Systematic Review and Meta-Analysis

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Effect of portal vein thrombosis on the prognosis of patients with cirrhosis without a liver transplant

A systematic review and meta-analysis

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Abstract

Background: Portal vein thrombosis (PVT) is a relatively common complication of cirrhosis. However, the effect of PVT on the prognosis might not be unequivocal. A systematic review and meta-analysis were performed to investigate the effect of PVT on the prognosis of patients with cirrhosis who have not received a liver transplant.

Methods: Three databases, including PubMed, EMBASE, and Cochrane Library, were searched for studies published up to March 2020. The survival or mortality rate of patients with PVT served as the main index to evaluate the prognosis of these patients. Hepatic decompensation served as the index of disease progression. Meta-analyses were conducted using Review Manager software 5.2.

Results: Sixteen clinical studies were included and analyzed. PVT was associated with an increased risk of mortality in patients with decompensated cirrhosis. According to the meta-analysis, patients with cirrhosis presenting with PVT had a lower 1-year survival rate than patients without PVT (odds ratio (OR), 0.32; 95% confidence interval (CI), 0.14–0.75; $P = .008$). The cumulative survival rates were similar between the 2 groups at 3 years (OR, 1.04; 95% CI, 1.00–1.08; $P = .06$), 5 years (OR, 1.33; 95% CI, 0.71–2.48; $P = .38$) and 10 years (OR, 1.24; 95% CI, 0.79–1.93; $P = .35$). PVT was associated with a higher mortality rate in patients with Child-Pugh class B and C disease. A significantly increased risk of death was observed in patients with complete PVT. Patients with both PVT and cirrhosis had a higher rate of decompensation than patients without PVT.

Conclusions: The presence of PVT might exert a slight effect on the overall prognosis of patients with cirrhosis. PVT might mainly affect the short-term prognosis by increasing hepatic decompensation events in patients with cirrhosis. However, PVT might not influence the long-term prognosis of patients with cirrhosis.

Abbreviations: GI = gastrointestinal, HE = hepatic encephalopathy, HCC = hepatocellular carcinoma, LT = liver transplantation, PVT = portal vein thrombosis.

Keywords: cirrhosis, portal vein thrombosis, prognosis

1. Introduction

Portal vein thrombosis (PVT) is a common complication of cirrhosis. The prevalence of PVT in patients with cirrhosis is estimated to be approximately 0.6% to 26%.[1,2] The incidence of PVT increases with the severity of cirrhosis and is less than 1% in patients with well-compensated cirrhosis but ranges from 7.4% to 16% in patients with advanced cirrhosis.[3] PVT is associated with adverse outcomes.[4] PVT has been shown to aggravate or induce portal hypertensive haemorrhage, hepatic encephalopathy (HE) or ascites and affect the survival rates of patients after liver transplantation (LT).[5–7] However, some studies have also reported that the occurrence of PVT is not significantly correlated with the increase in mortality and further progression of liver disease in patients with cirrhosis.[8,9]

The effect of PVT on cirrhosis outcomes has been investigated in a meta-analysis and systematic review in 2015 by Sting et al.[4] The study reported a significant association of PVT with both mortality and ascitic decompensation, but did not evaluate the pooled effect of PVT on other markers of hepatic decompensation, such as gastroesophageal variceal bleeding or HE. Due to

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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the heterogeneity in data reporting and lengths of follow-up among studies, Qi et al was unable to draw conclusions regarding the effects of PVT on cirrhosis outcomes after conducting a systematic review. As shown in the study by Luca et al,[5] a spontaneous improvement of PVT did not provide any benefit in terms of the development of cirrhosis-related complications, LT and survival. Therefore, the effect of PVT on the prognosis of patients with cirrhosis who have not undergone LT remains uncertain.

Several recent studies examining the effect of PVT on the prognosis of patients with cirrhosis have been published, but the results are inconsistent.[10,11] The prognosis is variable and highly dependent on underlying diseases, such as LT, liver tumors, etc.[12] The aim of this study is to systematically review and perform a meta-analysis of the effect of PVT on the prognosis and hepatic decompensation of non-LT patients with cirrhosis.

2. Methods

2.1. Search strategy

PubMed, EMBASE, and Cochrane Library were searched for studies published up to March 2020. The search terms were as follows: "cirrhosis or cirrhotic" and "portal vein (or venous) thrombosis," and "survival or mortality". Prospective and retrospective clinical studies evaluating humans were included.

