Original Article
Prevalence of portal or splenic vein thrombosis in cirrhotic patients after splenectomy: a systematic review and meta-analysis of observational studies

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Abstract: This systematic review and meta-analysis aims to explore the prevalence of portal or splenic vein thrombosis (PSVT) in cirrhotic patients after splenectomy. All observational studies regarding the prevalence of PSVT in cirrhotic patients after splenectomy were identified via PubMed and EMBASE databases. 33 studies fulfilled the inclusion criteria. Meta-analyses showed a pooled prevalence of PSVT of 22.2% in cirrhotic patients after splenectomy. According to the types of splenectomy, the pooled prevalence of PSVT was 20.6% and 17.0% in cirrhotic patients after open or laparoscopic splenectomy, respectively. According to the Child-Pugh classes, the pooled prevalence of PSVT after splenectomy was 32.9%, 38.7%, and 61.2% in cirrhotic patients with Child-Pugh class A, B, and C, respectively. The pooled prevalence of PSVT after splenectomy was 24.6% and 47.4% in cirrhotic patients with and without anticoagulants. In conclusion, the pooled prevalence of PSVT in cirrhotic patients after splenectomy could be up to 22.2%.

Keywords: Portal vein, splenic vein, thrombosis, cirrhosis, splenectomy

Introduction

In Asia, splenectomy in combination with devascularization of the upper stomach and esophageal transection is a major treatment option for portal hypertension-related complications and hypersplenism in liver cirrhosis, which can reduce the portal pressure and prevent from variceal bleeding [1-4]. However, portal or splenic vein thrombosis (PSVT) is a common and potentially life-threatening complication of splenectomy [5-7].

With the advance in diagnostic modalities, the incidence of PSVT may be apparently greater than clinically appreciated [8]. It may be asymptomatic, but severe PSVT can reduce hepatopetal blood flow in the portal system and generate the hypertension in the visceral side of portal vein, leading to liver failure, bowel ischemia and variceal bleeding [9-11].

It is important for the clinicians and patients to understand the knowledge about the epidemiology of PSVT in liver cirrhosis patients treated with splenectomy. However, the relevant information is heterogeneous among these published literatures. The aim of the present systematic review and meta-analysis is to obtain the prevalence of PSVT in cirrhotic patients after splenectomy by resolving the following questions. 1) What is the prevalence of PSVT in cirrhotic patients after splenectomy? 2) What is the prevalence of PSVT in cirrhotic patients according to the gender (i.e., male and female)? 3) What is the prevalence of PSVT in cirrhotic patients according to the Child-Pugh class? 4) What is the prevalence of PSVT in cirrhotic patients according to the type of surgery? 5) What is the prevalence of PSVT in cirrhotic patients according to the use of anticoagulants? 6) What is the prevalence of PSVT in cirrhotic patients according to the countries?

Methods

A study protocol for this systematic review and meta-analysis was drafted according to the current guideline [12].
Eligibility criteria

All cohort and case-control studies were eligible, regardless of the retrospective or prospective nature of the study, if the incidence of PSVT after splenectomy in the participants of any age and gender were diagnosed with liver cirrhosis was reported. The participants with underlying malignancy, trauma, pregnancy, intra-abdominal infections, primary myeloproliferative disorders, or other liver diseases were not deliberately excluded. The participants who developed PSVT preoperatively were excluded.

Animal studies were also excluded.

There were no publication date or publication status restrictions.

There were no language restrictions.

Number of participants in any included study was beyond 10.

Data extraction

Using a predefined protocol, two investigators (LX and QX) independently reviewed the titles and abstracts of all references to identify studies for inclusion in the analysis. Dealing with disagreement between the two reviewers, a consensus was achieved through discussion among all of the reviewers. A schematic diagram depicting reference flow is shown through the systematic review process. Additionally, Excel tables were generated that included the following data: the authors, publication year, study design, study population, gender of the patients, region where the study was conducted, period of enrolment, Child-Pugh class (A/B/C), type of operation, information regarding the prevention of PSVT after splenectomy, type and number of participants, inclusion and exclusion criteria, demographic data (age and sex), number of patients with PSVT.

Evaluation of study quality

Quality assessment of studies was carried out independently by two reviewers (LX and QX). Discrepancies of interpretation and comprehension were resolved by consensus. The higher quality studies should be fulfilled the following predetermined criteria:

Region where the study was conducted, interval of enrolment, inclusion and exclusion criteria and participant characteristics (age, gender) were clearly recorded.

Liver cirrhosis was diagnosed on the basis of the history of liver disease, clinical manifestations, laboratory tests, and imaging detection by ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI).

