

# Evaluation of plasma D-dimer for the diagnosis in Chinese patients with hepatocellular carcinoma

## A meta-analysis

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### Abstract

**Background:** To evaluate the value of plasma D-dimer levels for the diagnosis of hepatocellular carcinoma (HCC).

**Methods:** The following databases were searched for relevant studies published from 1990 to 2018: Wanfang Data, SinoMed, VIP Chinese Science and Technology Periodicals Database, China National Knowledge Infrastructure, Superstar Journals Database, Cochrane library, and PubMed. The studies were selected according to the diagnosis of HCC by plasma D-dimer levels. Quality assessment of the diagnostic accuracy of the studied items was conducted for rigorous quality evaluation of the studies that met the inclusion criteria. After extracting the relevant data, Stata 15.0 software was adopted for the analysis of the diagnostic odds ratio (DOR), sensitivity, specificity, and positive and negative likelihood ratios. A summary receiver operating characteristic (SROC) curve was constructed to comprehensively evaluate the value of plasma D-dimer levels for the diagnosis of HCC.

**Results:** A total of 6 studies conducted in China with 475 cases in the patient groups and 727 in the control groups were included. The confidence level was expressed as the 95% confidence interval (CI). The pooled sensitivity, specificity, positive and negative likelihood ratios, and DOR of plasma D-dimer levels for the diagnosis of HCC were 0.75 (95% CI=0.66–0.82), 0.93 (95% CI=0.86–0.97), 11.4 (95% CI=5.3–24.5), 0.27 (95% CI=0.20–0.36), and 42 (95% CI=19–93), respectively. The area under the SROC curve was 0.88 (95% CI=0.85–0.91).

**Conclusions:** Plasma D-dimer has high sensitivity and specificity, and is expected to be an important plasma marker for the clinical diagnosis of HCC. Due to the limited quality and quantity of the included studies, the above results should be further validated.

**Abbreviations:** AFP = alpha-fetoprotein, AUC = area under the SROC curve, CI = confidence interval, DOR = diagnostic odds ratio, FN = false negative, FP = false positive, HCC = hepatocellular carcinoma, NLR = negative likelihood ratio, PLR = positive likelihood ratio, QUADAS = quality assessment of diagnostic accuracy studies, SROC = summary receiver operating characteristic, TN = true negative, TP = true positive.

**Keywords:** diagnosis, hepatocellular carcinoma, meta-analysis, plasma D-dimer

## 1. Introduction

Thrombosis is a common complication of malignant tumors. A prethrombotic state refers to an increased risk of thrombosis in

vivo. Almost all coagulation factors, various anticoagulants, plasmin, and plasmin inhibitors are synthesized in the liver, and the liver is also the main inactivated organ of many factors mentioned above.<sup>[1]</sup> Therefore, complex hemostatic dysfunction can occur in patients with severe or advanced liver disease, which is characterized by a hyper-fibrinolytic state that contributes to an increased incidence of bleeding. Primary liver cancers are the most common malignant tumors that originate from hepatocytes and epithelial cells that line the intrahepatic bile duct. Hepatocellular carcinoma (HCC) accounts for >80% of primary liver cancers and is characterized by invasion, metastasis, poor prognosis, and high recurrence and mortality rates. HCC has an insidious onset with a low early diagnosis rate and a 5-year survival rate of <7%.<sup>[2]</sup> HCC is a commonest malignancy with the third highest cancer-related mortality rate in China. The incidence of HCC continues to increase annually and is usually diagnosed in the late and advanced stages.<sup>[3]</sup> Since, there is presently no effective therapy for HCC, it is very important to identify changes to the expression levels of biomarkers in the prethrombotic state, as effective indicators to predict the occurrence and development of thrombosis, and to implement early drug intervention to prevent thrombotic complications in high-risk patients in order to prolong life and reduce mortality. The monitoring of candidate biomarkers is an effective method for early diagnosis, prediction of recurrence and prognosis, and treatment selection for HCC. Although widely used a biomarker of HCC, the sensitivity of plasma alpha-fetoprotein (AFP) is insufficient for clinical needs.<sup>[4]</sup> Therefore, there is an urgent need

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for the discovery of novel biomarkers with high diagnostic accuracy.

