cochrane library, and EMBASE databases, 9 papers were potentially eligible [18–26]. In addition, one abstract paper, which was hand-searched from DDW, was potentially eligible [27]. After reviewing the RCTs regarding the use of NSBBs, no paper was eligible for the meta-analysis (Supplementary table1). Among the potentially eligible papers, one paper was further excluded from the meta-analysis, because it did not provide any detailed data [22]. Finally, 9 papers, which reported the specific data regarding the development of PVT in cirrhotic patients treated with and without NSBBs, were included in the meta-analysis [18–21, 23–27] (Fig. 1).

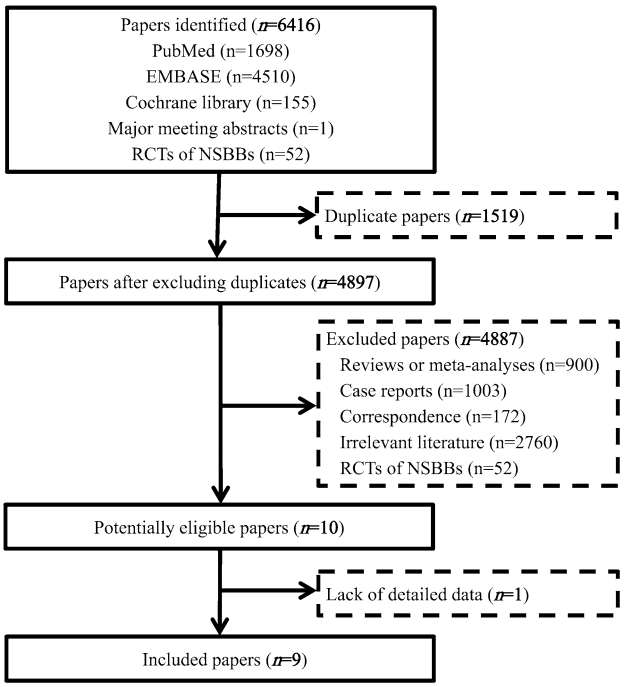

Fig. 1 Flowchart of study selection. *RCT* randomized-controlled trial, *NSBBs* nonselective beta-blockers

Study characteristics

Study characteristics were summarized in Table 1. Six of the included studies were published as full texts [19, 20, 23–26] and 3 as abstracts [18, 21, 27]. According to the countries, 4 of them came from Italy [18, 23–25], 1 from the United States of America [27], 1 from Spain [21], 1 from China [19], 1 from France [20], and 1 from Portugal [26]. The sample size ranged from 56 to 1243. The publication year ranged from 2011 to 2019. Five of them were cohort studies [18, 20, 24–26] and 4 were case–control studies [19, 21, 23, 27]. Among the 4 case–control studies, 1 study was matched by CP score [23], 1 study was matched by age, gender, CP score, MELD score, and etiology [27], and 2 studies did not report any detailed matching information [19, 21]. Type of NSBBs was unknown in 6 studies, propranolol alone in 1 study [23], and propranolol and carvedilol in 2 studies [24, 26]. Diagnostic method of PVT was unclear in 2 studies [18, 27], ultrasound alone in 2 studies [23, 25], ultrasound and/or

Table 1 Study characteristics

First author (year)	Country	Study design	Type of publication	Enrollment period	Follow-up duration	Target population	No. total pts.	No. pts. with Child–Pugh A (%)/B + C (%)	Type of NSBBs	No. pts. treated with NSBBs	No. pts. with/without PVT in NSBBs group	No. pts. with/without PVT in no NSBBs group	NOS score
Pellicelli (2011)	Italy	Cohort	Abstract	NA	19 months	LC without HCC	56	NA	NA	20	8/12	3/33	6
Gomez (2015)	Spain	Case–control	Abstract	Sep 2013–Sep 2014	NA	LC	568	NA	NA	160	15/145	8/400	7
Tang (2015)	China	Case–control	Full text	Jan 2014–Jul 2014	NA	Adult LC	151	46 (30.5%)/151 (69.5%)	NA	16	7/9	13/122	6
Nery (2015)	France	Cohort	Full text	Jun 2000–Mar 2006	47 months	Adult LC	1243	863 (69.4%)/380 (30.6%)	NA	282	40/242	78/883	8
Violi (2016)	Italy	Cohort	Full text	Jan 2012–Dec 2014	2 years	LC	753	397 (52.7%)/356 (47.3%)	NA	344	67/277	59/350	6
Zampino (2018)	Italy	Case–control	Full text	2011–2015	NA	LC	130	101 (77.7%)/29 (22.3%)	Propranolol	28	18/10	1/101	6
Menadier (2018)	USA	Case–control	Abstract	NA	NA	Adult LC	150	NA	NA	65	41/24	34/51	6
Giannitrapani (2018)	Italy	Cohort	Full text	NA	5 years	LC	230	203 (88.3%)/27 (11.7%)	Propranolol and carvedilol	45	11/34	8/177	9
Nery (2019)	Portugal	Cohort	Full text	Jan 2014–Feb 2017	19 months	LC	108	84 (77.8%)/24 (22.2%)	Propranolol and carvedilol	57	10/47	1/50	8