Data synthesis and statistical analysis

The proportion of PSVT in cirrhotic patients after splenectomy in each study was combined to give a pooled prevalence of PSVT for all studies. Furthermore, according the gender of the patients, the type of operation, the reason of the liver cirrhosis and the Child-Pugh class of the liver cirrhosis, the pooled prevalence of PSVT was also calculated. The number and crude proportion of participants with PSVT recorded by each study were used to pool the overall proportion, using the DerSimonian-Laird
random-effects method. Between-study heterogeneity was assessed by using the I² index (I² > 50% was considered as having substantial heterogeneity) and the Chi-squared test (P < 0.01 was considered to represent significant statistical heterogeneity) [3]. Individualized random effects meta-analyses were performed to estimate percentages and 95% confidence intervals (CIs) for all endpoints queried. Egg bias analysis was performed to evaluate the publication bias. Analyses were conducted using StatsDirect statistical software version 2.7.8 (StatsDirect Ltd, Sale, Cheshire, UK).

Results

Description of the included studies

In the initial search strategy, a total of 338 studies were selected. Thirty-three studies were finally included in the meta-analysis (Figure 1).

These included studies were published in full-texts (n = 27) or abstract (n = 6) between 1979 and 2014. Of them, 4 were randomized trials inclusion and exclusion criteria, but 19 studies had no eligibility criteria. Twenty-seven studies clearly reported the demographic data. The diagnostic criteria of liver cirrhosis were elaborated in four studies.

Prevalence of PSVT in cirrhotic patients after splenectomy

The prevalence of PSVT in cirrhotic patients after splenectomy ranged from 1.8% to 78.6% (Figure 2). A pooled prevalence was 22.2% (95% CI: 17.4%-27.6%) and a statistically significant heterogeneity among studies (I² = 90.1%, 95% CI: 87.6%-91.9%, P < 0.0001). There was a significant publication bias (Egg bias = 3.966716, P = 0.0005).

Prevalence of PSVT in cirrhotic patients after splenectomy with different gender

In male patients, the prevalence of PSVT in cirrhotic patients after splenectomy ranged from 18.2% to 70.6% (Figure 3A). A pooled prevalence was 33.7% (95% CI: 26.2%-41.5%) with a statistically significant heterogeneity among studies (I² = 70.8%, 95% CI: 39.9%-82.4%, P <
Table 1. An overview of included papers

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Regions</th>
<th>Enrollment period</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Male/Female</th>
<th>Type of patients</th>
<th>Demographic data</th>
<th>Eligibility criteria</th>
<th>Diagnostic criteria</th>
<th>Type of surgery</th>
<th>PSVT</th>
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<td>Shi R (2014)</td>
<td>China</td>
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<td>18</td>
<td>15/3</td>
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<td>No</td>
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<td>127</td>
<td>89/38</td>
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<td>OS (n = 127)</td>
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<td>No</td>
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<td>34/23</td>
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<td>Yes</td>
<td>OS (n = 29)</td>
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<td>No</td>
<td>No</td>
<td>Not reported</td>
<td>29</td>
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<td>25</td>
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<td>No</td>
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<td>Retrospective</td>
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PVST after splenectomy

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<th>Author</th>
<th>Country</th>
<th>Study Period</th>
<th>Study Type</th>
<th>Sample Size</th>
<th>Treatment arms</th>
<th>Liver cirrhosis</th>
<th>Past history of varicose veins</th>
<th>Status</th>
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<td>Randomized trial</td>
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<td>Randomized trial</td>
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<td>61/42</td>
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<td>Yes</td>
<td>No</td>
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<td>Eguchi A (1991)</td>
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<td>Prospective</td>
<td>106</td>
<td>83/23</td>
<td>Yes</td>
<td>No</td>
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</tbody>
</table>

Abbreviations: Open splenectomy (OS), Laparoscopic splenectomy (LS), hand-assisted laparoscopic surgery (HALS).
PVST after splenectomy


0.0001). There was a significant publication bias (Egg bias = 2.400235, P = 0.0166).

In female patients, the prevalence ranged from 14.7% to 90.9% (Figure 3B). A pooled prevalence was 39.4% (95% CI: 27.4%-52.1%) and a statistically significant heterogeneity among studies (I² = 89.5%, 95% CI: 85.8%-91.0%, P < 0.0001). There was a significant publication bias (Egg bias = 3.249148, P = 0.0183).

Ten studies reported the prevalence of PSVT in cirrhotic patients after laparoscopic splenectomy (LS), ranging from 4.3% to 40.0% (Figure 4B). The pooled prevalence was 17.0% (95% CI: 8.8%-52.1%) and a statistically significant heterogeneity among studies (I² = 78%, 95% CI: 44.6%-84.0%, P < 0.0001). There was no significant publication bias (Egg bias = 0.18495, P = 0.851).