The plasma concentration of D-dimer is a specific biomarker produced by the degradation of cross-linked fibrin by fibrinolytic enzymes, which reflects the high coagulation and enhancement of secondary fibrinolytic activity *in vivo*. The activation of coagulation and fibrinolysis have important direct interactions with malignancies and is related to angiogenesis, cell invasion, disease progression, and prognosis.<sup>[5]</sup> Elevated plasma D-dimer levels in patients with malignant tumors to reflect hemostatic and fibrinolytic activities may help to tailor the management of thromboprophylaxis for cancer patients.<sup>[6]</sup> It has been reported that high plasma D-dimer concentrations in patients without ascites are closely associated with HCC and high levels in patients with liver cirrhosis require more careful monitoring for HCC.<sup>[7]</sup> Thus, the role of plasma D-dimer has been widely investigated for the early diagnosis and prognosis of HCC.<sup>[8]</sup> Plasma levels of D-dimer are significantly elevated in Chinese patients with HCC, as compared to those with benign liver diseases.<sup>[9–14]</sup> However, the diagnostic sensitivity and specificity of plasma D-dimer have not yet been fully evaluated. Therefore, the aim of the present meta-analysis was to determine the value of plasma D-dimer for the clinical diagnosis of HCC.

## 2. Materials and methods

### 2.1. Retrieval strategy and study selection

Relevant peer-reviewed articles published from 1990 to 2018 were retrieved from the following databases: Wanfang Data, SinoMed, VIP Chinese Science and Technology Periodicals Database, China National Knowledge Infrastructure, Superstar Journals Database, Cochrane library, and PubMed with the keywords “D-dimer,” “D2,” “D-D,” “hepatocellular carcinoma,” “HCC,” “liver cancer,” “liver tumor,” “liver cell carcinoma,” and “hepatic cell carcinoma.”

### 2.2. Criteria for inclusion and exclusion of published studies

The inclusion criteria for articles were as follows:

- (1) type of research: studies that investigated the diagnostic accuracy of plasma D-dimer for HCC published in China and abroad;
- (2) participants of research: all patients in the study group were diagnosed with HCC by histopathology or imaging with a control group consisting of non-HCC patients and those with benign liver diseases, while those with metastatic liver cancer or recurrence after treatment were excluded;
- (3) requirements of data: the complete original 4-grid data of true positive (TP), false positive (FP), false negative (FN), and true negative (TN) cases that can be obtained directly or converted into 4-grid data after calculation; and
- (4) laboratory parameters: plasma concentrations of D-dimer. The gold standard for diagnosis is clinical histopathology or imaging examination.

The exclusion criteria were as follows:

- (1) not confirmed by the gold standard;
- (2) combined with other malignant tumors;
- (3) incomplete data or lack of controls with benign liver disease;
- (4) animal experiments;

- (5) reviews, patents, reports, and conference papers without original clinical data; and
- (6) duplicate studies.

### 2.3. Screening of eligible studies and data extraction

One author (Ping Fang) preliminarily screened the titles and abstracts of the eligible studies. Based on the inclusion and exclusion criteria described above, 2 authors (Ping Fang and Lijun Du) independently re-screened the eligible studies. Discrepancies were solved through discussion with a third author (Decheng Cai). After confirming the eligibility of the retrieved studies, the following basic characteristics were extracted: the first author, year of publication, geographic distribution of patients, cut-off values, number of cases in the control and experimental groups, sensitivity, specificity, and raw data, including the TP, FP, TN, and FN results. Because this meta-analysis was based on previous published studies, ethical approval and patient consent were not required.

### 2.4. Risk of bias and quality assessment of the included studies

The Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2, Cochrane Collaboration) was used to evaluate the risk of bias of the eligible studies.<sup>[15]</sup> The risk of bias included patient selection, index test, reference standard, and the flow and timing. Applicability included patient selection, index test, and the reference standard. Each of the included studies was evaluated according to the 14 items in the QUADAS-2 checklist. Each item was scored as “Yes (Y, low risk or good adaptability),” “Unclear (U, unclear or lack of relevant information),” or “No (N, high risk or poor adaptability).” The risk of bias among the included studies was independently evaluated by 2 authors (Ping Fang and LiJun Du). Differences in the opinions regarding the risk of bias and quality assessment were resolved by discussion with a third author (DeCheng Cai).