Studies were excluded if the paper did not meet the selection criteria for our systematic review. The exclusion criteria were as follows:

1. patients with PVT after surgery and interventional treatment,
2. non-cirrhotic patients with PVT,
3. patients with liver cancer or other malignant tumors,
4. patients with Budd-Chiari syndrome and other vascular diseases,
5. patients who underwent LT, and
6. patients who received a transjugular intrahepatic portosystemic shunt (TIPS).

2.2. Data extraction

Data were extracted and evaluated by 2 independent reviewers. Discrepancies were resolved by discussion among the reviewers. The author, publication year, country, Child-Pugh stage or MELD score, degree of obstruction of PVT, enrolment period, follow-up time, mortality or survival rate (%), hepatic decompensation rate (HDR), and type of study were extracted. The survival or mortality rate of patients with PVT served as the main index to evaluate the prognosis. Hepatic decompensation served as the index of disease progression. This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[13]

2.3. Data analysis

All meta-analyses were conducted using Review Manager software 5.2 (Cochrane). The random-effect model was used to generate a more conservative estimate. The heterogenecity between the groups was evaluated using the Chi-Squared test and I^2 statistic. Odds ratios or hazard ratios with 95% confidence intervals (CIs) were pooled to calculate the differences in the survival or mortality rates and hepatic decompensation between the PVT and control groups. A funnel plot was constructed to estimate the publication bias. Statistical significance was considered as $P < .05$.

2.4. Grade of evidence

High- and low-grade evidence were classified according to the study by Qi et al.[7] The evidence was defined as high grade if any one of the 2 following criteria were met:

1. the statistically significant difference was determined using a multivariate analysis; and
2. if only a univariate analysis was performed, the baseline Child-Pugh class or MELD score was matched between patients with and without PVT.

Otherwise, the evidence was of a low grade.

2.5. Ethics statement

All data were obtained from previously published studies. Hence, ethical approval and patient consent were not required.

3. Results

3.1. The basic characteristics of the citations included

A total of 1175 citations were retrieved, including 303 from PubMed, 815 from EMBASE and 57 from Cochrane Library. Two hundred fourteen duplicates were excluded. A total of articles were excluded by reading titles and abstracts, including 76 reviews, 13 letters or comments, 34 case reports, 39 studies involving noncirrhotic patients with PVT, 33 studies involving patients with hepatocellular carcinoma (HCC), 47 studies investigating surgery and interventional treatment, 29 studies analysing LT, 10 studies investigating anticoagulant therapy and 653 irrelevant studies. Twenty seven of the remaining studies were excluded after reading the abstracts or full text. Sixteen clinical studies were included and analyzed (Fig. 1). Sixteen studies, including 9 full-text articles and 7 abstracts, examined the effect of PVT on the prognosis and hepatic decompensation of patients with cirrhosis (Table 1). Of these studies, 9 were prospective cohort studies and 7 were retrospective cohort or control studies. The hepatic decompensation rate or events were reported in 6 articles. Ten studies were considered to have a relatively high grade of evidence.

3.2. Overall effect of PVT on the prognosis of patients with cirrhosis

Three large-sample studies reported an incidence rate of PVT of 1.59% to 3.32% in patients with cirrhosis. In the study with the maximum sample size (3,045,098 patients) reported to date, Cool et al showed that PVT (48,438 patients) was associated with an increased risk of mortality in patients with decompensated cirrhosis. As shown in the study by Shah et al (116,098 patients), PVT (2054 patients) increased the mortality rate in patients with cirrhosis. No differences in the cumulative survival rate or mortality were observed between the PVT and no PVT groups (2207 and 64,299 patients) during the follow-up period (1.78 ± 2.39 years) in the study by Berry. In addition, others small-sample studies also reported the effect of PVT on the prognosis of patients with cirrhosis. Violi et al identified PVT as an

