Original Article

Role of D-dimer in the Development of Portal Vein Thrombosis in Liver Cirrhosis: A Meta-analysis

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ABSTRACT

Background and Aims: A meta-analysis was performed to explore the role of the D-dimer in the development of portal vein thrombosis (PVT) in liver cirrhosis. **Methods:** All papers were searched via PubMed, EMBASE, China National Knowledge Infrastructure, Wan Fang, and VIP databases. A standardized mean difference (SMD) with 95% confidence interval (CI) was pooled. **Results:** Overall, 284 studies were initially identified, of which 21 were included. Cirrhotic patients with PVT had a significantly higher D-dimer concentration than those without PVT (pooled SMD = 1.249, 95%CI = 0.740–1.758). After the portal hypertension-related surgery, cirrhotic patients with PVT had a similar preoperative D-dimer concentration to those without PVT (pooled SMD = 0.820, 95%CI = −0.122–0.286), but a higher postoperative value of D-dimer concentration than those without PVT (pooled SMD = 2.505, 95%CI = 0.975–4.036). Notably, the D-dimer concentration at the 1st postoperative day was similar between cirrhotic patients with and without PVT (pooled SMD = 0.137, 95%CI = −0.827–1.101), but that at the 7th post-operative day was higher in cirrhotic patients with PVT than in those without PVT (pooled SMD = 1.224, 95%CI = 0.277–2.171). **Conclusion:** D-dimer might be regarded as a diagnostic marker for PVT in liver cirrhosis. In addition, postoperative D-dimer testing is worthwhile for the diagnosis of PVT after portal hypertension-related surgery.

Key Words: Diagnosis, etiology, predict, portal hypertension

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Portal vein thrombosis (PVT) is one of the severe complications of liver cirrhosis.[1-3] It is defined as the formation of a thrombus within the portal vein trunk and intrahepatic portal branches. The reported prevalence of PVT ranges from 0.6% to 26% in liver cirrhosis.[1-8] PVT deteriorates the liver dysfunction, increases the risk of bleeding, and influences the prognosis of patients with liver cirrhosis.[1-3] Development of PVT is associated with systemic prothrombotic factors and local risk factors.[9-11] Systemic risk factors include factor V Leiden mutation, G20210A prothrombin mutation, MTHFR C667T mutation, lupus anticoagulant, decreased level of proteins C and S and antithrombin III, and increased levels of factor VIII. Local factors include inflammatory lesions, pancreatitis, splenomegaly, a large splenic vein diameter, reduced portal flow velocity, and increased flow volume in the largest collateral vessel.[1-8] D-dimer level can reflect the fibrinolytic activity in humans, and is elevated in patients with deep vein thrombosis and pulmonary embolism due to the activation of fibrinolysis system. Recently, one study by Zhang *et al*. has also shown that D-dimer testing with a cutoff value of 0.24 mg/L has a high sensitivity of 100% and a negative predictive value of 100% in excluding a diagnosis of PVT.[12] But the specificity and predictive value are low (30.7% and 16.7%).[12] In addition, the association between D-dimer level and the presence of PVT was not supported by some studies.[13] Herein, we do a meta-analysis to detect the role of D-dimer in the development of PVT in liver cirrhosis.

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MATERIALS AND METHODS

Search strategy

Studies were identified using a search strategy in PubMed database, EMBASE database, China National Knowledge Infrastructure, Wan Fang, and VIP databases. Search items were listed as follows: ("D-dimer"[All Fields])

AND ("liver cirrhosis" [All Fields]) AND ("portal vein thrombosis" [All Fields]). The last search was performed on July 20, 2014. When the same data were reported in more than one publication, only the studies with more complete data and more extensive interval of enrolment were included in the meta-analysis.

Data extraction

A data extraction sheet included authors, publication year, country where the study was conducted, period of enrolment, study design, inclusion and exclusion criteria, type of diseases (liver cirrhosis or cirrhotic portal hypertension after surgery), total sample size, demographic data (age and gender), Child–Pugh Score or Class, and number of patients with and without PVT.

Inclusion criteria

- The participants of any age with diagnosis of liver cirrhosis
- All observational studies, including cohort and case–control studies, regardless of the retrospective or prospective nature of the study
- No publication date or publication status restrictions
- No language restrictions
- D-dimer levels were measured.