PVT portal vein thrombosis, *NSBBs* nonselective beta-blockers, *LC* liver cirrhosis, *HCC* hepatocellular carcinoma, *NOS* Newcastle–Ottawa Scale, *NA* not available

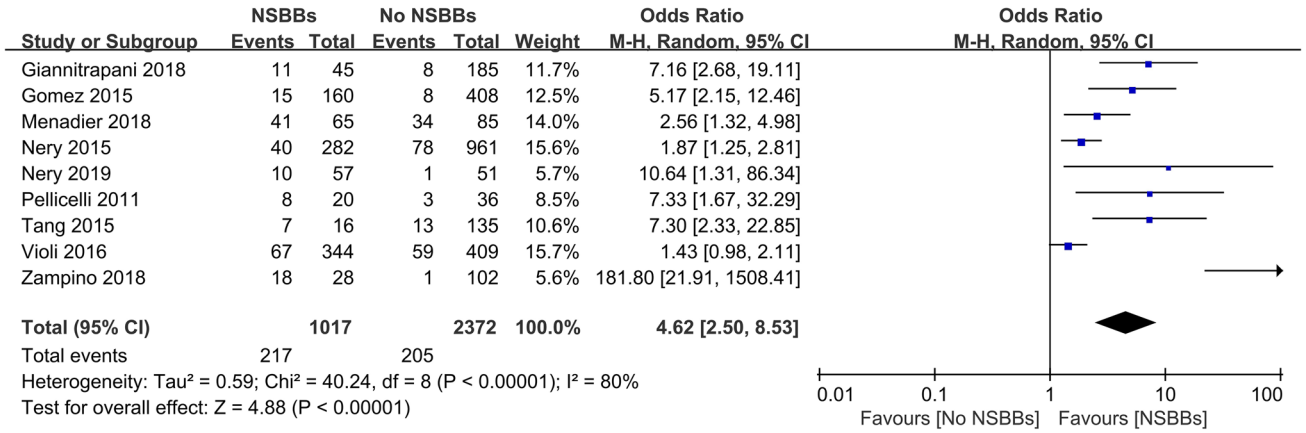

Fig. 2 Meta-analysis regarding the use of nonselective beta-blockers and development of portal vein thrombosis

computed tomography (CT) in 1 study [19], ultrasound followed by a confirmation with magnetic resonance imaging (MRI) and/or CT in 3 studies [20, 24, 26], and ultrasound followed by a confirmation with MRI or CT angiography in 1 study [21]. Only 1 study performed the subgroup analyses according to the grade of esophageal varices, CP class, ALT levels, AST levels, albumin, platelet count, ascites, longitudinal diameter of the spleen, platelet count/spleen diameter ratio, portal vein diameter, bilirubin levels, age, and gender. At multivariate analysis, only NSBBs and grade of esophageal varices were associated with PVT in this study [24].

Study quality

All of the included nine studies had a NOS of ≥ 6 points. Five studies had a score of 6 points [18, 19, 23, 25, 27], 1 had a score of 7 points [21], 2 had a score of 8 points [20, 26], and 1 had a score of 9 points [24] (Table 1).

Patient characteristics

There were 1017 patients treated with NSBBs, of whom 217 had or developed PVT and 800 did not have or develop PVT. There were 2372 patients treated without NSBBs, of whom 205 had or developed PVT and 2167 did not have or develop PVT. Age, gender, and etiology of cirrhosis were available in 7 studies [19–21, 23–26], CP class in 6 studies [19, 20, 23–26], MELD score in 5 studies [19, 21, 24–26], information regarding the portal vein velocity in 4 studies [18, 20, 21, 26], and information regarding ascites and esophageal varices in 6 studies [20, 21, 23–26]. Notably, most biomedical variables were missing in 3 studies published as abstracts [18, 21, 27].

Meta-analysis

Meta-analysis demonstrated a significantly positive association of NSBBs with the development of PVT (OR 4.62, 95% CI 2.50–8.53; $p < 0.00001$). The heterogeneity was statistically significant ($I^2 = 80\%$; $p < 0.00001$) (Fig. 2).