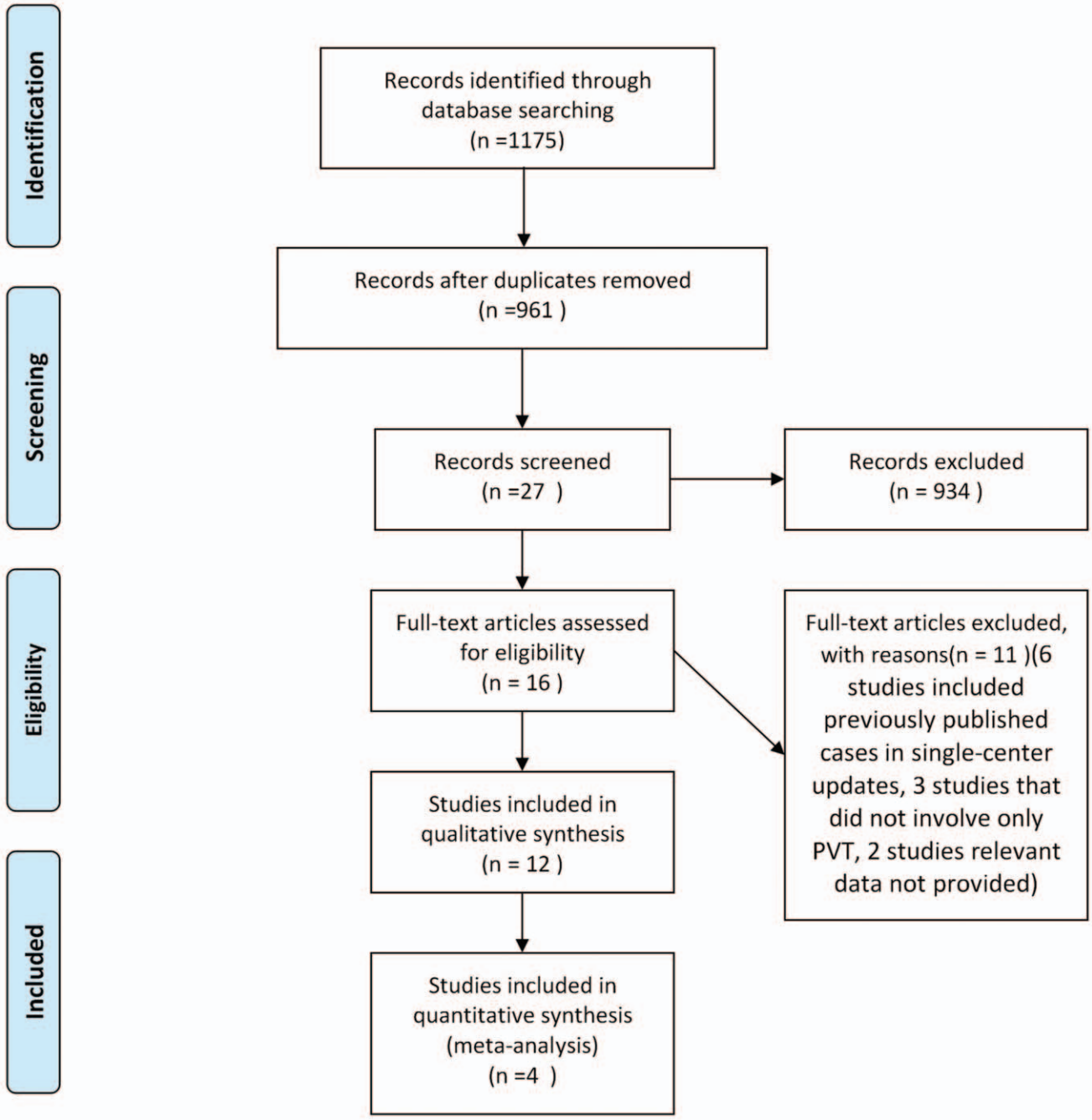

Figure 1. Flow diagram depicting the steps in this systematic review.

independent risk factor for death. The results of a prospective study by Attili revealed that PVT substantially altered the mortality of patients with cirrhosis. John et al reported similar mortality rates prior to orthotopic liver transplantation (OLT) between patients with and without PVT.