### 2.5. Statistical analysis

The meta-analysis was performed using STATA version 15.0 statistical software (StataCorp LLC, College Station, TX). For each included study, the pooled sensitivity, pooled specificity, pooled positive likelihood ratio (PLR), pooled negative likelihood ratio (NLR), pooled diagnostic odds ratio (DOR), and 95% confidence intervals (CIs) were calculated. The results are presented as forest plots and summary receiver operating characteristic curves (SROCs). In the meta-analysis of diagnostic accuracy studies, threshold effects are usually caused by cut-off values and are one of the main sources of heterogeneity. If the selected cut-off values in the original diagnostic accuracy studies were the optimal results based on sensitivity and/or specificity, the accuracy were likely to be overestimated. Therefore, the cut-off values were recommended to be set before the implementation of diagnostic accuracy studies. Heterogeneity analysis of the data extracted from the eligible studies was evaluated using the Chi-square ( $\chi^2$ ) test and the test statistic ( $I^2$ ) values of the DOR with a cut-off value of 10% for significance ( $P < .10$ ).<sup>[16]</sup> An  $I^2$  value of  $\geq 50\%$  was considered to represent substantial heterogeneity. If heterogeneity existed across the studies ( $I^2 > 25\%$ ), a random effects model was applied; otherwise, a fixed effect model was used.<sup>[17,18]</sup> With a statistical significance level at  $P < .05$ , Deeks'

funnel plot asymmetry test was applied to assess publication bias.<sup>[19]</sup>

### 3. Results

#### 3.1. Screening of the retrieved studies

A total of 454 studies were identified through preliminary screening. According to the inclusion and exclusion criteria, 6 studies<sup>[9-14]</sup> were considered suitable for inclusion in the meta-analysis. All of the included studies were published in Chinese. One English language study was retrieved, but later excluded, as none of the patients in the control group had benign liver disease.<sup>[8]</sup> The screening process and results are shown in Figure 1.

#### 3.2. Main characteristics of the included studies

As shown in Table 1, among the 6 studies that were eventually included for the meta-analysis, there were 475 patients with HCC and 727 controls.

#### 3.3. Quality assessment of the included studies

According to the quality evaluation system of QUADAS-2 for diagnostic studies established by Whiting et al,<sup>[15]</sup> the results of the quality assessment on the items in the QUADAS-2 checklist for each study are presented in Table 2. An overall risk of bias rating for each domain of QUADAS-2 are presented in Table 3.

#### 3.4. Analysis of publication bias

The Deeks' funnel plot asymmetry test was used to assess the publication bias of the studies included in the meta-analysis. As shown in Figure 2, the *P*-value was .09 (>.05), which indicated that there was no significant publication bias among the 6 included studies.

#### 3.5. Analysis of heterogeneity

In the meta-analysis of diagnostic research, heterogeneity is mainly generated from both threshold and non-threshold effects.

