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A Systematic Review of Des-γ-Carboxy Prothrombin for the Diagnosis of Primary Hepatocellular Carcinoma

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Abstract: Determining the serum des-γ-carboxy-prothrombin (DCP) level is of great importance for the diagnosis of primary hepatocellular carcinoma (PHC). Although several studies have investigated the accuracy of diagnostic DCP tests for PHC, the results have been inconsistent.

The aim of this study was to systematically evaluate DCP as a diagnostic standard for PHC.

Several databases, including PubMed, EMBASE, MEDLINE (Ovid), the Chinese National Knowledge Infrastructure (CNKI), the VIP Database for Chinese Technical Periodicals (VIP), WanFang Data, and the China Biological Medicine Database (CBM), were searched from the date of database inception until July 1, 2015 to collect published international and domestic studies of DCP in the diagnosis of PHC. Two investigators screened the literature according to the inclusion and exclusion criteria, extracted the data, and assessed the methodological quality of the included studies.

A total of 38 studies involving 11,124 cases were included (5298 cases in the PHC group and 5826 cases in the control group). A meta-analysis was then performed using Meta-Disc 1.4 and RevMan 5.2 software. The overall sensitivity, specificity, positive likelihood ratio (+LR), and negative likelihood ratio (−LR) of DCP for the detection of PHC were 0.66 (95% confidence interval [CI]: 0.65–0.68), 0.88 (95% CI: 0.87–0.90), 7.13 (95% CI: 5.73–8.87), and 0.33 (95% CI: 0.29–0.38), respectively. The area under the curve (AUC) of the summary receiver-operating characteristic curve (SROC) was 0.9002. In conclusion, DCP has moderate diagnostic utility for PHC. Owing to the heterogeneity and limitations of the included studies, the above conclusion requires further support from additional high-quality studies.

Abbreviations: +LR = positive likelihood ratio, AFP = Alpha-fetoprotein, ALD = alcoholic liver disease, AUC = area under the curve, CBM = China Biological Medicine Database, CI = confidence intervals, CNKI = Chinese National Knowledge Infrastructure, DCP = des-γ-carboxy-prothrombin, DOR = diagnostic odds ratio, ECL = electrochemiluminescence, ELISA = enzyme-linked immunosorbent assay, EMBASE = Excerpta Medica Database, FL = fatty liver, HCC = hepatocellular carcinoma, -LR = negative likelihood ratio, NALD = nonalcoholic liver disease, OR = odds ratio, PHC = primary hepatocellular carcinoma, PIVKA-II = protein induced by vitamin K absence or antagonists-II, QUADAS = Quality Assessment of Diagnostic Accuracy Studies, RIA = radio immunoassay, RREA = radiorocket electrophoresis autography, SCCA = squamous cell carcinoma antigen, SEN = sensitivity, SPE = specificity, SROC = summary receiver operating characteristic curve, VIP = VIP Database for Chinese Technical Periodicals.

INTRODUCTION

Primary hepatocellular carcinoma (PHC) is a malignant tumor with high morbidity and mortality worldwide, and the morbidity of PHC continues to increase.[1] Owing to the insidious onset of PHC, the optimal treatment window typically ends before a definitive diagnosis is made, and the 5-year survival rate is <10%. However, when PHC tumors are ≤2 cm in diameter, the 5-year survival rate is close to 100%.[1] Therefore, early diagnosis is key to improving the prognosis of PHC.[2] Early diagnosis of PHC primarily depends on specific serum tumor markers and liver imaging tests. Alpha-fetoprotein (AFP) has been widely used in the clinic as a serum marker of PHC, but its sensitivity and specificity are unsatisfactory. Recently used serum tumor markers that may improve the early diagnosis rate of PHC include AFP variants, alpha-L-fucosidase, epithelial-specific cell adhesion molecule, squamous cell carcinoma antigen, and des-γ-carboxy-prothrombin (DCP, which is also known as protein induced by vitamin K absence or antagonists-II, or PIVKA-II). In a 1984 study, Liebman et al[3] observed elevated DCP in some patients with PHC. DCP is a type of abnormal prothrombin that is secreted by PHC tumor cells. One or more glutamate residues of DCP are post-translationally carboxylated to γ-glutamic acid. In contrast to normal prothrombin, DCP has no coagulation function.[4] The sensitivity and specificity of DCP in the diagnosis of PHC have been reported as 83% and 96%, respectively.[5] Most of the numerous studies on the accuracy of DCP for the diagnosis of PHC have used small sample sizes as well as different criterion standards, levels of quality, detection methods, and critical values. Therefore, a strict and systematic diagnostic review is needed to provide the latest and best evidence for clinical practice.