3.3. Effect of PVT on the annual mortality or survival rate of patients with cirrhosis

The 1-year and 3-year survival rates were reported in 3 studies. Most patients included in the 3 studies had Child-Pugh class A and B disease. According to the meta-analysis, patients with both cirrhosis and PVT had a lower 1-year survival rate than patients without PVT (OR, 0.12; 95% CI, 0.04–0.34; $P < .001$) (Fig. 2). The patients with both cirrhosis and PVT had a slightly higher 3-year survival rate than patients without PVT (OR, 1.04; 95% CI, 1.00–1.08; $P = .06$) (Fig. 3). The cumulative survival rates were similar between the 2 groups at 5 years (OR, 1.33; 95% CI, 0.71–2.48; $P = .38$) and 10 years (OR, 1.24; 95% CI, 0.79–1.93; $P = .35$) (Figs. 4 and 5).

3.4. Effects of the severity of cirrhosis on prognosis of patients with both cirrhosis and PVT

The incidence of PVT increases with the severity of cirrhosis. The severity of cirrhosis might affect the prognosis of patients with

Table 1

Effect of PVT on the prognosis and hepatic decompensation of patients with cirrhosis.

Author, Year and Country	N (Yes/ no PVT)	Child-Pugh stage (A/B/C) or MELD score	PVT degree (Complete/Partial)	Enrollment period	Follow up period	Mortality or survival rate (%)	Year mortality or survival rate (%)	Hepatic decompensation rate (HDR)	Type of study
Cool,[10] 2019,USA	48438/2996660	decompensated cirrhosis	NA	1998–2014	NA	OR=1.12, 95% CI: 1.04–1.20	NA	hepatorenal syndrome (OR 1.62, $P<.001$).	Retrospective multi-center cohort study
Ferreria,[11] 2019. Portugal	18/223	A/B/C: 184/31/26	NA	2014.01–2019.03	29 (1–58) mo	NA	OLT-free survival was 100% and 82.8% at 3 yr, with and without PVT	NA	Prospective observational study
Violi F,[14] 2019, Italy	61/692	32/16/7 vs 365/236/91	46/15	2012.04–2017.12	21 (6.7–24) mo	PVT at the entry (HR: 1.70, 95% CI: 1.18–2.45)	NA	NA	Prospective multi-center cohort study
Berry,[6] 2015. USA	2207/64299	18.4±8.2/17.2±7.9	NA	2002.02–2013.09	1.78 ±2.39yr	Cumulative mortality, HR:1.07 (0.98–1.16)	NA	NA	Prospective cohort study
Nery.[7] 2015. France	118/1125	A/B (863/380)	31/87	2000.06–2006.03	47 mo	NA	NA	HR 1.32 (CI: 0.68–2.65)	Prospective multi-center longitudinal study
Maruyama.[15] 2013. Japan	42/108	14/22/6VS51/51/6	11/31	1998.01–2009.05	66.3±41.2 mo	Cumulative survival rate is similar	1–3 yr: 97.1 vs 94.6 (90.3) 5 yr: 70.4 vs 77.5 10 yr: 46.9 vs 46.2	NA	Prospective single-center case control
John.[16] 2013. USA	70/220	Base line 14.4±5.0 New PVT 15.3±6.7 No PVT 13.8±4.5	38/32	2004.07–2009.06	26.2±19.3vs 27.4±17.5 mo	Survival rate, 53/70 vs 175/220 (75.7% vs 79.5%)	NA	NA	Prospective single-center cohort study
Englesbe,[17] 2010. USA	148/3147	13.3±8.3 vs 12.1±7.2	Occlusive PVT	1995.01–2007.03	57.6±50.4 vs 49.6±62.8 mo	Mortality. HR=2.61 (95% CI, 1.97–3.51)	NA	NA	Retrospective single-center cohort study
Girleanu,[18] 2017. Romania	65/70	NA	NA	2014.12–2016.12	24 mo	Survival rate of 6 months no difference	NA	HDR at 6 and 18 mo was higher in worsened PVT than in those with stable/ improved group	Prospective single-center case control
Shah,[19] 2016. USA	2,054/114,044	NA	NA	2012 National Inpatient Sample	8 d (0–108) vs 6 d (0–133)	Mortality, 194 (9%) vs 6849 (5.6%), $P<.001$ OR=1.61.	NA	HE: 22.5% vs 17.7%; Ascites: 58.6% vs 32.8%; GIbleeding:19% vs 13.2%, $P<.001$	Retrospective observational study
Gokcan,[20] 2015. Turkey	92/148	150/120/7	NA	1988–2012	78.2 mo) 24–312)	Overall survival rates no difference ($P=.25$)	3 yr, 97.8/96 5 yr, 95.3 /87.3, 10 yr, 73.1/66	NA	Retrospective single-center case control
Girleanu,[21] 2014. Romania	32/30	NA	10/22	2011.01–2013.12	21.69 (4–31) mo	No influence on survival rate.	6 mo was 81.3% in PVT group vs 84.7% ($P=.067$). 18 mo: 63.1% vs 61.7% ($P=.122$).	6 mo (19% vs 20%,) 18 mo (54% vs 51%,). [HR= 1.56, $P=.032$]	Prospective cohort study referred to a tertiary center
Ferreria,[22] 2014. Portugal	65/175	A/B/C: 12/32/21 (PVT)	NA	NA	10 mo (0–376)	Overall mortality no difference (Child-C higher than Child-A and B (OR=6, 95% CI, 1.9–18.7). $P=.002$	NA	NA	Retrospective single-center case control
Attili,[23] 2012. Italy	25/104	NA	NA	2000.02-–2005.07	49 (4–115) mo	60/9.6 (15/25 vs 10/104). PVT were independent risk factors for mortality and complications	NA	ascites (92.9% vs 40%) (logrank $\chi^2=15.05$). $\chi^2=16.84$, for GI bleeding. $\chi^2=24.66$; for HE	Prospective single-center cohort study
Law,[24] 2014. USA	20/40	NA	NA	2002.01–2011.12	transplantation on the waitlist	mortality: OR=3.44 ($P=.03$). Complete: 10.33 ($P=.003$) Partial: 3.37 ($P=.08$)	NA	NA	Retrospective Single-center case control
Liaw,[25] 2011, Singapore	18/274	NA	NA	2006.09–2009.01	NA	NA	1 yr mortality 27.8/9.5%, $P=.015$	1 yr HDR 83.3/20.8% ($P<.001$) GI bleeding (33.3 vs 6.9%, ascites (61.1 vs 11.3%), HE (33.3 vs 9.0%)	Retrospective Single-center cohort study

