Inherited thrombophilia and portal vein thrombosis in cirrhosis: A systematic review and meta-analysis

Steven D. Ma BS1 | Jennifer Wang MD2 | Dmitri Bezinover MD, PhD3 | Zakiyah Kadry MD, FACS4 | Patrick G. Northup MD5 | Jonathan G. Stine MD, MSc, FACP6,7

1College of Medicine, Pennsylvania State University, Hershey, Pennsylvania
2Department of Medicine, University of Virginia, Charlottesville, Virginia
3Department of Anesthesiology & Perioperative Medicine, Pennsylvania State University Milton S. Hershey Medical Center, Hershey, Pennsylvania
4Department of Surgery, Pennsylvania State University Milton S. Hershey Medical Center, Hershey, Pennsylvania
5Center for the Study of Coagulation Disorders in Liver Disease, Division of Gastroenterology & Hepatology, Department of Medicine, University of Virginia, Charlottesville, Virginia
6Division of Gastroenterology & Hepatology, Department of Medicine, Pennsylvania State University, Milton S. Hershey Medical Center, Hershey, Pennsylvania
7Department of Public Health Sciences, Pennsylvania State University, Hershey, Pennsylvania

Correspondence
Jonathan G. Stine, Division of Gastroenterology and Hepatology, The Pennsylvania State University, Milton S. Hershey Medical Center, 200 Campus Drive, Hershey, PA 17033. Email: jstine@pennstatehealth.psu.edu

Funding information
This research was funded in part by NIH grant L30 DK118601. This project was also funded, in part, under a grant with the Pennsylvania Department of Health using Tobacco CURE Funds. The Department specifically disclaims responsibility for any analyses, interpretations, or conclusion.

Abstract

Background: Portal vein thrombosis (PVT) is common in cirrhosis. PVT is associated with high morbidity and mortality. Individual reports suggest that PVT occurs more frequently in patients with cirrhosis and inherited thrombophilia. The relationship between cirrhosis, PVT development, and inherited thrombophilia was explored in this study. The aim of the study was to determine whether cirrhotic patients with nontumoral PVT have an increased rate of inherited thrombophilia.

Methods: Studies were identified by searching electronic databases up to October 2017 with English language and human subject restrictions. Two independent reviewers screened citations and extracted data. Magnitude of effect was calculated to obtain aggregate estimates of effect size and 95% confidence intervals (CIs). Between-study variability and heterogeneity were assessed.

Results: Of 2893 citations identified, 9 studies composed of 1929 subjects with cirrhosis were included. The overall prevalence of PVT was 6.5% (n = 125). Both prothrombin G20210A mutation (odds ratio [OR], 2.43; 95% CI, 1.07-5.53; P = 0.03) and factor V Leiden (FVL) (OR, 1.98; 95% CI, 1.06-3.68; P = 0.03) were significantly associated with PVT risk. Methyltetrahydrofolate reductase C677T mutation was not associated with increased PVT risk. No heterogeneity or publication bias was observed. One important study with opposite findings could not be included due to lack of primary data.

Conclusions: FVL and PTG20210A mutation were associated with increased PVT risk in patients with cirrhosis. This finding reframes the role of inherited thrombophilia in PVT development in patients with cirrhosis. Future prospective studies investigating screening for inherited thrombophilia in all cirrhosis patients with PVT seem warranted.

KEYWORDS
factor V Leiden, hereditary, mutation, portal vein thrombosis, prothrombin, thrombophilia
Essentials

- Portal vein thrombosis (PVT) is common in cirrhosis and leads to inferior outcomes.
- This meta-analysis evaluated whether inherited thrombophilia increases PVT risk in cirrhosis.
- Prothrombin G20210A and factor V Leiden mutations were associated with PVT risk in patients with cirrhosis in these data.
- Further studies are needed for confirmation and to examine the clinical utility of screening.

1 | INTRODUCTION

Cirrhosis was initially thought to predispose patients to a hemorrhagic state due to a decrease in liver synthetic function and reduced production of coagulation factors. However, studies over the past decade now characterize cirrhosis as a precarious state existing with a “rebalanced” hemostasis. This places patients at risk for bleeding, thrombosis, or sometimes both simultaneously. PVT is a frequent and serious complication of cirrhosis, with prevalence between 7.4% and 16%. PVT is associated with increased risk of hepatic decompensation and inferior overall survival in comparison with patients without PVT, and it may lead to inferior posttransplant outcomes. Many risk factors for PVT development are well established, including reduced portal vein blood flow; however, the impact of hereditary thrombophilia remains controversial. Factor V Leiden (FVL), prothrombin G20210A, and methylenetetrahydrofolate reductase (MTHFR) C677T are well-established risk factors for deep vein thrombosis (DVT) and pulmonary embolism. FVL and prothrombin G20210A mutations affect roughly 5% of the general population. Whether inherited thrombophilia increases the risk of PVT development remains unclear, as recent consensus guidelines from the 7th International Coagulation in Liver Diseases Conference state that thrombophilia likely plays a role in PVT development but make no strong recommendation regarding testing for these conditions in either a screening capacity before PVT diagnosis or confirmatory once thrombosis has developed, largely due to conflicting data on this topic. No systemic review or meta-analysis has been conducted to clarify this uncertainty, and the role of hereditary thrombophilia in patients with cirrhosis remains unknown. Prior studies assessed FVL and prothrombin G20210A in the development of acute PVT without excluding subjects with malignancy.