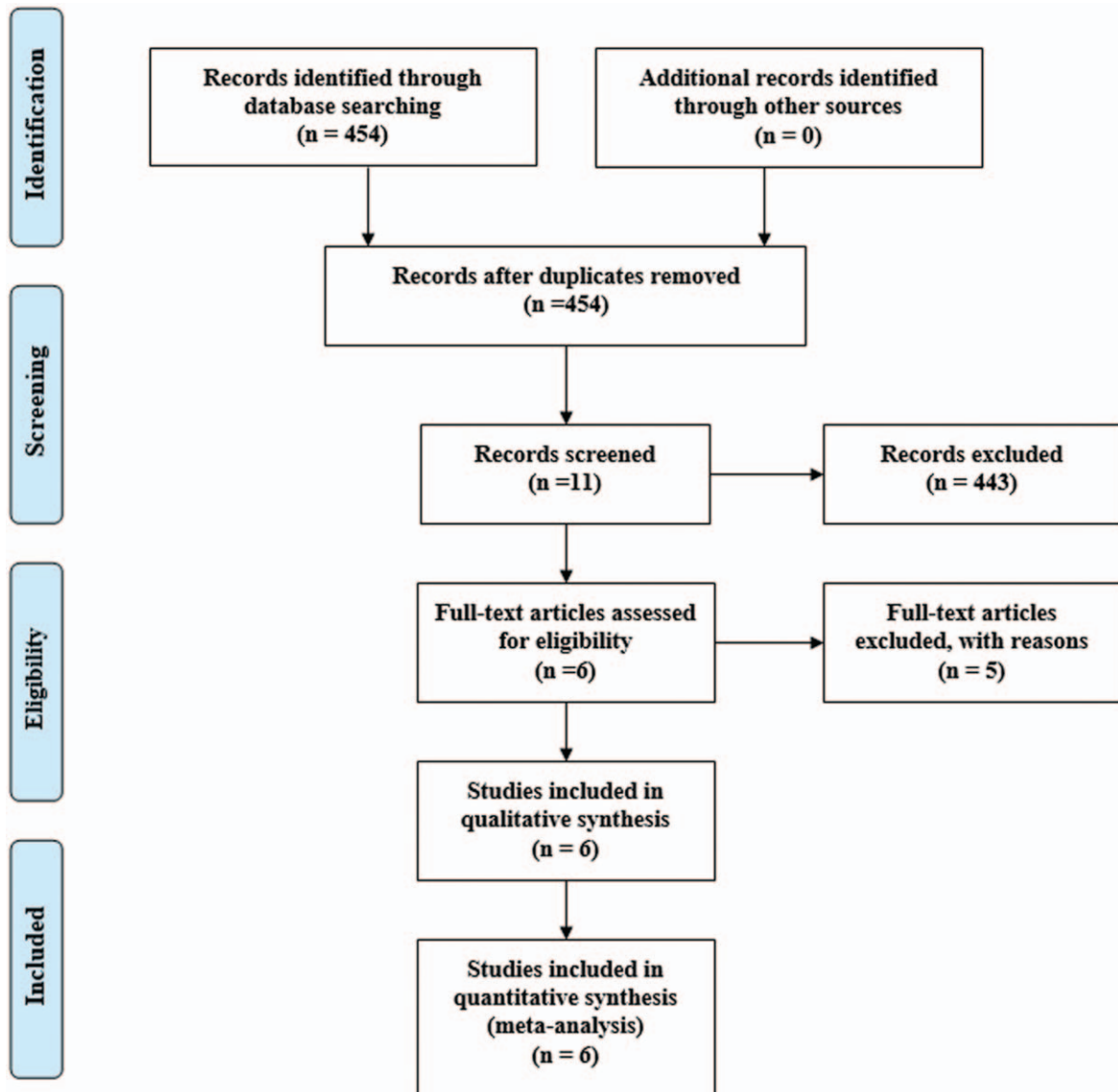


Figure 1. The flow chart of the literature selection.

**Table 1****Main characteristics of the included studies in the meta-analysis.**

Study	Country	Year	Sample number (case/control)	Cut-off value (ng/mL)	Sensitivity	Specificity	TP	FP	FN	TN
Haoyu Chen et al <sup>[9]</sup>	China	2013	50/60	1451	0.700	0.829	35	10	15	50
Qingchuan Ma <sup>[10]</sup>	China	2015	67/133	25	0.703	0.834	47	22	20	111
Yajing Yang et al <sup>[11]</sup>	China	2016	92/129	230	0.848	0.917	78	11	14	118
Li Xu <sup>[12]</sup>	China	2018	78/126	230	0.841	0.915	66	11	12	115
Yicheng Huang <sup>[13]</sup>	China	2018	68/149	550	0.750	0.971	51	4	17	145
Mingheng Liang et al <sup>[14]</sup>	China	2018	120/130	800	0.583	0.992	70	1	50	129

Sensitivity, the proportion of participants correctly classified as having hepatocellular carcinoma in all cases, Specificity, the proportion of participants correctly classified as not having hepatocellular carcinoma in all controls.

TN = true negative, participants correctly classified as not having hepatocellular carcinoma, TP = true positive, participants correctly classified as having hepatocellular carcinoma, FP = false positive, participants incorrectly classified as having hepatocellular carcinoma, FN = false negative, participants incorrectly classified as not having hepatocellular carcinoma.

**Table 2****Quality assessment of the included studies on the items in the QUADAS-2 checklist for each study.**

Risk of bias	[9]	[10]	[11]	[12]	[13]	[14]
Patient selection						
Continuous or random cases included?	N	N	N	N	N	N
Case-control design avoided?	Y	Y	Y	Y	Y	Y
Inappropriate exclusions avoided?	Y	Y	Y	Y	Y	Y
Index test						
Index test results blinded?	Y	Y	Y	Y	Y	Y
Threshold preset?	N	Y	Y	Y	Y	Y
Reference standard						
The target disease distinguished?	Y	Y	Y	Y	Y	Y
Reference standard results blinded?	Y	Y	Y	Y	Y	Y
Flow and timing						
Acceptable delay between tests?	Y	Y	Y	Y	Y	Y
The reference standard test received?	Y	Y	Y	Y	Y	Y
The same reference standard test received?	Y	Y	Y	Y	Y	Y
All subjects in the analysis included?	Y	Y	Y	Y	Y	Y
Applicability concerns						
Patient selection	Y	Y	Y	Y	Y	Y
Index test	Y	Y	Y	Y	Y	Y
Reference standard	Y	Y	Y	Y	Y	Y

Y = yes, N = no, U = unclear.