Exclusion criteria

- Case reports
- Animal studies
- Reviews or comments on the significance of liver cirrhosis
- Contents or indexes
- Patients with hepatocellular carcinoma or other malignancy, cholestatic liver diseases, Budd–Chiari syndrome, pancreatitis, preoperative had thrombosis, the use of anticoagulation or antiplatelet drugs, and recent abdominal trauma
- Noncomparative studies
- Studies which did not report the D-dimer levels
- Studies in which the data were not expressed as the mean value and standard deviation
- Duplicate studies.

Evaluation of study quality

The quality of included studies was evaluated according to the STROBE statement checklists (www.strobe-statement.org). It included 22 items to evaluate the title and abstracts, introduction, methods, results, discussion, and funding [Supplementary Table 1].

Data synthesis

The D-dimer levels were collected in cirrhotic patients with and without PVT. The difference of D-dimer levels between them was calculated as mean difference. A standardized mean difference (SMD) with 95% confidence interval (CI) was used to evaluate the association between D-dimer concentration and PVT in liver cirrhosis. A standardized value was employed, primarily because D-dimer level was measured by different units and methods in different studies. Then, the SMD of each study was combined to give a pooled SMD. An SMD >0 favored the effect of increased D-dimer concentration on PVT, and a $P < 0.05$ was considered statistically significant. Data were pooled using random-effect models. Heterogeneity between studies was assessed by using the I^2 statistic ($I^2 > 50\%$ was considered as having substantial heterogeneity) and the χ^2 test ($P < 0.10$ was considered to represent statistically significant heterogeneity). The Egger test was performed to evaluate the presence of publication bias for all pooled values with 95%CI. All analyses were conducted using Stats Direct statistical software version 2.7.8 (Stats Direct Ltd, Sale, Cheshire, UK).

RESULTS

Description of the included studies

A total of 284 studies were initially identified by the search strategy. Among them, 21 studies involving 602 cirrhotic patients with PVT and 1490 cirrhotic patients without PVT were eligible in the meta-analyses [Figure 1].[12-32] Baseline characteristics are summarized in Table 1 and D-dimer concentration is summarized in Table 2. The quality of the included studies are demonstrated in Supplementary Table 2.

Association between D-dimer concentrations and PVT in liver cirrhosis without surgery

D-dimer concentration between the PVT group and the non-PVT group was similar in three studies[13,19,25] and significantly different in 11 studies.[12,15-18,21,22,24,26,28,29] Additionally, the difference between the two groups was unclear in one study.[32] Using a random-effects model,