The aim of this study was to determine whether there is an increased rate of inherited thrombophilia in patients with cirrhosis who develop nontumoral PVT. Initial inherited thrombophilias of interest included common mutations such as protein C/S deficiency and prothrombin G20210A, FVL, and MTHFR C677T mutation. We hypothesized that there is an overall increased prevalence of inherited thrombophilia in cirrhotic patients who develop PVT.

2 | MATERIALS AND METHODS

2.1 | Literature search strategy

Trained study investigators independently systematically searched medical electronic databases for published literature (eg, observational studies and clinical trials) that studied the rates of hereditary thrombophilias in patients with cirrhosis who developed PVT. These databases included MEDLINE, Science Citation Index, Scopus, Allied and Complementary Medicine Database, and the Cochrane Library. Electronic search criteria included all publications through October 2017 with human restrictions using the following terms/keywords: cirrhosis, antithrombin, protein C, protein S, prothrombin, factor V Leiden, methylenetetrahydrofolate reductase, and JAK2. Duplicated article titles were removed after cross reference.

2.2 | Study selection

Two independent reviewers (SM and JW) screened the remaining list of studies for articles related to the research question. Studies were excluded if PVT was associated with malignancy including hepatocellular carcinoma (eg, tumoral thrombosis), developed after the procedure (eg, transjugular intrahepatic portosystemic shunt), if there were no primary data, or if no control/comparison group was included. Non-English studies were also excluded.

2.3 | Data extraction

Studies that met inclusion criteria underwent a full-text review by the 2 independent reviewers (SM and JW). Any disagreements about inclusion were resolved by an independent third clinical reviewer (JS). Data extraction from each study meeting inclusion criteria included patient characteristics (age/sex), study-level characteristics (author, publication year, study design, enrollment period, target population, total number of patients), and events of interest pertinent to the research question (prevalence of inherited thrombophilia in patients with cirrhosis who developed PVT vs. those who did not develop PVT). This study did not require institutional review board approval because no identifiable patient information was available or extracted.

2.4 | Statistical analysis

Descriptive statistical analysis of each identified study, along with meta-analysis of reported study effect measures, were calculated using review manager software (Rev-Man version 5.3; Copenhagen: The Nordic Cochrane Centre; The Cochrane Collaboration; 2014). Pooled odds ratios (ORs) were calculated by weighting study-specific risk ratios by the inverse of their individual variance. Magnitude of effect was calculated by DerSimonian and Laird random-effects ORs to obtain aggregate estimates of effect size and 95% confidence intervals (CIs) and to account for
3 | RESULTS

3.1 | Included studies

The search strategy resulted in a total of 8915 publications and adhered to the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) statement (Figure 1). After ensuring that no duplicates were present, 2893 article titles and abstracts were screened. A total of 25 articles underwent full-text review. After qualitative review of each study, 9 met inclusion criteria and were included in the meta-analysis. Articles that were excluded either contained no primary data (5), no thrombophilia data (5), duplicate data (3), no control (2), or incorrect clinical end points (1). The landmark study from Nery et al could not be included, as patient level data with the number of subjects with PVT and each individual inherited thrombophilia was unable to be discerned. Study level characteristics are found in Table 1. A summary of the search results is presented in Figure 1, reflecting PRISMA standards. No additional studies were appropriate for inclusion based on our a priori determined criteria.

In total, the 9 studies that met inclusion criteria comprised 1929 patients with cirrhosis. Overall prevalence of PVT was 6.4%. Subjects with PVT (n = 125) were compared to subjects without PVT (n = 1804). Mean individual study age ranged from 43 to 62 years and were predominantly male. The majority of the cohort had advanced cirrhosis, with Child-Turcotte-Pugh Class B or C disease. Chronic hepatitis C infection was the leading etiology of cirrhosis, followed by alcohol-related liver disease. Overall prevalence of thrombophilia was as follows: 17.3% MTHFR, 6.7% FVL, and 5.4% prothrombin G20102A. Table 2 provides details on patient-level characteristics.