Subgroup analyses

Meta-analysis of cohort studies still demonstrated a significantly positive association of NSBBs with the development of PVT (RR 2.57, 95% CI 1.46–4.51; $p = 0.001$). The heterogeneity was statistically significant ($I^2 = 73\%$; $p = 0.005$) (Fig. 3a).

Meta-analysis of case–control studies still demonstrated a significantly positive association of NSBBs with the development of PVT (OR 8.17, 95% CI 2.46–27.06; $p = 0.0006$). The heterogeneity was statistically significant ($I^2 = 81\%$; $p = 0.001$) (Fig. 3b).

Meta-analysis of European studies still demonstrated a significantly positive association of NSBBs with the development of PVT (OR 5.09, 95% CI 2.35–11.01; $p < 0.0001$). The heterogeneity was statistically significant ($I^2 = 84\%$; $p < 0.00001$) (Fig. 3c).

Meta-analysis of studies with NOS ≥ 7 also demonstrated a significantly positive association of NSBBs with the risk of developing PVT (OR 4.27, 95% CI 1.81–10.04; $p = 0.0009$). The heterogeneity was statistically significant ($I^2 = 84\%$; $p < 0.00001$) (Fig. 3d).

Subgroup meta-analyses regarding the portal vein velocity, type of NSBBs, and duration of NSBBs were not performed, because the relevant data were lacking in the majority of the studies.