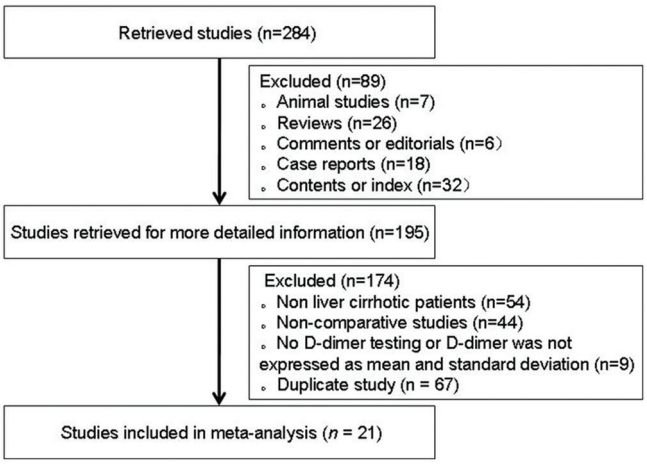

Figure 1: Study selection

Table 1: Study characteristics: An overview

Author (year)	Country	Enrollment period	Type of study	Study population	Patients (case/ control)	Age (case/ control)	Gender - male/ female (case/ control)	Age - and gender - matched	Child-Pugh score or class (case/control)	Child-Pugh score or class matched
Alkim (2012)	Turkey	NA	Retrospective	Liver cirrhosis	53 (10/13/17/13)[a]	(45.1±12.1) vs. (45.6±12.6) vs.(44.7±10.1) vs.(46.8±11.2)[a]	5/5 vs. 5/8 vs. 7/10 vs. 6/7[a]	Not different	NA	NA
Chen (2013)	China	2003.01-2009.12	Retrospective	Liver cirrhosis undergoing devascularization with splenectomy	166 (51/115)	(43.7±6.1) vs. (45.8±7.3)	38/13 vs. 84/31	Not different	Child-Pugh class A/B/C: 25/21/5 vs. 66/42/7	Not different
Fimognari (2005)	Italy	NA	Retrospective	Liver cirrhosis	136 (33/103)	(59.8±9.9) vs. (59.6±11.7)	21/12 vs. 66/37	Not different	Child-Pugh class A/B/C: 7/19/7 vs. 32/49/22	Not different
Guo (2010)	China	2005.01-2008.12	Retrospective	Liver cirrhosis	83 (39/44)	(52.21±10.46) vs. (50.17±11.58)	22/17 vs. 25/19	Not different	Child-Pugh class A/B/C: 8/10/21 vs. 8/11/25	Not different
Jia (2013)	China	2009.01-2011.12	Retrospective	Liver cirrhosis	128 (16/112)	NA	NA	Not different	NA	Not different
Jiang (2012)	China	2004-2010	Retrospective	Liver cirrhosis	77 (31/46)	NA	NA	NA	NA	NA
Kuang (2012)	China	2008.01-2010.07	Retrospective	Cirrhotic portal hypertension after operation	92 (40/52)	47.4 (10.7) vs. 49.4 (9.8)	24/16 vs. 32/20	Not different	Child-Pugh class A/B: 19/21 vs. 20/32	Not different
Li (2014)	China	2011.11-2013.03	Retrospective	Liver cirrhosis undergoing splenectomy and devascularization	47 (21/26)	NA	NA	NA	NA	NA
Shi (2011)	China	2008.10-2011.03	Retrospective	Liver cirrhosis undergoing devascularization with splenectomy	49 (15/34)	NA	NA	NA	NA	NA
Tian (2012)	China	2006.05-2007.11	Retrospective	Liver cirrhosis	137 (37/100)	(57.7±11.0) vs. (55.9±11.9)	28/9 vs. 78/22	Not different	Child-Pugh class A/B/C: 7/16/14 vs. 19/43/38	Not different
Wang (2010)	China	2006.08-2008.08	Retrospective	Liver cirrhosis	82 (27/55)	NA	18/39 vs. 9/16	Not different	Child-Pugh class A/B/C: 6/16/5 vs. 10/43/2	Not different
Wang (2013)	China	2010.01-2012.12	Retrospective	Liver cirrhosis	82 (17/65)	NA	NA	NA	NA	NA

Contd...

Table 1: Contd...

Author (year)	Country	Enrollment period	Type of study	Study population	Patients (case/control)	Age (case/control)	Gender - male/female (case/control)	Age - and gender - matched	Child-Pugh score or class (case/control)	Child-Pugh score or class matched
Wu (2012)	China	2011.01-2011.12	Retrospective	Liver cirrhosis	40 (7/33)	NA	NA	NA	NA	NA
Yang (2009)	China	2006.05-2008.06	Retrospective	Liver cirrhosis	87 (26/61)	(59.12±11.39) vs. (59.25±11.76)	18/8 vs. 39/22	Not different	Child-Pugh class A/B/C: 3/15/8 vs. 13/26/22	Not different
Yang (2010)	China	2004.01-2009.11	Retrospective	Liver cirrhosis undergoing devascularization with splenectomy	64 (27/37)	(44±11) vs. (46±12)	19/8 vs. 26/11	Not different	Child-Pugh class A/B: 19/8 vs. 26/11	Not different
Zhang (2013)	China	2008.01-2011.01	Retrospective	Liver cirrhosis	188 (51/137)	(58.0±10.5) vs. (57.3±12.4)	39/12 vs. 103/34	Not different	Child-Pugh class A/B/C: 7/26/18 vs. 25/63/49	Not different
Zhang (2014)	China	2009.01-2011.12	Retrospective	Liver cirrhosis	294 (55/239)	(52.3±10.8) vs. (54.4±12.0)	39/16 vs. 178/61	Not different	Child-Pugh score: (11.73±2.01) vs. (8.18±3.05)	Different
Zheng (2010)	China	2007-2008	Retrospective	Liver cirrhosis	80 (19/61)	(56.2±5.6) vs. (58.1±9.6)	12/7 vs. 45/16	Not different	Child-Pugh score: (9.2±2.6) vs. (9.8±2.5)	Not different
Zhou (2008)	China	2006.01-2007.12	Retrospective	Liver cirrhosis undergoing devascularization with splenectomy	37 (18/19)	(48.9±7.4) vs. (48.5±7.8)	15/3 vs. 16/3	Not different	Child-Pugh class A/B/C: 7/8/3 vs. 3/14/2	Not different
Zhou (2013)	China	2011.09-2012.09	Retrospective	Liver cirrhosis undergoing devascularization with splenectomy	77 (30/47)	(47±8) vs. (46±11)	22/8 vs. 32/15	Not different	Child-Pugh score: (6.57±0.89) vs. (5.94±0.98)	Different
Zocco (2009)	Italy	NA	Retrospective	Liver cirrhosis	73 (12/61)	55.2 (10.9) vs. 59.2 (11.3)	10 (83.3%) vs. 44 (72.1%)	Not different	NA	NA