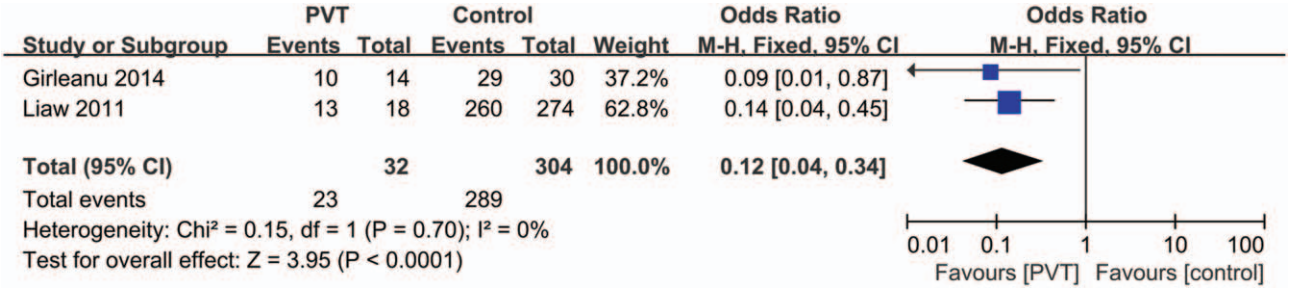

Figure 2. Forest chart of the effect of PVT on survival rate of patients with cirrhosis at 1-year.

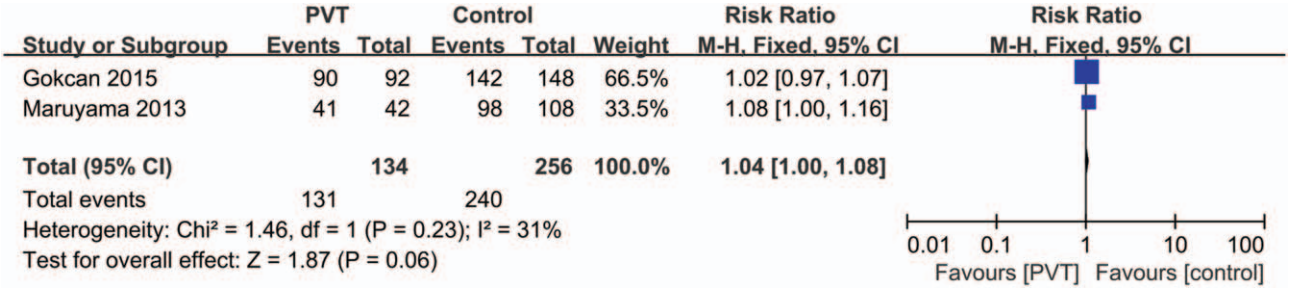

Figure 3. Forest chart of the effect of PVT on survival rate of patients with cirrhosis at 3-year.