**Table 3****Quality assessment of the included studies on the main domains of QUADAS-2 for each study.**

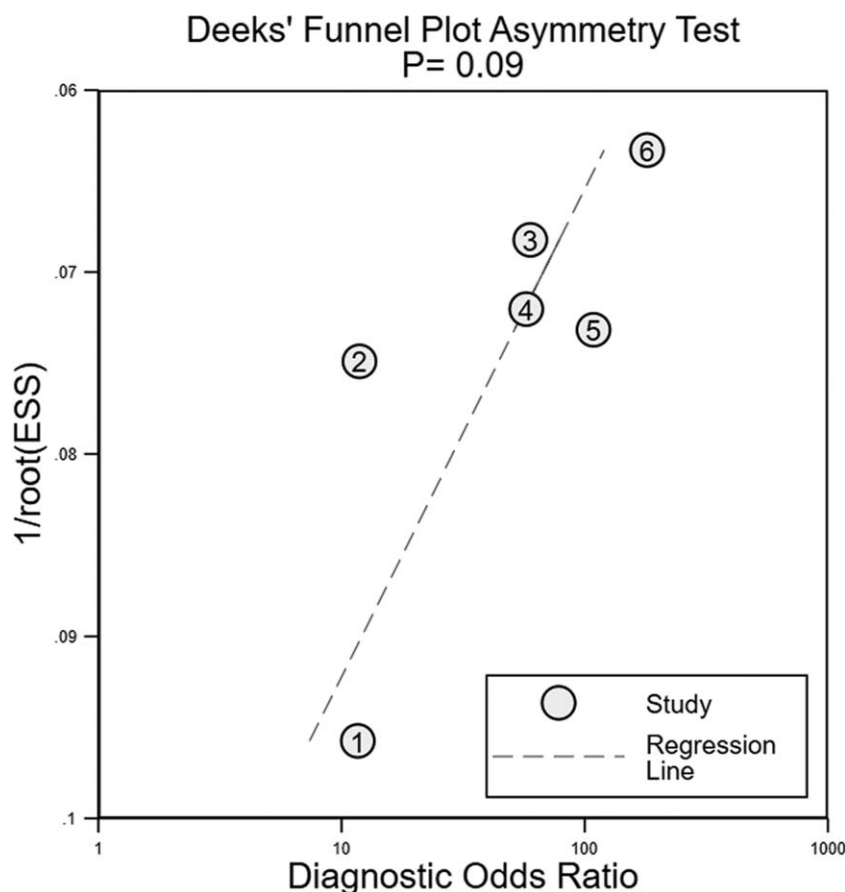
Study	Risk of bias				Applicability Concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Haoyu Chen et al <sup>[9]</sup>	High	High	Low	Low	Low	Low	Low
Qingchuan Ma <sup>[10]</sup>	High	Low	Low	Low	Low	Low	Low
Yajing Yang et al <sup>[11]</sup>	High	Low	Low	Low	Low	Low	Low
Li Xu <sup>[12]</sup>	High	Low	Low	Low	Low	Low	Low
Yicheng Huang <sup>[13]</sup>	High	Low	Low	Low	Low	Low	Low
Mingheng Liang et al <sup>[14]</sup>	High	Low	Low	Low	Low	Low	Low

Based on Table 2, rules for producing an overall risk of bias rating for each domain are as follows: (1) If all signaling questions within the domain are answered "Yes" then the risk of bias for this domain is rated "Low Risk;" (2) If at least 1 signaling question within the domain is answered "No" then the risk of bias for this domain is rated "High Risk;" (3) If at least 1 signaling question within the domain is answered "Unclear" while the remaining signaling questions are answered "Yes" then the risk of bias is rated "Unclear Risk."

Low = low risk, High = high risk, Unclear = unclear risk.