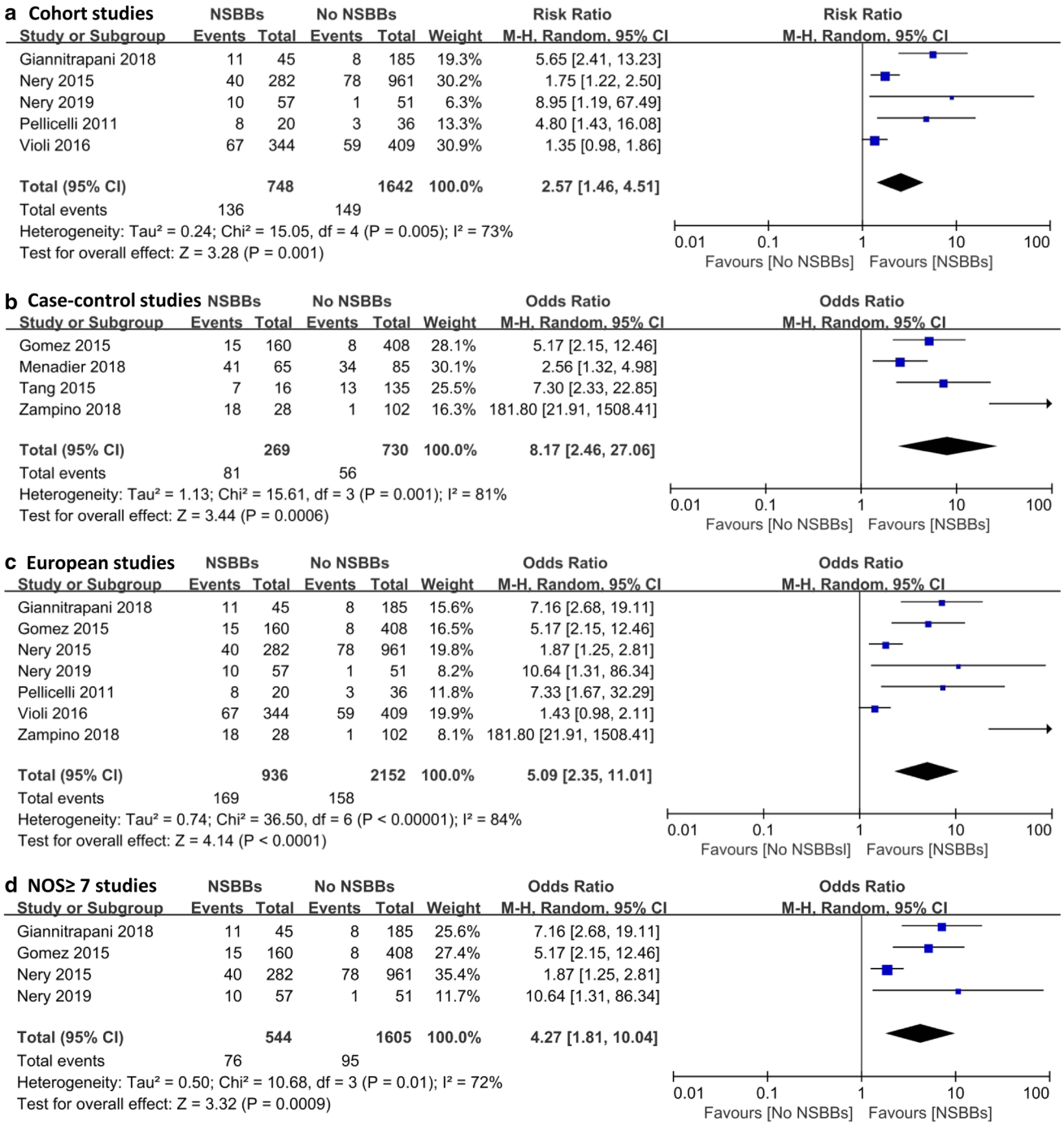

Fig. 3 Subgroup meta-analyses regarding the use of nonselective beta-blockers and development of portal vein thrombosis. Panel **a**: cohort studies; panel **b**: case–control studies; panel **c**: European studies; panel **d**: NOS≥ 7 studies

Meta-regression analyses

The results of meta-regression analyses were reported (Supplementary table 2). Among the meta-analyses, heterogeneity was not related to the publication year (before 2016 vs. after 2016) ($p = 0.744$), sample size (> 200 vs. < 200) ($p = 0.199$), type of study design (case–control vs. cohort) ($p = 0.379$), study quality (NOS ≥ 7 vs. < 7) ($p = 0.814$), percentage of CP class A ($p = 0.564$), esophageal varices ($p = 0.461$), esophageal variceal bleeding ($p = 0.754$), ascites ($p = 0.498$), and encephalopathy ($p = 0.251$).

Sensitivity analyses

Sensitivity analyses based on all included studies, cohort studies, and European studies failed to demonstrate any source of heterogeneity (Supplementary table 3). Sensitivity analyses based on the case–control studies found that the heterogeneity became non-significant after ruling out the study by Zampino et al. ($I^2 = 36\%$, $p = 0.21$) [23]. Sensitivity analyses on studies with NOS ≥ 7 found that the heterogeneity became non-significant after removing the study by Nery et al. [20] ($I^2 = 0\%$, $p = 0.78$).

Additional meta-analyses regarding the association of portal vein velocity with the development of PVT

Four of the included studies also explored the association of portal vein velocity with the development of PVT. Meta-analyses demonstrated that a lower portal vein velocity was significantly associated with a higher risk of PVT (MD 2.16, 95% CI 0.72–3.60; $p = 0.003$) (Supplementary Fig. 1).

Additional meta-analyses regarding the association of platelet count with the development of PVT

Six of the included studies also explored the association of platelet count with the development of PVT. Interestingly, meta-analysis demonstrated that a lower platelet count was significantly associated with a higher risk of PVT (MD 13.71, 95% CI 6.94–20.47; $p < 0.0001$) (Supplementary Fig. 2).

Discussion

This is a hypothesis-driven systematic review and meta-analysis to explore whether or not the use of NSBBs is associated with the development of PVT. The present work validated our previous hypothesis [15] and demonstrated that the use of NSBBs was associated with a 4.62-fold increased risk of PVT.

NSBBs and portal vein velocity. Literature with respect to the impact of NSBBs on the portal vein velocity, hepatic blood flow, and portal blood flow should be reviewed (Table 2) [28–37]. First, seven studies found that propranolol significantly decreased the portal vein velocity, with a range of reduction by 11.3–29% [29–33, 35, 37]. Similarly, atenolol (β1 receptor blocker) [29, 30], isosorbide dinitrate (vasodilator) [29], and isosorbide 5 mononitrate (vasodilator) [32] had an effect on decreasing the portal vein velocity. Notably, propranolol was superior to atenolol in reducing the portal vein velocity [30]. By contrast, neither clonidine (α2 receptor blocker) [33] nor labetalol (β1, β2, and α1 receptor blockers) [30] led to a significant change in the portal vein velocity. Captopril (angiotensin-converting enzyme inhibitor) led to an opposite effect with increasing the portal vein velocity of 6.6% from the baseline [37]. As for the hepatic blood flow as an outcome, two studies suggested that propranolol significantly decreased the hepatic blood flow, with a range of reduction by 14.1–20.4% [28, 36]. By comparison, carvedilol (β1, β2, and α1 receptor blockers) had no significant effect on decreasing the hepatic blood flow [34, 36]. Metoprolol (β1 receptor blocker) did not have a reduction on the hepatic blood flow [28]. As for the portal blood flow as an outcome, propranolol in three studies [29, 30, 35] and atenolol in two studies [29, 30] significantly decreased the portal blood flow. By comparison, the portal blood flow was not significantly changed in isosorbide dinitrate or labetalol group [29, 30].