MATERIALS AND METHODS

Criteria for Selection and Exclusion

The selection criteria were as follows:

1. Type of study: published international and domestic diagnostic tests of DCP used for the diagnosis of PHC.

The included studies were limited to those published in Chinese and English.

2. Object of the study: PHC patients were compared with control patients, which included individuals without PHC (healthy volunteers or those with chronic hepatitis, cirrhosis, or secondary hepatic carcinoma, among other diseases). Four-fold table data must be reported or obtainable by the appropriate calculations.
3. Diagnostic method: the detection method was not restricted, and a pathological examination or generally accepted imaging method was regarded as the criterion standard.
4. Detection of the serum DCP concentration.

The exclusion criteria were as follows:

1. Studies included ambiguous diagnostic criteria for hepatocellular carcinoma, and articles did not specify the gold standard for diagnosis.
2. The data provided by the articles could not be transformed, or the full text could not be accessed.
3. The test samples were tissues or body fluids other than serum. (4) The articles were reviews or abstracts.

Index of Results

The sensitivity (SEN), specificity (SPE), positive likelihood ratio (+LR), negative likelihood ratio (-LR), diagnostic odds ratio (DOR), and area under the summary receiver-operating characteristic (SROC) curve (AUC) were calculated.

Search Strategy

PubMed, EMBASE, Ovid MEDLINE, CNKI, VIP, WanFang Data, and CBM were searched to collect all published international and domestic studies of DCP used for the diagnosis of PHC from the date of database inception to July 1, 2015. The languages of the retrieved studies were limited to Chinese and English. The references in the included studies were also reviewed. The strategy for the retrieval of the literature combined subject headings and synonyms. The Chinese search terms were liver cancer, PHC, liver tumor, abnormal prothrombin, des-γ-carboxy-prothrombin, protein induced by vitamin K absence, DCP, PIVKA-II, diagnosis, and tests, among others. The English search terms were primary hepatocellular carcinoma, PHC, HCC, liver cancer, des-gammacarboxyprothrombin, des-γ-carboxy-prothrombin, DCP, PIVKA-II, protein induced by vitamin K absence, diagnosis, detection, and early detection, among others. The elements of the following 3 categories were applied in various combinations when interrogating databases: (''primary hepatocellular carcinoma'' OR ''PHC'' OR ''HCC'' OR ''liver cancer'') AND (''desgammacarboxy prothrombin'' OR ''des-gamma-carboxy prothrombin'' OR ''DCP'' OR ''PIVKA-II'' OR ''Protein Induced by Vitamin K Absence'') AND (''diagnosis'').

Literature Screening, Data Extraction, and Quality Evaluation

Two investigators independently screened the literature according to the inclusion and exclusion criteria, extracted the data, and assessed the methodological quality of the included studies. Any differences or disagreements were resolved by discussion or by a third party. A form was generated to extract the data, which included the title of the article, the first author, the publication year, the language, the country, the sample number tested, the test method, the critical values,

the criterion standards used, the etiology, the composition of the control group, the true-positive value, the false-positive value, the true-negative value, and the false-negative value. The QUADAS list[6] was used to assess the methodological quality of the included studies, and each item in the QUADAS checklist was used to assess the parameters in each study using the answers ''yes,'' ''no,'' or ''unclear.'' ''Yes'' indicated that the criterion was satisfied, ''no'' signified that the criterion was unsatisfied or unmentioned, and ''unclear'' signified that the criterion was partly satisfied or that insufficient information was available.