[a]Case vs. Child-Pugh Class A vs. Child-Pugh Class B vs. Child-Pugh Class C

a meta-analysis demonstrated that the pooled SMD was significant (1.249, 95%CI = 0.740–1.758, $P < 0.0001$), suggesting a higher D-dimer concentration in cirrhotic patients with PVT than in those without PVT [Figure 2]. The heterogeneity among studies was significant ($I^2 = 93.6\%$, $P < 0.0001$). Egger test implied no proof of publication bias ($P = 0.205$).

Association between preoperative D-dimer concentration and PVT after the surgery of cirrhotic portal hypertension

Preoperative D-dimer concentration between the PVT group and the non-PVT group was similar in all five studies.[14,20,23,30,31] Using a random-effects model, a meta-analysis demonstrated that the pooled SMD was not significant (0.820, 95%CI = −0.122–0.286, $P = 0.431$), showing that D-dimer concentration was similar between the PVT group and the non-PVT group [Figure 3]. The heterogeneity among studies was not significant ($I^2 = 0\%$, $P = 0.721$). Egger test implied no proof of publication bias ($P = 0.179$).

Association between postoperative D-dimer concentration and PVT after the surgery of cirrhotic portal hypertension

Postoperative D-dimer concentration between the PVT group and the non-PVT group was significantly different in all four studies.[14,23,27,30] Using a random-effects model, a meta-analysis demonstrated that the pooled SMD was significant (2.505, 95%CI = 0.975–4.036, $P = 0.0013$), showing that D-dimer concentration was significantly higher in the PVT group than in the non-PVT group [Figure 4]. The heterogeneity among studies was significant ($I^2 = 96\%$, $P < 0.0001$). Egger test implied no proof of publication bias ($P = 0.153$).

Association between 1st postoperative D-dimer concentration and PVT after the surgery of cirrhotic portal hypertension

First postoperative D-dimer concentration between the PVT group and the non-PVT group was similar in one study[20] and significantly different in the other study.[31] Using a random-effects model, a meta-analysis demonstrated that the pooled SMD was not significant (0.137, 95%CI = −0.827–1.101, $P = 0.781$), showing that D-dimer concentration was similar between the PVT group and the non-PVT group [Figure 5]. The heterogeneity among studies was significant ($P = 0.0096$). Egger test could not evaluate the publication bias.

Association between 7th postoperative D-dimer concentration and PVT after the surgery of cirrhotic portal hypertension

Seventh postoperative D-dimer concentration between the PVT group and the non-PVT group was significantly different in the two studies.[20,31] Using a random-effects model, a meta-analysis demonstrated that the pooled SMD was significant (1.224, 95%CI = 0.277–2.171, $P = 0.0113$), suggesting a higher D-dimer concentration in cirrhotic patients with PVT than in those without PVT [Figure 6]. The heterogeneity among studies was significant ($P = 0.0212$). Egger test could not evaluate the publication bias.