Threshold effects are usually caused by cut-off values, while non-threshold effects are caused by many factors, such as objects and experimental conditions. In this meta-analysis, the analysis of heterogeneity was conventionally interpreted as being significant at a *P*-value of 0.00. The *I*<sup>2</sup> values of inconsistency, sensitivity, and specificity were 92 (95% CI = 84–99), 80.61 (95% CI = 65.70–95.52), and 85.50 (95% CI = 75.15–95.85), respectively,

indicating substantial heterogeneity among the included studies. By analysis of the diagnostic threshold, the Spearman correlation coefficient between the logic of sensitivity and the logic of 1-specificity was 0.029 (*P* = .96), indicating that the heterogeneity among the included studies was not caused by a threshold effect. The proportion of heterogeneity likely due to threshold effects was 0.27.



**Figure 2.** Linear regression test of funnel plot asymmetry. Each study was plotted near the regression line, indicating symmetry of the data and no significant publication bias among the 6 included studies ( $P = .09$ ).

### 3.6. Results of meta-analysis

Based on the analysis of heterogeneity described above, a random effects model was applied. The pooled sensitivity, specificity, PLR, NLR, and DOR values were 0.75 (95% CI=0.66–0.82), 0.93 (95% CI=0.86–0.97), 11.4 (95% CI=5.3–24.5), 0.27 (95% CI=0.20–0.36), and 42 (95% CI=19–93), respectively. Forest plots of sensitivity, specificity, PLR, NLR, and DOR were shown in Supplemental Digital Content (Figs. S1–S3, <http://links.lww.com/MD/D915>). The area under the SROC curve (area under the SROC curve [AUC]=0.88; 95% CI=0.85–0.91) is presented in Figure 3.

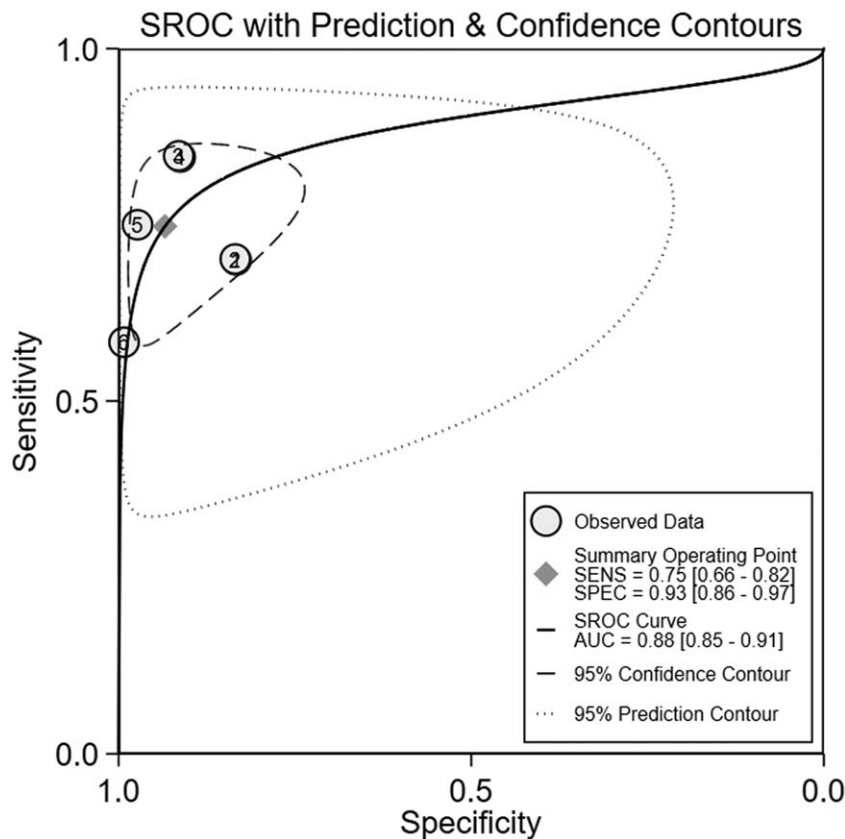
## 4. Discussion

HCC is a lethal malignancy with a survival rate of <10% and the incidence of histologically unconfirmed HCC has increased more rapidly than that of confirmed HCC worldwide.<sup>[20]</sup> At present, the diagnosis of HCC mainly relies on imaging studies and hematological, hepatocyte biopsy, and/or cytological examinations. HCC with small lesions is often misdiagnosed by imaging studies. Hepatocyte biopsy and cytological examinations are accurate and reliable, but rather invasive, thus these examinations are not used for screening of HCC in the early stage, which is likely to cause a delay of the diagnosis. In contrast, hematological biomarkers for HCC have the advantage of early screening of high-risk populations and prevention of disease