Statistical Analysis

RevMan 5.2 software and Meta-Disc 1.4 software provided by the Cochrane Collaboration were used for the statistical analysis. The statistical heterogeneity of the clinical trial results was tested by the χ^2 test (I^2 test) at $P = 0.1$. The I^2 value describes the heterogeneity after the removal of the sampling error. In a range of I^2 values from 0% to 100%, 0% indicates no heterogeneity, and the heterogeneity increases as the I^2 value increases. $P \geq 0.1$ and $I^2 \leq 50\%$ indicate that the results of multiple similar studies are homogeneous, and a fixed-effect model was then adopted for the meta-analysis. $P < 0.1$ and $I^2 < 50\%$ indicate a low degree of heterogeneity among the results of the studies, and a random-effects model was then used for the meta-analysis. $P < 0.1$ and $I^2 > 50\%$ indicate that the results of the studies have a large degree of heterogeneity, and a qualitative systematic review was then used. The 4-fold tables for DCP in the diagnosis of PHC were used to calculate the pooled SEN, pooled SPE, +LR, −LR, and DOR. The SROC curve was then drawn, and the AUC was calculated to estimate the total diagnostic accuracy of the test. Based on the characteristics of the study objectives, a meta-regression analysis was performed to determine potential sources of heterogeneity. The method introduced by Deville et al[7] was also used to screen and eliminate studies with obvious heterogeneity and to perform subgroup analyses.

All analyses were based on previous published studies; thus, no ethical approval and patient consent are required.

RESULTS

The Basic Process of Study Inclusion was as Follows

The primary screening identified 848 relevant studies, and 750 articles remained after the elimination of duplicate studies. A total of 246 articles remained after eliminating reviews, abstracts, and those not written in English or Chinese. After carefully reading the full text of the articles, the studies were screened according to the strict inclusion and exclusion criteria. Finally, 38 articles[8–45] that met the inclusion criteria were selected (including a total of 11,124 patients: 5298 in the case group and 5826 in the control group) (Figure 1). All patients in the case group were confirmed to have PHC by histopathological examination or by imaging assessment. The studies included 18 reports published in Chinese and 20 reports published in English. The basic characteristics of the included studies are provided in Table 1.[8–45]