3.2 | Inherited thrombophilia and PVT

3.2.1 | FVL mutation

Eight studies were used to determine the association of FVL mutation (either heterozygosity or homozygosity) with the odds of PVT in patients with cirrhosis. Overall prevalence of FVL was 6.7%. Heterogeneity between the studies was not significant ($I^2 = 26\%$). Overall, there was an increased prevalence of FVL in patients with cirrhosis who developed PVT, with an OR of 1.98 ($95\%$ CI, 1.06-3.68; $P = 0.03$) (Figure 2A).

3.2.2 | Prothrombin G20210A mutation

Seven studies were used to determine the association of prothrombin G20210A with PVT in cirrhosis. Overall prevalence of prothrombin G20210A (either heterozygosity or homozygosity) was 5.4%. Heterogeneity between the studies was not significant ($I^2 = 58\%$). Prothrombin G20210A also increased the odds of PVT in cirrhosis, with an OR of 2.43 ($95\%$ CI, 1.07-5.53; $P = 0.03$) (Figure 2B).
3.2.3 | MTHFR C677T mutation

Three studies were used to determine the prevalence of MTHFR C677T mutations in patients with cirrhosis who developed PVT. MTHFR C677T mutation was the most common thrombophilia, with a prevalence of 17.3% in the entire cohort. Heterogeneity between the studies was not significant ($I^2 = 70\%$). The measure of effect suggested no association of MTHFR C677T with PVT in cirrhosis (OR, 1.54; 95% CI, 0.66-3.55; $P = 0.32$) (Figure 2C).

3.2.4 | Other thrombophilias

One study included in this meta-analysis evaluated the plasminogen activator inhibitor-1 (PAI-1) 4G/5G mutation and found a statistically significant increased prevalence in patients with cirrhosis who developed PVT. However, no pooled measure of effect could be calculated with this single study.

3.3 | Bias assessment

No heterogeneity bias was observed in this analysis. $I^2$ was <75% in all thrombophilia that had a pooled measurable effect (Figure 2). No publication bias based on funnel plot analysis was observed as well (Figure 3).

4 | DISCUSSION

In this study, patients with cirrhosis had a greater prevalence of inherited thrombophilia than the general population, with rates between 5% and 17%. Of the 3 thrombophilias that had adequate data for statistical analysis, FVL and prothrombin G20210A mutation were significantly higher in patients with cirrhosis who developed PVT than cirrhotic patients without PVT. The presence of either FVL or prothrombin G20210A mutation was associated with an upwards of a 2-fold increased risk of PVT. MTHFR C677T was not associated with PVT risk in patients with cirrhosis. This is the first study to offer quantitative analysis investigating the prevalence of inherited thrombophilia in patients with cirrhosis who develop PVT. These findings suggest a need to reconsider the role of thrombophilia (eg, FVL and prothrombin G20210A) in the development of PVT in patients with cirrhosis. This issue might be particularly important in liver transplant candidates where pretransplant PVT is associated with significant pretransplant morbidity and mortality and may lead to inferior posttransplantation outcomes.

### TABLE 1 Study-level characteristics

| Reference          | Year published | Years enrolled     | Study design              | Liver cirrhosis diagnosis | Confounders controlled for | PVT diagnosis                                                                 |
|--------------------|----------------|--------------------|----------------------------|----------------------------|-----------------------------|-------------------------------------------------------------------------------|
| Amitrano et al      | 2004           | January 1998-December 2002 | Case-control study         | Morphological or clinical  | Sex, age, Child-Pugh score   | Preliminary abdominal US with Doppler; confirmed with spiral CT or MRI        |
| De Santis et al     | 2005 (Abstract) | Not specified       | Case-control study         | Histological or clinical   | Not specified               | Abdominal US with Doppler                                                    |
| Erkan et al         | 2005           | January 2000-December 2001 | Case-control study         | Liver biopsy or clinical   | Sex, age, etiology of cirrhosis | Abdominal US with Doppler                                                    |
| Mangia et al        | 2005           | April 1999-December 1999 | Case-control study         | Histological or clinical   | Sex, age, etiology/ complication of cirrhosis | Abdominal US with Doppler; confirmed with CT or angiography |
| Pasta et al         | 2005 (Abstract) | January 2000-September 2003 | Case-control study         | Not specified              | Not specified               | Not specified                                                                |
| Maras et al         | 2010 (Abstract) | Not specified       | Case-control study         | Not specified              | Not specified               | Not specified                                                                |
| Pellicelli et al     | 2011 (Abstract) | Not specified       | Prospective case-control study (19-mo follow-up) | Not specified              | Not specified               | Not specified                                                                |
| D’Amico et al       | 2015           | June 2008-January 2014 | Case-control study         | Not specified              | Sex, age, etiology/ complication of cirrhosis | Not specified                                                               |
| Saugel et al        | 2015           | December 2009-August 2011 | Case-control study         | Not specified              | Sex, age, etiology/ complication of cirrhosis, Child-Pugh/MELD score (partially) | Abdominal US, CT, or MRI                                                    |