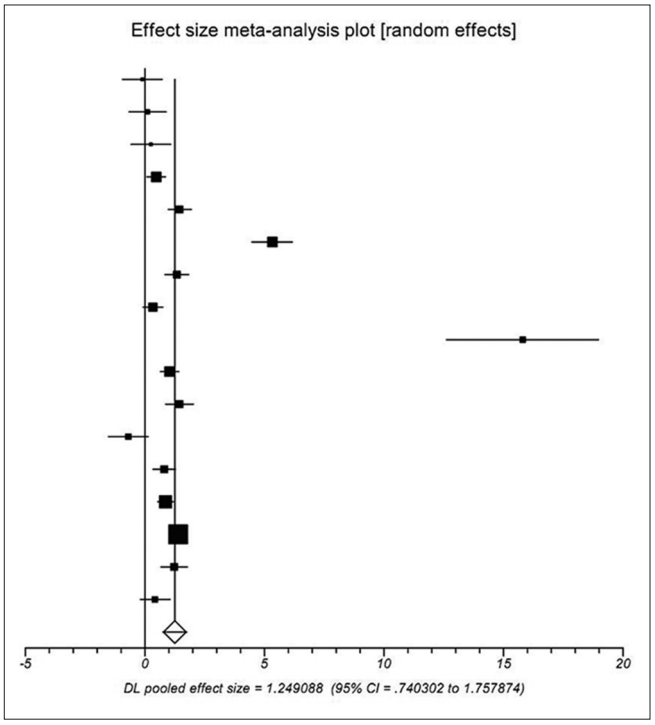

Figure 2: Meta-analysis regarding D-dimer concentration on portal vein thrombosis in liver cirrhosis without surgery

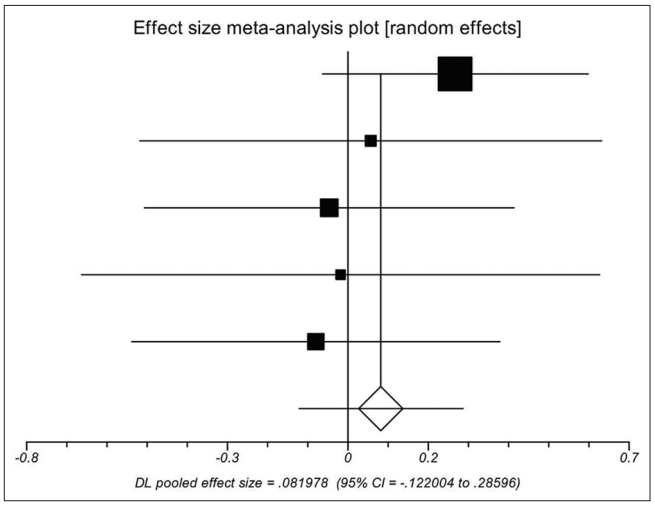

Figure 3: Meta-analysis regarding preoperative D-dimer concentration on portal vein thrombosis after the surgery of cirrhotic portal hypertension

Table 2: Comparison of D-dimer concentration between cirrhotic patients with and without PVT: An overview