Methodological Quality Evaluation of the Included Studies

The QUADAS tool was used to evaluate the methodological quality of the 38 included studies. The determination of
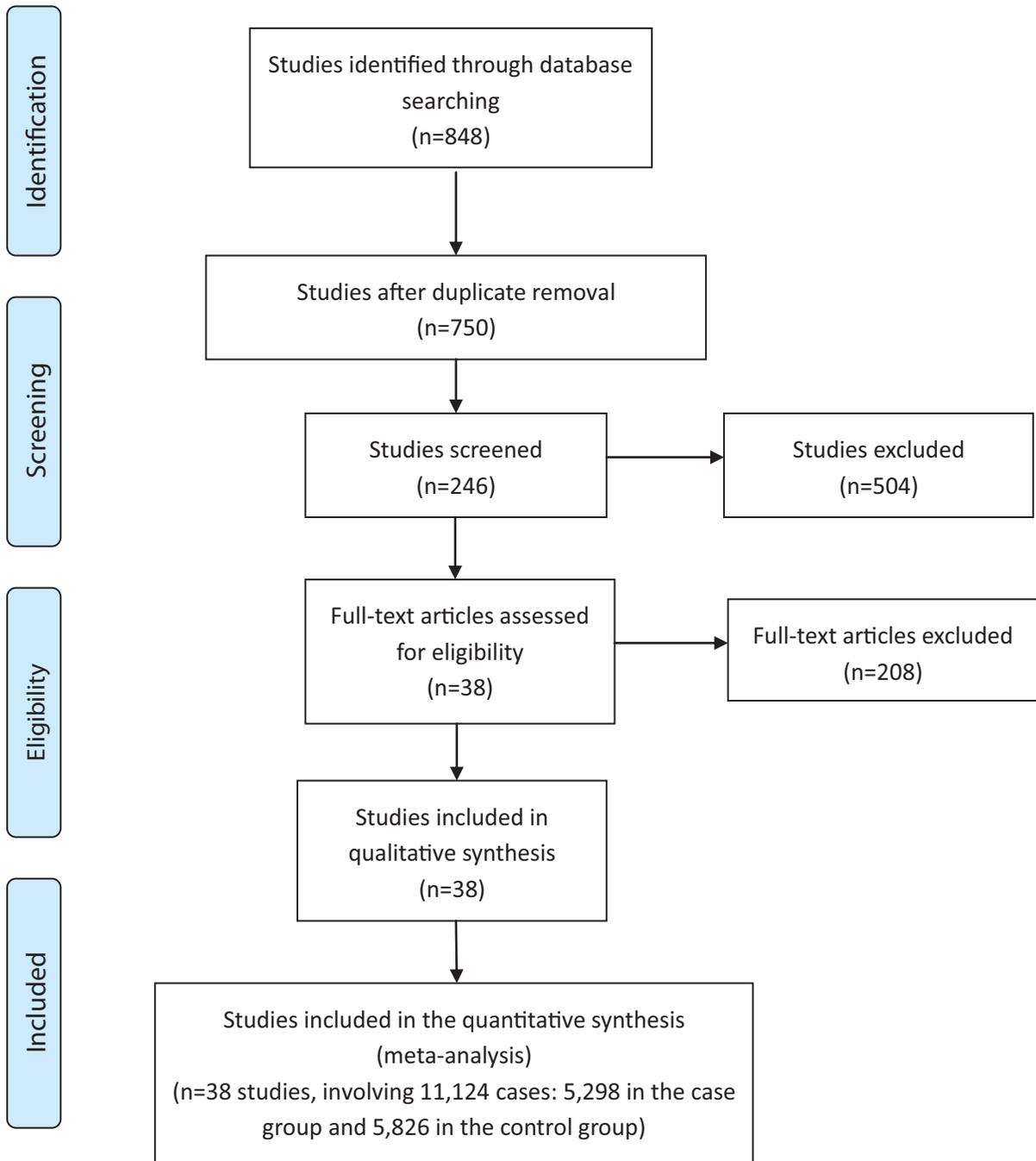
FIGURE 1. Flow chart of the search strategy used for the review.

serum DCP involves automatic instrument detection, and thus, there is no subjectivity. Therefore, there was no possibility of an unexplainable or intermediate result, and the clinical data were not used in the blinded method. Accordingly, items 10, 12, and 13 in the QUADAS checklist were deleted. The results are presented in Figure 2.

Global Meta-Analysis

A planar graph of the ROC curve was used to assess the presence of a threshold effect. The ROC planar scatter diagram generated using Meta-Disc 1.4 software did not exhibit a "shoulder" shape (Figure 3), indicating the absence of a threshold effect. To calculate the SEN and (1-SPE), the Spearman correlation coefficient of $logarithm = 0.302$ was used ($P = 0.065$), which confirmed the absence of a threshold effect. The DOR forest plot (Figure 4) and Q value indicated that the distribution of the DORs in each study was relatively discrete ($Q = 183.97$, $P = 0.0000$), suggesting that heterogeneity originated from nonthreshold effects. In addition, Meta-Disc 1.4 software was used to calculate the values $b = 0.121$ and