CT, computed tomography; MRI, magnetic resonance imaging; PVT, portal vein thrombosis; US, ultrasound.
### TABLE 2  Patient characteristics from included studies

|                        | Amitrano et al 2004 | De Santis et al 2005 [Abstract] | Erkan et al 2005 |
|------------------------|----------------------|---------------------------------|------------------|
|                        | + PVT  | - PVT  | + PVT  | - PVT  | + PVT  | - PVT  |
| **Total number cirrhosis patients/PVT events** | 701/79 | 87/17 | 74/17 |
| **Sample size** | 79     | 79 (study produced) | 17 | 70 | 17 | 57 |
| **Mean age (y)** | 59.3 ± 11.1 | 59.3 ± 11.1 | 61.8 ± 10.9 | 43 ± 11 | 45 ± 10 |
| **Male-to-female ratio** | 47/32 | 47/32 | 49/38 | 10/7 | 42/15 |
| **Child-Pugh Class** |                     |                                 |                  |
| A                      | 7 (10%) | 7 (10%) | 37 (42.5%) | 6 (35%) | 8 (14%) |
| B                      | 41 (51.9%) | 41 (51.9%) | 40 (46.0%) | 6 (35%) | 23 (40%) |
| C                      | 31 (39.1%) | 31 (39.1%) | 10 (11.5%) | 5 (30%) | 26 (46%) |
| **Cirrhosis etiology** |                     |                                 |                  |
| HBV                    | 9 (11.3%) | 8 (10.1%) | ... | ... | 3 (18%) | 29 (50.5%) |
| HCV                    | 36 (45.5%) | 49 (62%) | ... | ... | 6 (35%) | 12 (21%) |
| Alcohol                | 11 (13.8%) | 10 (12.6%) | ... | ... | 3 (18%) | 5 (9%) |
| Cryptogenic            | 11 (13.8%) | 4 (5.1%) | ... | ... | 5 (29%) | 9 (16%) |
| Mixed                  | 12 (15.6%) | 8 (10.1%) | ... | ... | 3 (18%) | 2 (3.5%) |
| **Presence of thrombophilia** |                     |                                 |                  |
| FVL                     | 8 (11.4%) | 4 (5.1%) | 11.8%<sup>a</sup> | 1.4% | 5 (29)<sup>a</sup> | 2 (3.5) |
| PTHR                 | 15 (21.4)<sup>a</sup> | 4 (5.1%) | No values provided | No values provided | 5 (29)<sup>a</sup> | 2 (3.5) |
| MTHFR                 | 15 (21.4) | 11 (14.1) |                |                | 3 (18) | 10 (17.5) |
| **Mangia et al 2005**  |                     |                                 |                  |
| + PVT  | - PVT  |                    |                  |                  |
| **Total number cirrhotics/PVT events** | 219/43 | 183/65 | 270/70 |
| **Sample size** | 43 | 176 | 65 | 71 | 70 | 200 |
| **Mean age (y)** | 61.6 (33-84) median (range) | 56.7 (21-84) median (range) | ... | ... | ... | ...
| **Male-to-female ratio** | 22/21 | 90/86 | ... | ... | ...
| **Child-Pugh Class** |                     |                                 |                  |
| A | 17 (39.5%) | 104 (59.1%) | ... | ... | ...
| B | B + C: 26 (60.5%) | B + C: 72 (40.9) | ... | ... | ...
| C | ... | ... | ...
| **Cirrhosis etiology** |                     |                                 |                  |
| HBV | 4 (9.3%) | 17 (9.7%) | ... | ... | ...
| HCV | 19 (44.2%) | 80 (45.5%) | ... | ... | ...
| Alcohol | 9 (20.9%) | 33 (18.8%) | ... | ... | ...
| Cryptogenic | 7 (16.3%) | 18 (10.2%) | ... | ... | ...
| Mixed | 4 (9.3%) | 28 (31.2%) | ... | ... | ...
| **Presence of thrombophilia** |                     |                                 |                  |
| FVL | 1 (2.3%) | 6 (3.4%) | 2 (3.1) | 2 (2.8) | ... | ...
| PTHR | 2 (4.7) | 6 (3.4) | 1 (1.5) | 5 (7.0) | 17%<sup>a</sup> | 4% |
| MTHFR | 9 (20.9) | 39 (22.1) | ... | ... | 41.2% | 28% |
| Homozygous | 14 (25.9)<sup>b</sup> | 7 (9.9) | 12.8% | 6% |
| Heterozygous | 30 (55.6) | 38 (53.5) | 28% | 22% |