First author (year)	No. of cases with PVT	D-dimer in case group (mean)	D-dimer in case group (SD)	Units	No. of controls without PVT	D-dimer in control group (mean)	D-dimer in control group (SD)	Units	Statistically significant difference between case and control groups
Alkim (2012) child A	10	254	71	µg/L	13	262	68	µg/L	NA
Alkim (2012) child B	10	254	71	µg/L	17	246	78	µg/L	NA
Alkim (2012) child C	10	254	71	µg/L	13	238	56	µg/L	NA
Fimognari (2005)	33	1.23	1.87	µg/ml	103	0.68	0.82	µg/ml	Yes
Guo (2010)	39	2.17	1.08	mg/L	44	0.97	0.48	mg/L	Yes
Jia (2013)	16	0.96	0.14	mg/L	112	0.35	0.11	mg/L	Yes
Jiang (2012)	31	1.2	0.5	mg/L	46	0.6	0.4	mg/L	Yes
Kuang (2012)	40	0.85	1.2	µg/mL	52	0.57	0.35	µg/ml	No
Shi (2011)	15	0.48	0.02	mg/L	34	0.04	0.03	mg/L	Yes
Tian (2012)	37	1.15	0.61	mg/L	100	0.63	0.46	mg/L	Yes
Wang (2013)	17	1.29	0.41	mg/L	65	0.76	0.35	mg/L	Yes
Wu (2012)	7	0.222	0.094	g/L	33	0.309	0.127	g/L	No
Yang (2009)	26	0.97	0.53	mg/L	61	0.61	0.4	mg/L	Yes
Zhang (2013)	51	1.13	0.65	mg/L	137	0.66	0.49	mg/L	Yes
Zhang (2014)	55	1	0.22	mg/L	239	0.77	0.15	mg/L	Yes
Zheng (2010)	19	1.1	0.4	mg/L	61	0.7	0.3	mg/L	Yes
Zocco (2009)	12	1660	2405	ng/mL	61	1038	1209	ng/mL	No
Chen (2013) preoperative value	51	0.13	0.05	mg/L	115	0.12	0.03	mg/L	No
Li (2014) preoperative value	21	1.01	0.82	mg/L	26	0.97	0.56	mg/L	No
Wang (2010) preoperative value	27	322.59	91.19	µg/L	55	327.09	97.85	µg/L	No
Zhou (2008) preoperative value	18	333.9	269.1	µg/L	19	338.6	241.6	µg/L	No
Zhou (2013) preoperative value	30	0.196	0.127	mg/L	47	0.211	0.216	mg/L	No
Chen (2013) postoperative day value	51	4.96	3.27	mg/L	115	2.76	1.28	mg/L	Yes
Wang (2010) postoperative day value	27	869.67	123.09	µg/L	55	297.2	89.49	µg/L	Yes
Yang (2010) postoperative day value	27	1984	899	µg/L	37	817	258	µg/L	Yes
Zhou (2008) postoperative day value	18	2304.8	1617.5	µg/L	19	306.6	160.2	µg/L	Yes
Li (2014) 1st postoperative day value	21	3.57	3.68	mg/L	26	4.73	2.49	mg/L	No
Zhou (2013) 1st postoperative day value	30	1.261	1.168	mg/L	47	0.758	0.462	mg/L	Yes
Li (2014) 7th postoperative day value	21	18.12	4.93	mg/L	26	11.24	2.79	mg/L	Yes
Zhou (2013) 7th postoperative day value	30	1.769	1.084	mg/L	47	1.128	0.604	mg/L	Yes
Li (2014) 14th postoperative day value	21	27.18	7.24	mg/L	26	16.32	1.45	mg/L	Yes

PVT: Portal vein thrombosis

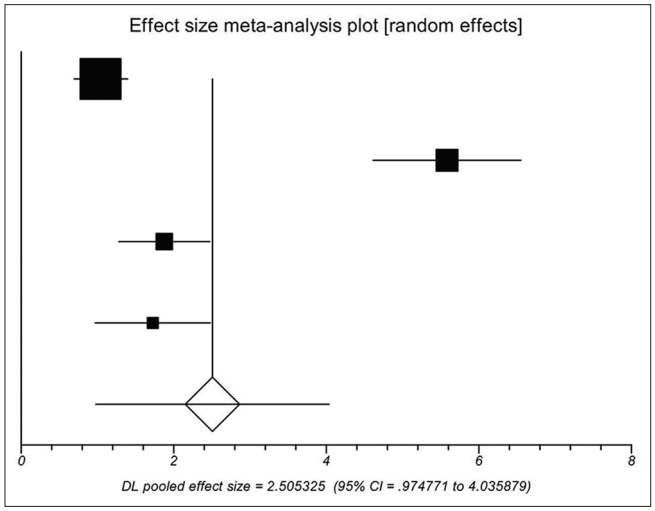

Figure 4: Meta-analysis regarding postoperative D-dimer concentration on portal vein thrombosis after the surgery of cirrhotic portal hypertension

DISCUSSION

D-dimer is produced during the fibrinolysis. D-dimer testing is cheap and readily available, and importantly, it has a high negative predictive value and sensitivity for deep vein thrombosis and pulmonary embolism.[33] At present, it has been widely used for the diagnostic workup of suspected venous thromboembolism in clinical practice. Evidence suggests that a negative D-dimer in the combination with clinical probability tools can effectively rule out the diagnosis of deep vein thrombosis and pulmonary embolism, which reduce the need for ultrasound testing.[34,35] However, the role of D-dimer in the diagnosis of PVT in liver cirrhosis remained unclear. The present study for the first time systematically reviewed the currently available data to clarify the issue. The most important finding was that an increased D-dimer concentration was associated with a higher risk of PVT in liver cirrhosis in the absence of surgery, which potentially