Portal vein velocity and PVT. Literature with respect to the impact of decreased portal vein velocity on the development of PVT should be reviewed (Table 3) [18, 20, 26, 38–46]. These studies included cirrhotic patients [18, 20, 26, 38, 42, 43, 45, 46], cirrhotic patients undergoing splenectomy with and without devascularization [39, 41, 44], and liver transplantation recipients [40]. Nine of the 12 relevant studies found that the portal vein velocity was significantly lower in PVT group than no PVT group [18, 38–41, 43–46]. By comparison, only 3 studies by Nery et al. and Chen et al. did not observe any significant difference in the portal vein velocity between patients with and without PVT (Nery : 11 cm/s vs. 13 cm/s [20]; Nery : 19.9 ± 7.5 cm/s vs. 21.8 ± 5.5 cm/s [26]; Chen: 17.3 ± 6.2 cm/s vs. 17.8 ± 4.8 cm/s [42]). Notably, the Nery et al. study [20] suggested that such an unexpected finding should be attributed to the heterogeneity in the measurement of instruments and operators and the screening of the portal vein velocity in only a proportion of included patients. Though there is no specific evidence to verify the relationship between the type, dose and duration of NSBBs, and the portal vein velocity, the baseline value of portal vein velocity should also be suspected due to the lack of available data in terms of duration of NSBBs before admission in the Nery et al. study [26]. In the Chen et al. paper, the portal vein velocity was measured after the occurrence of PVT, and the number of patients without PVT who underwent the portal vein velocity measurement was unclear [42].

Portal vein velocity ranged from 12.4 ± 1.7 cm/s to 15.7 ± 3.2 cm/s in healthy subjects of different age groups [47]. Portal vein velocity was 10.0 ± 3.7 cm/s in cirrhotic patients and a decreased portal vein velocity of lower than 10 cm/s was associated with worse survival [48]. The portal vein velocity in cirrhotic patients with and without PVT was heterogeneous among the above-mentioned studies probably due to different instruments for the portal vein velocity measurement and patient characteristics (Table 3). In detail, the portal vein velocity in cirrhotic patients with

Table 2 Correlation between NSBBs and portal vein velocity, hepatic blood flow, and portal blood flow

First author (year)	Country	Target population	Groups	Mechanisms of drugs	Dosage	Route	Interval[#]	Results (change)	Results (reduction %)	*p* value
Portal vein velocity (cm/s)										
Zoli (1986)	Italy	LC with large, high-risk EVs but without previous GIB	Propranolol	β1, β2 blockers	40 mg	Oral	3 h	From 14.2 to 10.2	29 ± 2	0.02
			Atenolol	β1 blocker	100 mg	Oral	3 h	From 13.7 to 10.0	26 ± 2	0.007
			Isosorbide dinitrate	vasodilator	5 mg	Sublingually	0.25 h	From 13.8 to 9.7	31 ± 3	0.01
Ljubicić (1991)	Yugoslavia	LC without previous history of altering hemodynamic drugs	Propranolol	β1, β2 blockers	80 mg	Oral	3 h	From 13.1 ± 2.5 to 10.9 ± 1.8	16.2 ± 6.5	< 0.001
			Atenolol	β1 blocker	100 mg	Oral	3 h	From 12.9 ± 2.4 to 11.1 ± 1.8	13.1 ± 7.2	< 0.001
			Labetalol	β1, β2, α1 blockers	100 mg	Oral	3 h	From 12.9 ± 2.3 to 12.8 ± 2.6	0.78	NS
Cioni (1992)	Italy	LC with EVs	Propranolol	β1, β2 blockers	40 mg	Oral	2 d	From 15.3 ± 4.1 to 13.2 ± 3.1	13.40	< 0.005
			Placebo		40 mg	Oral	2 d	NA	NA	NS
Tincani (1993)	Italy	LC with large EVs	Propranolol	β1, β2 blockers	40 mg	Oral	4 h	From 14.2 ± 3.2 to 12.6 ± 3.3	11.3	0.021
			ISMN	vasodilator	60 mg	Oral	4 h	From 13.9 ± 3.4 to 11.9 ± 3.9	14.4	0.032
Tincani (1995)	Italy	LC with large EVs	Propranolol	β1, β2 blockers	40 mg	Oral	NA	NA	NA	< 0.001
			Clonidine	α2 blocker	0.15 mg	Oral	NA	NA	NA	0.194
Albillos (1997)	Spain	LC with EVs	Propranolol	β1, β2 blockers	0.15 mg/kg	Intravenous infusion	0.5 h	NA	18.3 ± 12	< 0.001
			Placebo		NA	Intravenous infusion	0.5 h	NA	NA	NA
Baik (2003)	South Korea	LC with endoscopic treatment after VB	Propranolol	β1, β2 blockers	25–75 mg/day	Oral	3 m	From 14.7 ± 0.7 to 11.6 ± 0.5	19.8 ± 2.8	< 0.001
			Captopril	ACEI	40–240 mg/day	Oral	3 m	From 15.2 ± 0.7 to 15.5 ± 0.6	6.6 ± 5.5*	NS
Hepatic blood flow (L/min)										
Westaby (1984)	London	LC with recent VB	Propranolol	β1, β2 blockers	11.25 mg	Intravenous bolus	0.25 h	From 1.4 ± 0.2 to 1.1 ± 0.2	20.40	< 0.005
			Metoprolol	β1 blocker	13.8 mg	Intravenous bolus	0.25 h	From 1.2 ± 0.2 to 1.2 ± 0.2	0	NS
Forrest (1996)	UK	LC	Carvedilol	β1, β2, α1 blockers	25 mg	Oral	1 h	From 1.45 ± 0.20 to 1.21 ± 0.19	16.6%	NS