(Continues)
Maximizing transplant utility is of the utmost interest, given the continued inequity between organ supply and demand with the organ deficit of nearly 10,000 each year in the United States. Both FVL and prothrombin G20210A are predominantly found in Caucasian populations in a heterozygous-carrying manner. Although prevalence of heterozygous FVL is 5%, approximately 12% of patients who develop venous thromboembolism (VTE) in the general population have FVL. Prothrombin G20210A carriership is likewise observed in about 2% to 5% of the general population and in 4% to 17% of those with VTE. Taken in concert with the high prevalence of inherited thrombophilia in VTE from previous studies, our findings support consideration of testing for FVL and prothrombin G20210A mutations in patients with cirrhosis and newly diagnosed PVT.

While the optimal treatment choice remains controversial (eg, anticoagulation), we would suggest consultation with a hematologist to discern both the optimal treatment regimen and duration of therapy. The role of transjugular or transsplenic intrahepatic portosystemic shunts in the treatment of PVT in patients with cirrhosis with thrombophilia will also need to be addressed with future studies; however, the argument can be made that even if endovascular intervention is pursued, patients with thrombophilia likely will need anticoagulation even if mechanical portal vein recanalization is obtained. Consideration of consultation with a hematologist would also be helpful and should be sought once a thrombophilia has been diagnosed in the patient with cirrhosis and PVT.

While our data do not answer the question regarding the utility of universal screening in all patients with cirrhosis at risk for PVT, prevalence rates of thrombophilia in PVT are similar to other general medical conditions where universal screening is recommended (eg, breast and colon cancer). Research suggests that FVL and prothrombin G20210A mutations increase only the first but not recurrent DVT. Other studies have shown that thrombophilia screening does not reduce the risk of DVT recurrence. Nevertheless, PVT as a consequence of cirrhosis involves additional risk factors that may not play a role in typical DVT development outside the setting of cirrhosis. These include cirrhosis-induced coagulopathy and hemodynamic changes as a result of cirrhosis and portal hypertension. More research is needed to better distinguish the role of inherited thrombophilia specifically in the development of cirrhotic PVT and in defining its clinical course.
have an increased rate of inherited thrombophilias remains unclear and is an interesting avenue for future study. In general, data on inherited thrombophilia and risk of PVT in malignancy are limited; however, several small studies have documented both FVL and prothrombin G20210A mutation as independent risk factors for VTE in malignancy with a similar 2- to 4-fold increased risk.28,29 Antiphospholipid antibodies and acquired resistance to activated protein C can also contribute to the development of PVT.27

Although this meta-analysis excluded neoplasms and inflammatory conditions to avoid heterogeneity and selection bias, previous research studies have also found these conditions to be independent risk factors for patients with cirrhosis without inherited thrombophilias to develop PVT.27 Whether patients with tumoral PVT have an increased rate of inherited thrombophilias remains unclear and is an interesting avenue for future study. In general, data on inherited thrombophilia and risk of PVT in malignancy are limited; however, several small studies have documented both FVL and prothrombin G20210A mutation as independent risk factors for VTE in malignancy with a similar 2- to 4-fold increased risk.28,29 Antiphospholipid antibodies and acquired resistance to activated protein C can also contribute to the development of PVT.27

**FIGURE 2** Pooled measure of effects for patients with cirrhosis with/without PVT and with/without presence of: A, Factor V Leiden (FVL); B, prothrombin mutation (prothrombin G20210A); C, methyltetrahydrofolate reductase mutation (MTHFR C677T)

**FIGURE 3** Funnel plot analyzing publication bias for: A, factor V Leiden (FVL); B, prothrombin mutation (prothrombin G20210A); C, methyltetrahydrofolate reductase mutation (MTHFR C677T)
protein C may also predispose independently to thrombosis in patients with malignancy.29

The findings from this study warrant a renewed focus to better understand the role of prophylactic anticoagulation in patients with cirrhosis who are at a greater risk for PVT development, including those with inherited thrombophilia. To date, there has been only 1 controlled trial published on the effective use of prophylactic anticoagulation for patients with cirrhosis.30 In this study, no patients receiving enoxaparin developed PVT after 96 weeks, while 36% of subjects in the nonanticoagulated group developed PVT; interestingly, there was a survival benefit with no significant increase in hemorrhagic events or adverse effects in the anticoagulated group.30 We propose that anticoagulants should be studied for their potential to prevent PVT in patients with cirrhosis and inherited thrombophilia. Currently, 1 multicenter randomized trial has been initiated with a similar research question (Multicenter Prospective Randomized Trial of the Effect of Rivaroxaban on Survival and Development of Complications of Portal Hypertension in Patients with Cirrhosis [CIRROXABAN])30 which may provide evidence for the need of prophylactic coagulation in cirrhotic patients.