Supplementary Table 1: Study quality STROBE checklists

Item	Item no	Recommendations
Title and abstract	1 (a)	Indicate the study's design with a commonly used term in the title or the abstract
Title and abstract	1 (b)	Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction-background/ rationale	2	Explain the scientific background and rationale for the investigation being reported
Introduction-objectives	3	State specific objectives, including any prespecified hypotheses
Methods-study design	4	Present key elements of study design early in the paper
Methods-setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Methods-participants	6 (a)	Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
Methods-participants	6 (b)	For matched studies, give matching criteria and the number of controls per case
Methods-Variables	7	Clearly define all outcomes, exposures,predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Methods-data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Methods-bias	9	Describe any efforts to address potential sources of bias
Methods-study size	10	Explain how the study size was arrived at
Methods-quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Methods-statistical methods	12 (a)	Describe all statistical methods, including those used to control for confounding
Methods-statistical methods	12 (b)	Describe any methods used to examine subgroups and interactions
Methods-statistical methods	12 (c)	Explain how missing data were addressed
Methods-statistical methods	12 (d)	If applicable, explain how matching of cases and controls was addressed
Methods-statistical methods	12 (e)	Describe any sensitivity analyses
Results-participants	13 (a)	Report numbers of individuals at each stage of study-eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
Results-participants	13 (b)	Give reasons for non-participation at each stage
Results-participants	13 (c)	Consider use of a flow diagram
Results-descriptive data	14 (a)	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
Results-descriptive data	14 (b)	Indicate number of participants with missing data for each variable of interest
Results-outcome data	15	Report numbers in each exposure category, or summary measures of exposure
Results-main results	16 (a)	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
Results-main results	16 (b)	Report category boundaries when continuous variables were categorized
Results-main results	16 (c)	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Results-other analyses	17	Report other analyses done-eg analyses of subgroups and interactions, and sensitivity analyses
Discussion-key results	18	Summarise key results with reference to study objectives
Discussion-limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Discussion-interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Discussion-generalisability	21	Discuss the generalisability (external validity) of the study results
Other information-funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

suggested that D-dimer should be a diagnostic marker for PVT in cirrhotic patients. However, the accurate cutoffs of D-dimer for predicting the development of PVT were largely lacking. In one included study, Zhang *et al*. calculated the area under curve (AUC) of D-dimer for the diagnosis of PVT.[28] They found that D-dimer had the largest AUC of

Supplementary Table 2: Results of study quality

Item no	Alkim (2012)	Chen (2013)	Fimognari (2005)	Guo (2010)	Jia (2013)	Jiang (2012)	Kuang (2012)	Li (2014)	Shi (2011)	Tian (2012)	Wang (2010)	Wang (2013)	Wu (2012)	Yang (2009)	Yang (2010)	Zhang (2013)	Zhang (2014)	Zheng (2010)	Zhou (2008)	Zhou (2013)	Zocco (2009)
1 (a)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1 (b)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6 (a)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
6 (b)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
7	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
8	Yes	Yes	Yes	Yes	Yes	NA	Yes	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes
10	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12 (a)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12 (b)	No	Yes	No	Yes	No	No	Yes	Yes	No	Yes	No	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes
12 (c)	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
12 (d)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12 (e)	No	Yes	Yes	Yes	No	No	Yes	No	No	Yes	No	Yes	No	Yes	No	No	No	No	No	No	No
13 (a)	No	No	No	No	No	No	No	Yes	Yes	No	No	No	Yes	No	No	No	No	No	No	No	Yes
13 (b)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
13 (c)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14 (a)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14 (b)	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
15	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
16 (a)	No	Yes	No	No	No	No	Yes	Yes	No	Yes	No	No	No	No	Yes	No	No	Yes	No	Yes	Yes
16 (b)	No	Yes	Yes	No	No	No	Yes	Yes	No	No	No	No	Yes	No	No	Yes	Yes	No	No	No	Yes
16 (c)	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
17	No	Yes	No	Yes	Yes	No	Yes	No	No	Yes	No	Yes	No	Yes	No	No	Yes	No	No	Yes	No
18	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
20	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
21	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
22	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No