Table 2 (continued)

First author (year)	Country	Target population	Groups	Mechanisms of drugs	Dosage	Route	Interval[#]	Results (change)	Results (reduction %)	*p* value
Bañares (1999)	Spain	LC with EVs	Propranolol	β1, β2 blockers	0.15–0.2 mg/kg	Intravenous infusion	1 h	From 1.42 ± 0.12 to 1.22 ± 0.11	14.1 ± 5.4	< 0.05
			Carvedilol	β1, β2, α1 blockers	25 mg	Oral	1 h	From 1.35 ± 0.21 to 1.21 ± 0.19	10.4 ± 4.5	0.05
			Placebo		NA	Oral	1 h	From 1.52 ± 0.21 to 1.45 ± 0.33	4.6	NS
Portal blood flow (L/min)										
Zoli (1986)	Italy	LC with large, high-risk EVs but without previous GIB	Propranolol	β1, β2 blockers	40 mg	Oral	3 h	From 0.90 to 0.61	34 ± 4	0.04
			Atenolol	β1 blocker	100 mg	Oral	3 h	From 0.86 to 0.52	40 ± 5	0.04
			Isosorbide dinitrate	vasodilator	5 mg	Sublingually	0.25 h	From 0.89 to 0.62	31 ± 3	0.05
Ljubicić (1991)	Yugoslavia	LC without previous history of altering hemodynamic drugs	Propranolol	β1, β2 blockers	80 mg	Oral	3 h	From 0.89 ± 0.06 to 0.56 ± 0.06	37	< 0.001
			Atenolol	β1 blocker	100 mg	Oral	3 h	From 0.89 ± 0.06 to 0.54 ± 0.06	39.3	< 0.001
			Labetalol	β1, β2, α1 blockers	100 mg	Oral	4 h	From 0.87 ± 0.05 to 0.85 ± 0.06	2.3	NS
Albillos (1997)	Spain	LC with EVs	Propranolol	β1, β2 blockers	0.15 mg/kg	Intravenous infusion	0.5 h	From 1.12 ± 0.36 to 0.90 ± 0.33	33.2	< 0.0001
			Placebo		NA	Intravenous infusion	0.5 h	From 1.15 ± 0.23 to 1.16 ± 0.19	0.9*	NS

NSBBs nonselective beta-blockers, *LC* liver cirrhosis, *EVs* esophageal varices, *GIB* gastrointestinal bleeding, *VB* variceal bleeding, *ISMN* isosorbide 5 mononitrate, *ACEI* angiotensin-converting enzyme inhibitors, *h* hours, *m* months, *d* days, *NS* not significant, *NA* not available

*Increase

[#]Interval from use of drugs to measurement of portal vein velocity, hepatic blood flow, and portal blood flow