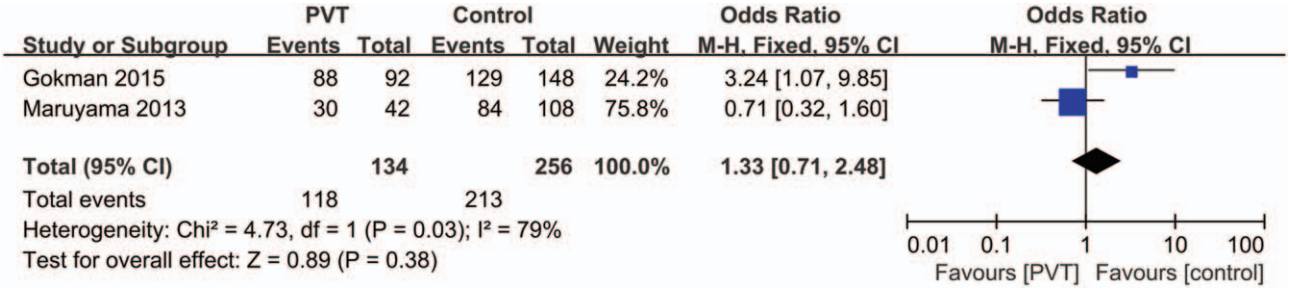

Figure 4. Forest chart of the effect of PVT on survival rate of patients with cirrhosis at 5-year.

cirrhosis presenting with PVT. Although patients with both cirrhosis and PVT generally had similar mortality rates to patients without PVT, PVT was associated with a higher mortality rate in patients with Child-Pugh class C disease, as reported by Ferreria. Senzolo[29] only observed an effect of splanchnic vein thrombosis (SVT) (88% PVT) on survival in patients with more advanced liver disease (Child-Pugh class B-C).

3.5. Effects of the degree of obstruction of PVT on the prognosis of patients with cirrhosis

Patients who developed PVT while on a waitlist had an increased risk of death compared with patients who did not develop PVT. A significantly increased risk of death was observed in patients with complete PVT but not in those with partial PVT in the study by Law et al. However, the survival rate at 6 months was the same in

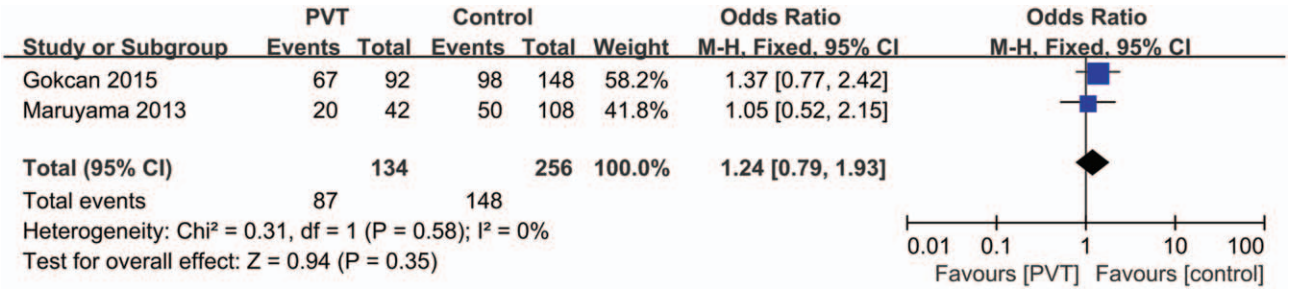

Figure 5. Forest chart of the effect of PVT on survival rate of patients with cirrhosis at 10-year.

the PVT and no PVT groups in the study by Girleanu et al, and PVT was partial. According to the study by Englesbe, patients with cirrhosis complicated with occlusive PVT have an increased risk of death.