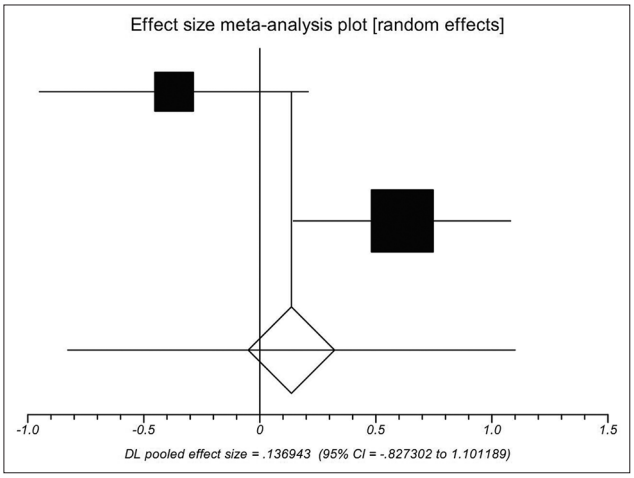

Figure 5: Meta-analysis regarding 1st postoperative D-dimer concentration on portal vein thrombosis after the surgery of cirrhotic portal hypertension

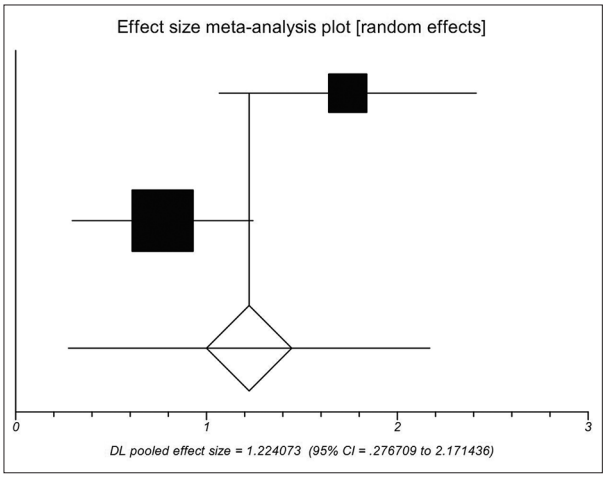

Figure 6: Meta-analysis regarding 7th postoperative D-dimer concentration on portal vein thrombosis after the surgery of cirrhotic portal hypertension

0.868, followed by Child–Pugh Score of 0.823, diameter of main portal vein of 0.810, and portal vein velocity of 0.756. Another included study also demonstrated that the AUC of D-dimer was 0.782 for the diagnosis of PVT in all cirrhotic patients, and the cutoff value was 0.52 mg/dL.[36] The subgroup analyses according to the Child–Pugh class further demonstrated that the AUC of D-dimer was 0.963, 0.75, and 0.698 in Child–Pugh class A, B, and C patients, respectively. The cutoff value was heterogeneous, such as 0.52, 0.56, 1.12 mg/dL in Child–Pugh Class A, B, and C patients, respectively.

Considering a high risk of PVT in cirrhotic patients undergoing the portal hypertension-related surgery, we analyzed the association between D-dimer concentration and PVT in such patients. Ideally, D-dimer should have an early predictive probability of developing PVT. However, we found that the postoperative value of D-dimer, but not preoperative value of D-dimer, could predict the development of PVT after surgery. In addition, the 7th postoperative value of D-dimer, but not 1st postoperative value of D-dimer, was associated with the development of PVT after surgery. Because PVT developed within the 7th postoperative days, these unexpected findings might suggest that the change in the D-dimer concentrations was accompanied by the occurrence of PVT after surgery; however, a simple D-dimer test could not provide any possibilities of early prediction of PVT.

The study had several limitations as follows. First, we could only establish the association between D-dimer and the development of PVT in liver cirrhosis. However, we did not identify the negative predictive value of D-dimer in ruling out PVT. Second, a clinical probability tool could further stratify the risk for the assessment of venous thromboembolism and pulmonary embolism, thereby increasing the negative predictive value of D-dimer tests.[34,37] However, no clinical probability tools were established for the risk of the assessment of PVT. Third, only a few studies explored the association between D-dimer and PVT after portal hypertension-related surgery, especially the 1st and 7th postoperative value of D-dimer. Thus, the conclusions needed to be confirmed. Fourth, a majority of the reviewed studies were of poor quality, which potentially influenced the reliability of these findings.

In conclusion, D-dimer might be regarded as a diagnostic marker of PVT in liver cirrhosis, but further work should identify the accurate cutoff value of D-dimer for excluding the diagnosis of PVT. In addition, postoperative D-dimer testing is worthwhile for the diagnosis of PVT after portal hypertension-related surgery in liver cirrhosis, but the timing of D-dimer testing after surgery should be further explored.

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