Table 3 Correlation between PVT and portal vein velocity

First author (year)	Country	Enrollment period	Study design	Target population	No. pts.	Follow-up duration	Diagnosis of PVT	Measurement of portal flow velocity	Cut-off (cm/s)	Groups	No. pts.	Portal vein velocity (cm/s)
Zocco (2009)	Italy	NA	Cohort	LC	73	1 year	CT	Doppler US	15	PVT	12	11.8 ± 2.6
										No PVT	61	19.6 ± 5.7
Zhang (2009)	China	Jan 2007–Jul 2008	Cohort	LC undergoing splenectomy with periesophagogastric devascularization	43	Postoperative	NA	Doppler US	NA	PVT	13	19.5 ± 5.3
										No PVT	32	29.6 ± 8.0
Tao (2009)	China	Dec 2002–Dec 2006	Cohort	Liver transplantation recipients	465	Dec 2002–Dec 2007	Intraoperation	Doppler US	NA	PVT	42	48.881 ± 12.788
										No PVT	423	57.172 ± 21.715
Pellicelli (2011)	Italy	NA	Cohort	LC	56	19 months	NA	NA	NA	PVT	11	9 ± 0.9
										No PVT	45	12.5 ± 2.3
Zhang (2012)	China	Jan 2007–Aug 2010	Cohort	LC undergoing splenectomy with periesophagogastric devascularization	69	Postoperative	NA	Doppler US	24.45	PVT	33	18.06 ± 5.97
										No PVT	36	29.79 ± 7.75
Chen (2014)	China	Mar 2011–Mar 2012	Case-control	LC	162	NA	CTPA/US	Doppler US	NA	PVT	40	17.3 ± 6.2
										No PVT	122	17.8 ± 4.8
Abdel-Razik (2015)	Egypt	Mar 2012–Oct 2014	Cohort	LC	95	1 year	CT	Doppler US	15	PVT	17	11.6 ± 4.3
										No PVT	78	17.9 ± 4.5
Nery (2015)	France	Jun 2000–Mar 2006	Cohort	Adult LC	535	47 months	US/CT/MRI	Doppler US	NA	PVT	50	11 (8 - 16)
										No PVT	485	13 (10 - 18)
Yang (2015)	China	Mar 2012–Apr 2014	Cohort	LC who underwent splenectomy	98	6 months	Contrast-enhanced CT and Doppler US	Doppler US	NA	PVT	18	16.4 ± 4.2
										No PVT	80	29.4 ± 3.9
Stine (2018)	USA	Jan 2005–Jul 2015	Case-control	LC	100	NA	US/CT/MRI	Doppler US	15	PVT	50	16.9 (13.9 - 20)
										No PVT	50	25 (21.8 - 28.2)
Cui (2018)	China	NA	Cohort	LC	109	De novo PVT or 12 months	US	Doppler US	NA	PVT	14	12.1 ± 3.4
										No PVT	95	14.5 ± 1.7
Nery (2019)	Portugal	Jan 2014–Feb 2017	Cohort	LC	108	19 months	US	Doppler US	NA	PVT	11	19.9 ± 7.5
										No PVT	97	21.8 ± 5.5

PVT portal vein thrombosis, *LC* liver cirrhosis, *CT* computed tomography, *CTPA* computed tomography portal angiography, *US* ultrasound, *MRI* magnetic resonance imaging, *NA* not available

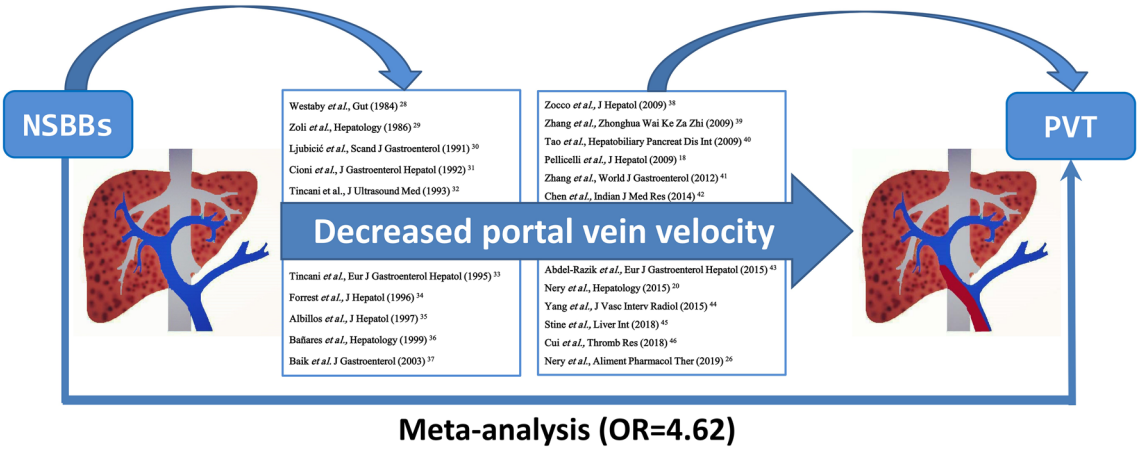

Fig. 4 A schematic diagram showing the relationship among nonselective beta-blockers, portal vein velocity, and portal vein thrombosis