Although we observed an association of thrombophilia with PVT in cirrhosis and that this could guide anticoagulant prevention, patients with cirrhosis with other risk factors might also benefit from prophylaxis. More research needs to be done on this topic to better distinguish the role of anticoagulation in all high-risk patients with cirrhosis, as prophylactic use may do more harm than good for different subsets of patients.

Our study has several limitations, primarily in regards to the availability of published studies on the research topic. Multiple studies were excluded due to lack of primary data or presence of duplicate data, including a landmark study published by Nery et al,14 which found no relationship between inherited thrombophilia (e.g., FVL and prothrombin 20210A mutations) and risk of cirrhotic PVT. Exclusion of such a study does affect our data but continues to highlight the uncertainty of this research question. Other studies were excluded due to lack of a control group. Furthermore, several studies included in the meta-analysis were only abstracts of lower quality (Table 3). Additionally, the lack of clarity surrounding what imaging modality was used to diagnose PVT in several studies is somewhat limiting. Although there was an increased prevalence of MTHFR C677T mutation in the patient population of interest, there was no pooled statistically significant increased risk in PVT, and the inclusion of only 3 studies limited statistical power (Figure 2C) and led to greater heterogeneity. Additionally, data for PAI-1 4G/5G polymorphism was even more limited, with 1 study. However, it is important to note that neither MTHFR or PAI-1 4G/5G polymorphisms are established risk factors for the development of DVT. No concrete conclusions about either of these inherited thrombophilias can be made at this time, but future research may establish this.

In summary, patients with cirrhosis and concomitant inherited thrombophilia FVL and prothrombin G20102A are at higher risk for developing PVT than those without thrombophilia, with a 2-fold increased risk of PVT. Data for confident conclusions regarding MTHFR C677T and PAI-1 4G/5G mutation are lacking at this time. Although we were unable to include a recent longitudinal study that found no relationship between thrombophilia and PVT risk,15 our conflicting conclusion provides greater insight into the need to study this topic further. Future prospective studies investigating thrombophilia screening in patients with cirrhosis after PVT diagnosis seems warranted to better understand the role of genetics and clotting risk in patients with chronic liver disease, with the goal of impacting patient-centered outcomes.

### RELATIONSHIP DISCLOSURE

None.

### AUTHOR CONTRIBUTIONS

JGS was the guarantor of the article. SDM was responsible for the literature search, study selection, data extraction and interpretation, and manuscript drafting and preparation. JW was responsible for the literature search, study selection, data extraction, and manuscript preparation. DM, ZK, and PGN were responsible for the study design and manuscript preparation. JGS was responsible for the study idea, study design, literature search, study selection, data analysis and interpretation, and manuscript revision.

### ACKNOWLEDGMENTS

None.

### REFERENCES

1. De Santis et al.
2. D’Amico et al.
3. Saugel et al.
4. Amitrano et al.
5. Pasta et al.
6. Maras et al.
7. Pellicelli et al.
8. Mangia et al.
9. Erkan et al.
10. Peng et al.
11. De Leo et al.
12. De Leo et al.
13. De Leo et al.
14. Nery et al.
15. D’Souza et al.
16. De Santis et al.
17. D’Amico et al.
18. Saugel et al.
19. De Santis et al.
20. D’Amico et al.
21. Saugel et al.
22. D’Amico et al.
23. De Santis et al.
24. D’Amico et al.
25. Saugel et al.
26. De Santis et al.
27. D’Amico et al.
28. Saugel et al.
29. De Santis et al.
30. D’Amico et al.
31. Saugel et al.
32. D’Amico et al.
33. De Santis et al.
34. D’Amico et al.
35. Saugel et al.
36. Maras et al.
37. Pellicelli et al.

**Table 3: Bias assessment of included studies by Newcastle-Ottawa scale**

| References       | Year published | Selection | Comparability | Outcome |
|------------------|----------------|-----------|---------------|---------|
| Amitrano et al   | 2004           | ****      | **            | ***     |
| De Santis et al  | 2005 (Abstract) | **        | *             | **      |
| Erkan et al      | 2005           | ****      | **            | ***     |
| Mangia et al     | 2005           | ****      | **            | **      |
| Pasta et al      | 2005 (Abstract) | **        | *             | **      |
| Maras et al      | 2010 (Abstract) | ***       | **            | **      |
| Pellicelli et al | 2011 (Abstract) | **        | *             | **      |
| D’Amico et al    | 2015           | ****      | **            | **      |
| Saugel et al     | 2015           | ****      | **            | ***     |

Note: A maximum of 4 stars can be awarded for selection, 2 for comparability, and 3 for outcomes. A score of >6 indicates a high-quality study.
and preparation. All authors approved the final version of the manuscript.