3.6. Effects of PVT on the hepatic decompensation of cirrhosis

As shown in the study by Cool et al, PVT significantly increases the risk of hepatorenal syndrome, which included the largest sample to date. Shah et al reported that admissions for cirrhosis and PVT were associated with statistically significant increases in the rates of concurrent HE, abdominal ascites, and gastrointestinal (GI) bleeding. However, the hepatic decompensation rates were similar between the 2 groups in the study by Nery et al. Patients with both PVT and cirrhosis had a higher rate of decompensation than patients without PVT (83.3 vs 20.8%), as reported by Liaw et al. The hepatic decompensation rates at 6 and 18 months were higher in patients with worsened PVT than in patients with stable/improved PVT and individuals in the control group in the study by Girleanu et al. Attili reported a higher occurrence of ascites in patients with PVT (92.9%) than in patients without PVT (40%). Incidences of GI bleeding from any source and HE were also higher in patients with PVT than in patients without PVT.

4. Discussion

PVT is a relatively common complication in patients with cirrhosis. However, a consensus on the effect of PVT on the prognosis of patients with cirrhosis has not been reached.[26] Based on the results of our analysis, the presence of PVT might exert a slight effect on the prognosis of patients with cirrhosis who have not undergone LT, and it increased the incidence of hepatic decompensation events. PVT exerted a noticeable effect on the survival of patients with more advanced liver disease (Child-Pugh class B-C) and completely obstructed PVT.

According to previous studies, the major factors that affect the prognosis of patients with cirrhosis complicated with PVT include the degree of thrombus and the severity of cirrhosis, among other factors.[27,28] In the present study, the effect of PVT on the mortality rate of patients with Child-Pugh class B and C disease was significantly greater than on patients with Child-Pugh class A disease. An effect of SVT (88% PVT) on survival was only apparent in patients with more advanced liver disease.[29] Occlusive PVT was shown to significantly affect the prognosis of patients with cirrhosis. Spontaneous resolution or an unchanged appearance was the most common outcome of thrombosis, which had little effect on the prognosis.[15,21] Although partial PVT did not alter the prognosis of patients with different stages of cirrhosis, certain cases of progressive PVT might affect the prognosis of patients with cirrhosis.

The incidence of hepatic decompensation, including HE, abdominal ascites, GI bleeding and hepatorenal syndrome, was significantly increased in patients with PVT compared with patients without PVT.[10,18,19,21,23,25] In patients with cirrhosis, the development of PVT is associated with the severity of liver disease at baseline, but does not follow the recent progression of liver disease in the study by Nery. Zhang[30] reported a prevalence of nonmalignant PVT in patients with acute decompensation (AD) of 9.36%, which was significantly higher than in patients without AD (5.24%). Because PVT might possibly progress or exacerbate portal hypertension-related variceal bleeding, PVT potentially increases the risk of death by contributing to the development of AD.

Based on the results of our studies, the 1-year survival rates of patients with and without PVT are significantly different. No significant differences were observed in the 3-, 5- and 10-year survival rates between patients with and without PVT. However, the small sample size was the major limitation of these investigations. We speculated that PVT may affect the prognosis of patients with cirrhosis by increasing the hepatic decompensation of patients with cirrhosis. However, this effect is relatively small and only limited to the short-term prognosis. Furthermore, this effect was counteracted over time, and PVT no longer affected the long-term prognosis.

The current study has some limitations. Although we selected clinical case-control studies, the sample size varied substantially, and some of the studies were retrospective analyses. Of the 16 studies, 7 were available only in abstract form and were not written as full articles. We were unable to obtain additional information by contacting the authors of the abstracts, which might have limited the interpretation. In addition, the duration of follow-up and the methods and time of evaluation of the prognosis were different. These factors affected the quality of the results to a certain extent. More prospective RCTs are needed to confirm these results.

5. Conclusions

In general, the presence of PVT might exert a slight effect on the prognosis of patients with cirrhosis. The size of the effect more apparent in patients with complete obstructive PVT and Child-Pugh class B-C disease. PVT might increase the incidence of hepatic decompensation events and affect the short-term prognosis of patients with cirrhosis. However, the presence of PVT might not alter the long-term prognosis of patients with cirrhosis.

Author contributions

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Visualization: Wang Xuequan.
Writing – original draft: Tongjing Xing.
Writing – review & editing: Jianchun Xian.

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