Prevalence of PSVT in cirrhotic patients with different Child-Pugh classes after splenectomy

Eleven studies reported the prevalence of PSVT in cirrhotic patients with Child-Pugh class A after splenectomy, ranging from 16.1% to 63.6% (Figure 5A). The pooled prevalence was 32.9% (95% CI: 24.0%-42.1%) and a statistically significant heterogeneity among studies (I² = 73.4%, 95% CI: 68.6%-83.4%, P < 0.0001). There was a significant publication bias (Egg bias = 0.240235, P = 0.0181).

Ten studies reported the prevalence of PSVT in cirrhotic patients with Child-Pugh class B after splenectomy, ranging from 23.5% to 86.7% (Figure 5B). The pooled prevalence was 38.7% (95% CI: 28.5%-49.4%) and a statistically significant heterogeneity among studies (I² = 65.1%, 95% CI: 46.6%-80.6%, P = 0.0022). There was no significant publication bias (Egg bias = 2.114049, P = 0.2773).

Six studies reported the prevalence of PSVT in cirrhotic patients with Child-Pugh class C after splenectomy (OS), ranging from 1.9% to 55.6% (Figure 4A). The pooled prevalence was 20.6% (95% CI: 15.3%-26.6%) with a statistically significant heterogeneity among studies (I² = 89.5%, 95% CI: 85.8%-91.0%, P < 0.0001). There was a significant publication bias (Egg bias = 3.249148, P = 0.0183).

Figure 2. Forest plots showing the prevalence of PSVT in cirrhotic patients after splenectomy.

Figure 3. Forest plots showing the prevalence of PSVT in cirrhotic patients after different type of splenectomy.

Figure 4. Forest plots showing the prevalence of PSVT in cirrhotic patients with different Child-Pugh classes after splenectomy.
PVST after splenectomy

A

Proportion meta-analysis plot [random effects]

B

Proportion meta-analysis plot [random effects]
PVST after splenectomy

(95% CI: 41.1%-79.4%) and there was no statistical heterogeneity among studies ($I^2 = 36.4\%, 95\%\ CI: 0.0\%-73.8\%, P = 0.1642$). There was no significant publication bias (Egger bias = 1.213827, $P = 0.6506$).

**Prevalence of PSVT in cirrhotic patients after splenectomy with and without anticoagulants**

Eight studies reported the prevalence of PSVT in cirrhotic patients after splenectomy with anticoagulants, ranging from 4.0% to 62.5% (Figure 6A). The pooled prevalence was 24.6% (95% CI: 15.5%-35.0%) and a statistically significant heterogeneity among studies ($I^2 = 83.6\%, 95\%\ CI: 66.9\%-90.0\%, P < 0.0001$). There was no significant publication bias (Egger bias = 0.072909, $P = 0.9799$).

Six studies reported the prevalence of PSVT in cirrhotic patients after splenectomy without anticoagulants, ranging from 33.3% to 85.7% (Figure 6B). The pooled prevalence was 47.4% (95% CI: 32.6%-62.4%) and a statistically significant heterogeneity among studies ($I^2 = 65.8\%, 95\%\ CI: 0.0\%-83.7\%, P = 0.0121$). There was no significant publication bias (Egger bias = 1.493166, $P = 0.6324$).

**Prevalence of PSVT in cirrhotic patients after splenectomy in different countries**

The involved countries of all studies could be divided into three countries (China, Japan and Australia). In Australia, only one study reported the prevalence of PSVT in cirrhotic patients after splenectomy (32.9%).

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Figure 3. Forest plots showing the prevalence of PSVT in male cirrhotic patients after splenectomy according to the sex. A. Male. B. Female.

Figure 4. Forest plots showing the prevalence of PSVT in cirrhotic patients after splenectomy according to the approaches of surgery. A. Open splenectomy. B. Laparoscopic splenectomy.

splenectomy, ranging from 33.3% to 100% (Figure 5C). The pooled prevalence was 61.2%
In China, 21 studies reported the prevalence of PSVT in cirrhotic patients after splenectomy, ranging from 3.1% to 55.6% (Figure 7A). The pooled prevalence was 20.2% (95% CI: 15.3%-25.8%) with a statistically significant heterogeneity among studies ($I^2 = 90.1\%$, 95% CI: 86.7%-92.2%, $P < 0.0001$). There was a significant publication bias (Egger bias = 2.812266, $P = 0.0792$).

In Japan, 11 studies reported the prevalence of PSVT in cirrhotic patients after splenectomy, ranging from 1.9% to 78.6% (Figure 7B). The pooled prevalence was 24.7% (95% CI: 12.9%-38.9%) with a statistically significant heterogeneity among studies ($I^2 = 91.3\%$, 95% CI: 87.0%-93.7%, $P < 0.0001$). There was a significant publication bias (Egger bias = 4.757252, $P = 0.0017$).