REFERENCES

1. Lisman T, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. Blood. 2010;116:878–85.
2. Sarin SK, Philips CA, Kamath PS, Choudhury A, Maruyama H, Nery FG, et al. Toward a comprehensive new classification of portal vein thrombosis in patients with cirrhosis. Gastroenterology. 2016;151:574–7.
3. Englesbe MJ, Kubus J, Muhammad W, Sonnenday CJ, Welling T, Punch JD, et al. Portal vein thrombosis and survival in patients with cirrhosis. Liver Transpl. 2010;16:83–90.
4. Amitrano L, Guardascione M, Brancaccio V, Margaglione M, Manguso F, Iannaccone L, et al. Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis. J Hepatol. 2004;40:736–41.
5. Stine JG, Shah PM, Cornella SL, Rudnick SR, Ghabril MS, Stukenborg GJ, et al. Portal vein thrombosis, mortality and hepatic decompensation in patients with cirrhosis: a meta-analysis. World J Hepatol. 2015;7(27):2744–80.
6. Zocco MA, Di Stasio E, De Cristofaro R, Novi M, Ainora ME, Ponziani MA et al. Causes and consequences of portal venous thrombosis in patients with cirrhosis: an evidence-based approach. Liver Int. 2016;36(8):279–86.
7. Stine JG, Wang J, Shah PM, Argo CK, Intagliata N, Uflacker A, et al. Decreased portal vein velocity is predictive of the development of portal vein thrombosis: a matched case-control study. Liver Int. 2018;38(1):94–101.
8. Intagliata NM, Argo CK, Stine JG, Lisman T, Caldwell SH, ViolI F. Thrombotic risk factors in patients with liver cirrhosis: correlation with MELD scoring system and portal vein thrombosis development. J Hepatol. 2009;51:682–9.
9. Stine JG, Wang J, Shah PM, Argo CK, Intagliata N, Uflacker A, et al. Decreased portal vein velocity is predictive of the development of portal vein thrombosis: a matched case-control study. Liver Int. 2018;38(1):94–101.
10. Connors JM. Thrombophilia testing and venous thrombosis. N Engl J Med. 2017;377:1177–87.
11. Stevens SM, Woller SC, Bauer KA, Kasthuri R, Cushman M, Streiff M, et al. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. J Thromb Thrombolysis. 2016;41:154–64.
12. Qi C, Ren W, Stefano V, Fan D. Associations of coagulation factor V Leiden and prothrombin G20210A mutations with Budd-Chiari syndrome and portal vein thrombosis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2004;12:1801–12.
13. Murad MH, Montori VM, Ioannidis JP, Jaeschke R, Devereaux PJ, Prasad K, et al. How to read a systematic review and meta-analysis and apply the results to patient care: users’ guides to the medical literature. JAMA. 2014;312:171–9.
14. Nery F, Chevret S, Condat B, de Raucourt E, Boudaoud L, Rautou PE, et al. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. Hepatology. 2015;61(2):660–7.
15. D’Amico M, Pasta D, Pasta L. Thrombophilic genetic factors PAI-1 4G-4G and MTHFR 677TT as risk factors of alcohol, cryptogenic liver cirrhosis and portal vein thrombosis, in a Caucasian population. Gene. 2015;568:85–8.
16. Stine JG, Pelletier SJ, Schmitt TM, Porte RJ, Northup PG. Pre-transplant portal vein thrombosis is an independent risk factor for graft loss due to hepatic artery thrombosis in liver transplant recipients. HPB. 2016;18(3):279–86.
17. Stine JG, Argo CK, Pelletier SJ, Maluf DG, Northup PG. Liver transplant recipients with portal vein thrombosis receiving an organ from a high-risk donor are at an increased risk for graft loss due to hepatic artery thrombosis. Transpl Int. 2016;29(12):1286–95.
18. Ridker PM, Miletich JP, Hennekens CH, Buring JE. Ethnic distribution of factor V Leiden in 4047 men and women. Implications for venous thromboembolism screening. JAMA. 1997;277(10):1305–7.
19. Ridker PM, Hennekens CH, Lindpaintner K, Stampfer MJ, Eisenberg PR, Miletich JP. Mutation in the gene coding for coagulation factor V and the risk of myocardial infarction, stroke, and venous thrombosis in apparently healthy men. N Engl J Med. 1995;332(14):912–7.