PVT was 9–19.9 cm/s in cohort studies [18, 20, 26, 38, 43, 46] and 16.9–17.3 cm/s in case–control studies [42, 45]; by comparison, in cirrhotic patients without PVT, the portal vein velocity ranged from 12.5 to 21.8 cm/s in cohort studies [18, 20, 26, 38, 43, 46] and from 17.8 to 25 cm/s in case–control studies [42, 45]. The cut-off values of the portal vein velocity at baseline for the development of PVT in cirrhotic patients were explored in four studies [38, 41, 43, 45]. A portal vein velocity of 15 cm/s was defined as the best cut-off value in three studies where generalized cirrhotic patients were included [38, 43, 45], but a portal vein velocity of 24.45 cm/s in 1 study where only cirrhotic patients with hepatitis B undergoing splenectomy with periesophagogastric devascularization were included [41]. Notably, the mean portal flow velocity was found to be below this cut-off value of 15 cm/s after the intervention of propranolol [31].

Screening, prevention, and treatment of PVT. In the case that NSBBs are warranted, the primary task for physicians is to screen the occurrence of PVT and to identify the patients at a high risk of developing PVT. Doppler ultrasonography may be preferred for routine screening of portal venous patency in cirrhotic patients treated with NSBBs (Table 3) [20, 26, 38–46]. Meanwhile, it is useful to identify patients with decreased portal vein velocity, who are at a high risk of developing PVT. The secondary task is to prevent from the development and progression of PVT in cirrhotic patients. Recent evidence suggested that anticoagulants should be effective for the prevention of de novo PVT in cirrhotic patients. A RCT found that cirrhotic patients receiving enoxaparin had a significantly lower incidence of de novo PVT than those without any treatment during follow-up (48 weeks: 0% vs. 16.6%; 96 weeks: 0% vs. 27.7%; the end of the follow-up: 8.8% vs. 27.7%) [49]. A meta-analysis also found that the use of drug prophylaxis (i.e., anticoagulants, thrombolytics, and prostaglandin E1) could significantly reduce the incidence of PVT in cirrhotic patients after splenectomy (OR 0.29) [50]. As for the treatment of PVT, a meta-analysis found that the rate of complete portal vein recanalization was significantly increased (OR 4.16) and the rate of thrombus progression was significantly decreased (OR 0.061) in anticoagulation group [51]. More recently, an updated meta-analysis further showed that the overall portal vein recanalization was significantly increased (OR 4.8) and the rate of spontaneous variceal bleeding was significantly decreased (OR 0.232) in anticoagulation group [52]. Therefore, a combination of NSBBs with anticoagulants might be theoretically considered in cirrhotic patients at a high risk of developing PVT. Certainly, the risk of bleeding secondary to use of anticoagulants should be closely monitored.

Limitations. Our study had several limitations. First, a relatively small number of included studies and a limited availability of data restricted us to conduct further subgroup analyses. Second, a majority of included studies were retrospective. Third, the heterogeneity among studies was significant. Fourth, the follow-up duration was varied among the cohort studies. Fifth, except for the risk of PVT, dynamic changes of varices and variceal bleeding among users of NSBBs versus nonusers could not be obtained simultaneously. Thus, the use of NSBBs should be fully weighed to further explore the benefits and potential risks.

Conclusion. Based on the present systematic review and meta-analysis, we found that NSBBs would increase the risk of PVT in liver cirrhosis. Decreased portal vein velocity might establish a cause-and-effect relationship between NSBBs and PVT (Fig. 4). Follow-up ultrasound to detect the portal vein velocity and potential prophylactic strategy should be considered for cirrhotic patients treated with long-term NSBBs. Follow-up ultrasound to detect the portal vein velocity and potential prophylactic strategy should be considered for cirrhotic patients treated with long-term NSBBs with signs and symptoms suggestive of decompensation. Until more evidence regarding effect of PVT on prognosis

is obtained, NSBBs should not be readily withheld due to its clear survival benefit in the population needing primary and secondary prophylaxis of variceal bleeding. Therefore, there is an urgent need of high-quality studies to estimate the net clinical benefit of NSBBs in cirrhotic patients, having a composite outcome of PVT, varices, variceal bleeding, and overall death. How to identify the cirrhotic patients at a high risk of developing PVT and its related worse outcomes may be more clinically important.

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Compliance with ethical standards

Conflict of interest Xiangbo Xu, Xiaozhong Guo, Valerio De Stefano, Gilberto Silva-Junior, Hemant Goyal, Zhaohui Bai, Qingchun Zhao and Xingshun Qi declare that they have no conflict of interest.

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