**Discussion**

Splenectomy is associated with a variety of vascular complications including PSVT in cirrhotic patients. Clinically, PSVT is becoming common with the advancement of imaging techniques. Among the previous published studies, the prevalence of PSVT in cirrhotic patients after splenectomy varied from 1.8% to 78.6%. However, no systematic search was performed in any previous studies. Most of previous studies were single-center studies with a limited enrollment period and target population. By comparison, our meta-analysis included all studies conducted from 1991 to 2014 and 2997 cirrhotic patients after splenectomy. Furthermore, we made a distinction on the source of patients according to the continents. Our research also reported the prevalence of PSVT on the basis of the different genders, different types of splenectomy, different Child-
Figure 6. Forest plots showing the prevalence of PSVT in cirrhotic patients after splenectomy according to the use of anticoagulants. A. With anticoagulants. B. Without anticoagulants.
PVST after splenectomy

Pugh classes, with and without anticoagulants, and different countries.

In the current systematic review and meta-analysis, we demonstrated that 22.2% of cirrhotic patients after splenectomy had PSVT. The prevalence of PSVT was mildly different among the genders. We found that the prevalence of PSVT appeared to be higher in female cirrhotic patients than in male cirrhotic patients (39.4% versus 33.7%).

There are two major types of splenectomy commonly used for the treatment of portal hypertension from cirrhosis, including OS and LS. Among the previous studies that reported the vascular complications of splenectomy, the highest prevalence of PSVT reached 55.6% in cirrhotic patients after OS [26], and 78.6% after LS [33]. This meta-analysis demonstrated that the prevalence of PSVT appeared to be higher in OS group than in LS group (20.6% versus 17.0%).

Child-Pugh score is used to assess the prognosis of liver cirrhosis [47]. Among the previous studies, the highest prevalence of PSVT after splenectomy reached 63.6%, 86.7%, and 100% in cirrhotic patients with Child-Pugh A, B, and C, respectively [33]. Our study showed that the prevalence of PSVT was 32.9%, 38.7%, and 61.2% in Child-Pugh A, B and C patients, respectively. This might suggest that the severity of liver dysfunction is closely associated with the occurrence of PSVT after splenectomy.

Recent research suggests that preventive measures are safe and effective for the prevention of PSVT in patients with laparoscopic splenectomy and esophagogastroduodenostomy for cirrhosis and portal hypertension [48, 49]. Our meta-analysis also confirmed that the prevalence of PSVT might be higher in

Figure 7. Forest plots showing the prevalence of PSVT in cirrhotic patients after splenectomy according to the countries. A. China. B. Japan.
patients without anticoagulants than in patients with anticoagulants (47.4% versus 24.6%). This might suggest the role of anticoagulant in cirrhotic patients after splenectomy.

The prevalence of PSVT in cirrhotic patients after splenectomy showed some regional differences. All involved studies were performed in China, Japan and Australia. In Australia, only one study reported that the prevalence was 32.9%. Among the previous studies, the highest prevalence of PSVT after splenectomy reached 78.6% [33]. Our study found that the prevalence of PSVT was 24.7% in Japan, which was mildly higher than 20.2% in China.

Limitation

Our study has several limitations. First, although the number of involved papers is relatively large, the heterogeneity of available data among studies was significant. They were performed during a very long span. The diagnostic accuracy of PSVT was gradually improved over time. At present, many asymptomatic patients could be diagnosed with PSVT earlier by using advanced imaging techniques. Therefore, there were some differences in the incidence of PSVT after splenectomy over time. Additionally, considering the potential heterogeneity, only the random-effects model was applied in our meta-analysis to generate a more conservative estimate of the proportion. Indeed, we attempted to pool the incidence of PSVT after splenectomy in different subgroups (genders, countries, Child-Pugh score, type of surgery, and use of anticoagulants) to explore the source of heterogeneity. Second, although there were different results among different subgroups, we could not draw any firm conclusions to assess which subgroup has a higher incidence of PSVT after splenectomy. Therefore, we just described the results, but not conclude any comparative findings.

Conclusion

Our systematic review and meta-analysis attempt to quantify the incidence of PSVT in cirrhotic patients after splenectomy according to the genders, type of surgery, Child-Pugh class, use of anticoagulants, and regions. These preliminary findings were useful to improve our understanding regarding the epidemiology of PSVT after splenectomy. Large, multicentre, and collaborative studies might be required to confirm them. Additionally, based on the present findings, randomized studies might be worthwhile to explore the necessity of anticoagulant for the prevention of PSVT after splenectomy.

Disclosure of conflict of interest

None.

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References

PVST after splenectomy


PVST after splenectomy