20. Rosendaal FR, Doggen CJ, Zivelin A, Arruda VR, Aiach M, Siscovick DS, et al. Geographic distribution of the 20210 G to A prothrombin variant. Thromb Haemost. 1998;79(4):706–8.
21. Lerooyer C, Mercier B, Oger E, Chenu E, Abgrall F, Férec C, et al. Prevalence of 20210 A allele of the prothrombin gene in venous thromboembolism patients. Thromb Haemost. 1998;80(1):49.
22. Souto JC, Coll I, Llobet D, del Rio E, Oliver A, Mateo J, et al. The prothrombin 20210A allele is the most prevalent genetic risk factor for venous thromboembolism in the Spanish population. Thromb Haemost. 1998;80(3):366.
23. Walker AJ, West J, Card TR, Crooks C, Kirwan CC, Grainge MJ. When are breast cancer patients at highest risk of venous thromboembolism? A cohort study using English health care data. Blood. 2016;127(7):849–57.
24. Alcalay A, Wun T, Khatri V, Chew HK, Harvey D, Zhou H, et al. Venous thromboembolism in patients with colorectal cancer: incidence and effect on survival. J Clin Oncol. 2006;24(7):1112–8.
25. Christiansen SC, Cannegiether SC, Koster T, Vandenbroucke JP, Rosendaal FR. Thrombophilia, clinical factors, and recurrent venous thrombotic events. JAMA. 2005;293(19):2352–61.
26. Coppens M, Reijnders JH, Middeldorp S, Doggen CJ, Rosendaal FR. Testing for inherited thrombophilia does not reduce the recurrence of venous thrombosis. J Thromb Haemost. 2008;6(9):1474–7.
27. Kockritz LV, Gottardi AD, Trebicka J, Praktiknjo M. Portal vein thrombosis in patients with cirrhosis. Gastroenterol Rep. 2017;5:148–56.
28. Horowitz N, Brenner B. Thrombophilia and cancer. Physiother Haemost Thromb. 2008;36(3–4):131–6.
29. Decousus H, Moulin N, Quenet S, Bost V, Rivron-Guillot K, Laporte S, et al. Thrombophilia and risk of venous thrombosis in patients with cancer. Thromb Res. 2007;120(suppl 2):S51–61.
30. Leonardi F, Maria ND, Villa R. Anticoagulation in cirrhosis: a new paradigm. Clin Mol Hepatol. 2017;23:13–21.
31. De Santis A, Cristofari F, Gigliotti F, Trapani S, Moscatelli R, Conti L, et al. Inherited coagulation disorders in cirrhotic patients with and without portal vein thrombosis (PVT). J Hepatol. 2005;42:65.
32. Erkan O, Bozdayi AM, Disibeyaz S, Oguz D, Ozcan M, Bahar K, et al. Thrombophilic gene mutations in cirrhotic patients with portal vein thrombosis. Eur J Gastroenterol Hepatol. 2005;17:339–43.
33. Mangia A, Villani MR, Cappucci G, Santoro R, Ricciardi R, Facciorusso D, et al. Causes of portal venous thrombosis in cirrhotic patients: the role of genetic and acquired factors. Eur J Gastroenterol Hepatol. 2005;17:745–51.
34. Pasta L, Marrone C, D’Amico M, Virdone R, Fabiano C, Sammarco P, et al. MTHFR C677T and other inherited coagulation disorder in Budd Chiari Syndrome (BCS) and portal vein thrombosis (PVT) with or without liver cirrhosis. J Hepatol. 2005;128:A735.
35. Maras JS, Garg V, Sarin SK. MTHFR C677T, prothrombin G20210A and JAK2 V617F mutations are associated with increased risk of portal vein thrombosis in patients with chronic liver disease. Hepatology. 2010;52:904A.
36. Pellicelli AM, D’Ambrosia C, Barbaro G, Villani R, Guarascio P, Fondacaro L, et al. Clinical and genetic factors associated to development of portal vein thrombosis in cirrhotic patients without hepatocellular carcinoma. J Hepatol. 2011;54:S77.

37. Saugel B, Lee M, Feichtinger S, Hapfelmeier A, Schmid RM, Siveke JT. Thrombophilic factor analysis in cirrhotic patients with portal vein thrombosis. J Thromb Thrombolysis. 2015;40:54–60.

How to cite this article: Ma SD, Wang J, Bezinower D, Kadry Z, Northup PG, Stine JG. Inherited thrombophilia and portal vein thrombosis in cirrhosis: A systematic review and meta-analysis. Res Pract Thromb Haemost. 2019;3:658–667. https://doi.org/10.1002/rth2.12253