progression.<sup>[21]</sup> Moreover, the detection of hematological biomarkers is convenient and noninvasive, and allows for dynamic observation of the progression of hepatic lesions. At present, several hematological biomarkers are used for diagnosis of HCC, which include AFP, alpha fetoprotein heterosome, Golgi protein 73, glypican-3, des-gamma carboxyl prothrombin, and vascular endothelial growth factor, among others.<sup>[22,23]</sup> However, the sensitivity and specificity of traditional plasma markers of HCC are often poor. AFP is currently the most widely used hematological biomarker for the screening and diagnosis of HCC, but expression levels are also increased in benign liver diseases. A plasma AFP level of >200 ng/mL has been established as a diagnostic criterion for HCC, but its sensitivity is only about 40%, thus it is not an ideal indicator.<sup>[24]</sup> In addition, plasma AFP levels are also increased in pancreatic cancer, bladder cancer, and abnormal pregnancy,<sup>[25,26]</sup> which interferes with the diagnosis of HCC. According to typical guidelines worldwide,<sup>[27]</sup> ultrasonography is highly recommended for the surveillance of HCC. However, the overall sensitivity of noncontrast-enhanced ultrasonography is rather low at only 59.3%.<sup>[28]</sup> Thus, there is an urgent need to identify hematological biomarkers with greater sensitivity and specificity based on the characteristics of HCC in an early stage.

Since first described as a thrombotic disease,<sup>[29]</sup> abnormal coagulation associated with cancer has been the focus of many studies. As a degradation product of cross-linked fibrin, D-dimer





**Figure 3.** The SROC curve of plasma D-dimer. Each dot represented 1 observed study. The coincident dots indicated the studies with the same or similar specificity and sensitivity. The rhombus one represented the summary operating point with the high sensitivity (0.75) and specificity (0.93). The area under the SROC curve (AUC=0.88) indicated that plasma D-dimer is a diagnostic marker for HCC. AUC= area under the SROC curve, SROC = summary receiver operating characteristic.

is commonly used as a specific indicator of secondary fibrinolysis and the effect of thrombolytic therapy. The release of large amounts of procoagulant substances by tumor cells results in the production of thrombin and fibrin. Meanwhile, excessive secretion of plasminogen activators by malignant tumor cells converts plasminogen into plasmin, leading to enhanced fibrinolytic activity and elevated plasma D-dimer levels in patients with malignant tumors.<sup>[30]</sup> Therefore, an elevation in D-dimer levels is a relatively specific indicator of the growth of malignant tumor cells. Spadaro et al<sup>[7]</sup> found that, D-dimer levels in patients with HCC in liver cirrhosis were significantly higher than those in other patients with cirrhosis. In addition, several Chinese studies<sup>[31–33]</sup> had shown that the positive rate of plasma D-dimer in patients with different malignant tumors was different, with the highest in HCC. D-dimer levels were significantly elevated in patients with HCC, while D-dimers were only slightly elevated in bladder and pancreatic cancer. The D-dimer level was significantly associated with the degree of liver dysfunction.<sup>[34]</sup> Thus, it can be highly suspected that high D-dimer levels are significantly associated with Chinese patients with HCC. There was a significant difference of D-dimer levels between pregnant women and non-pregnant women. The D-dimer levels in pregnant women with abnormal pregnancy, such as pregnancy induced hypertension, were significantly higher than those in normal pregnant women. However, it could be considered to use methods of combined detection of D-dimer

with traditional markers to identify HCC and pancreatic cancer, bladder, abnormal pregnancy. As an indirect marker of fibrinolysis and fibrin turnover, the D-dimer exhibits unique properties as a biological marker of hemostatic abnormalities as well as an indicator of intravascular thrombosis. In addition to HCC which could cause high levels of D-dimer, also in conditions like long term bed-rest or strokes due to blood clot accumulation, patients getting treated with anticoagulants or blood thinners, under such conditions the D-dimer level might be increasing because of fibrinolysis. D-dimer generation requires the activity of 3 enzymes: thrombin, activated factor XIII and plasmin, all of which are synthesized in the liver. D-dimer levels might be temporarily elevated in thrombus unrelated to liver function in the conditions mentioned above. After treating with low molecular weight heparin sodium, warfarin, aspirin, and so on, levels of D-dimer could be restored to physiological balance. Long-term bed rest often led to deep venous thrombosis of lower extremity, D-dimer positive patients could be further diagnosed by venography of lower extremity or color Doppler ultrasonography. Moreover, if the course of thrombosis was long and the fresh thrombus load was small, levels of D-dimer could not be increased. In all, it suggested that D-dimer was expected to be a novel hematological marker for HCC, which might add new biomarkers of early diagnosis for HCC in Chinese population and can be used as a relatively independent risk factor for HCC.<sup>[9–14]</sup>

In this meta-analysis, 6 studies with 475 cases and 727 controls were included to comprehensively evaluate plasma D-dimer levels for the diagnosis of HCC in Chinese patients. The 6 included studies were all recently published in Chinese, with 3 in 2018. The pooled sensitivity and specificity of the included studies were 0.75 and 0.93, respectively, indicating greater sensitivity than with ultrasonography.

In addition to sensitivity and specificity, PLR, NLR, DOR, and AUROC are indices of diagnostic efficacy. The likelihood ratio can comprehensively reflect the accuracy of diagnosis by combining the sensitivity and specificity. PLR is a composite indicator reflecting sensitivity and specificity. The larger the PLR and the smaller the NLR, the better the diagnosis. DOR is an indicator of the specificity of diagnostic tests to distinguish diseases. The higher the value, the better capacity to identify diseases. In this meta-analysis, the pooled PLR, NLR, and DOR values were 11.4, 0.27, and 42, respectively. For studies with heterogeneity, an SROC curve and AUC are more reasonable for meta-analysis.<sup>[35]</sup> The SROC curve is a combined indicator reflecting sensitivity and specificity, as measures of the accuracy and reliability of the results. The AUC has the highest efficacy in homogeneity tests and is also very reliable for testing of heterogeneity. The AUC of D-dimer for HCC was 0.88, indicating that D-dimer has a high diagnostic accuracy for HCC.<sup>[36]</sup> In summary, although the window of time for detection is relatively short, D-dimer has strong specificity and high diagnostic value for early prevention and treatment, evaluation of therapeutic effects, and dynamic observation of thrombotic diseases. Therefore, monitoring of D-dimer levels should be promoted for the clinical diagnosis of HCC.

There were several limitations to this meta-analysis that should be acknowledged. First, there were only 6 studies fulfilling the criteria and all of them were retrospective cohort studies. The included studies were all published in Chinese, as unpublished gray literature and related studies in other languages were excluded. Second, although the diagnosis of HCC involves clinical staging, it was difficult to unify the baseline characteristics of the study populations. Significant heterogeneity mainly caused by non-threshold effects was observed in the included 6 studies, likely due to different patient's clinic-pathological characteristics (gender, age, tumor stage, and tumor grade) and different assay methods and experimental conditions. In addition, the cut-off values were different among the included studies. One of the main reasons was the examination of plasma D-dimer by using different automatic coagulation analyzers. The relatively high cut-off value was the fact that all cases of HCC were diagnosed by histopathology. Comparison with imaging characteristics, histopathology was considered to be the gold standard with higher diagnostic sensitivity and specificity for diagnosis of all cancers.<sup>[37]</sup> Third, the differential diagnosis of HCC requires combined examination of multiple sensitive and specific hematological biomarkers. The diagnostic value of plasma D-dimer for HCC was analyzed separately in this meta-analysis, thus its diagnostic sensitivity and specificity were limited.

To the best of our knowledge, from the perspective of evidence-based medicine, this is the first meta-analysis of plasma D-dimer for the diagnosis of HCC, suggesting that D-dimer is expected to be a novel and important plasma marker for HCC. Similarly, the results of this meta-analysis also suggested that the detection of plasma D-dimer levels and the design of laboratory examinations should be constantly improved. Meta-analysis allows for a more accurate and reliable evaluation to promote the clinical

application of plasma D-dimer levels for the early diagnosis of HCC.

### Author contributions

**Conceptualization:** Ping Fang, Lijun Du.  
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**Methodology:** Lijun Du, Decheng Cai.  
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**Software:** Lijun Du.  
**Writing – original draft:** Ping Fang.  
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