TABLE 1. Clinical Characteristics of the Included Studies

Author and Year	Country	Number of Cases	TP	FP	TN	FN	Cutoff Value	Assay Type	Etiology of liver Cancer	Diagnostic Criteria
Bachtiar et al, 2010[8]	Indonesia	220	88	4	92	36	4.5 ng/mL	ELISA	Hepatitis B, Hepatitis C	Histopathology or clinical synthesis
Beale et al, 2008[9]	Britain	91	39	8	33	11	40 mAU/mL	ELISA	ALD, NALD	Histopathology or clinical synthesis
Choi et al, 2013[10]	South Korea	168	56	4	74	34	40 mAU/mL	ELISA	Hepatitis B, Hepatitis C, ALD, FL	Histopathology or clinical synthesis
Cui et al, 2003[11]	China	210	64	13	77	56	40 mAU/mL	ELISA	Hepatitis B	Histopathology or clinical synthesis
Durazo et al, 2008[12]	United States	240	125	14	82	19	84 mAU/mL	ELISA	Hepatitis B, Hepatitis C	Clinical synthesis
Ertel et al, 2013[13]	Germany	586	104	24	398	60	5 ng/mL	ELISA	Hepatitis B, Hepatitis C, ALD, etc.	Clinical synthesis
Gvazi et al, 1995[14]	Italy	227	59	14	102	52	90 mAU/mL	ELISA	Hepatitis B, Hepatitis C	Clinical synthesis
Kuromatsu et al, 1997[15]	Japan	212	58	6	77	71	40 mAU/mL	ELISA	Hepatitis B, Hepatitis C	Histopathology or clinical synthesis
Lok et al, 2009[16]	United States	116	29	11	66	10	40 mAU/mL	ELISA	Hepatitis B, Hepatitis C	Histopathology or clinical synthesis
Marrero et al, 2003[17]	United States	159	49	5	99	6	125 mAU/mL	ELISA	Hepatitis C	Clinical synthesis
Marrero et al, 2009[18]	United States	836	310	125	292	109	150 mAU/mL	ELISA	Hepatitis B, Hepatitis C, ALD, etc.	Histopathology or clinical synthesis
Mittal et al,2012[19]	Nepal	60	21	3	27	9	40 mAU/mL	ELISA	Unclear	Clinical synthesis
Morota et al, 2011[20]	Japan	226	55	8	148	15	57.7 mAU/mL	ELISA	Hepatitis B, Hepatitis C	Histopathology or clinical synthesis
Nakamura et al, 2006[21]	Japan	1709	789	10	338	572	40 mAU/mL	ELISA	Hepatitis B, Hepatitis C	Histopathology or clinical synthesis
Okuda et al, 1998[22]	Japan	177	36	9	108	24	40 mAU/mL	ELISA	Hepatitis B, Hepatitis C	Histopathology
Sassa et al, 1999[23]	Japan	120	27	1	58	34	40 mAU/mL	ECL	Hepatitis B, Hepatitis C	Histopathology
Sharma et al, 2010[24]	India	108	56	14	35	3	6.98 ng/mL	ELISA	Hepatitis B, Hepatitis C	Histopathology or clinical synthesis
Sterling et al, 2009[25]	United States	372	29	31	267	45	7.5 ng/mL	ELISA	Hepatitis C	Histopathology or clinical synthesis
Wang et al, 2005[26]	Taipei	127	47	9	57	14	40 mAU/mL	ELISA	Hepatitis B, Hepatitis C	Histopathology or clinical synthesis
Young et al, 2009[27]	South Korea	206	55	3	97	51	40 mAU/mL	ELISA	Hepatitis B	Histopathology or clinical synthesis
Bu et al, 2000[28]	China	331	150	23	142	16	240 ng/mL	ELISA	Unclear	Not described
Chen et al, 2002[29]	China	90	31	4	26	29	40 mAU/mL	ELISA	Unclear	Histopathology or clinical synthesis
Fu et al, 2013[30]	China	216	41	17	146	12	40 mAU/mL	ELISA	Unclear	Not described
Kuang et al, 2010[31]	China	209	55	7	122	25	25 mAU/mL	ELISA	Unclear	Histopathology
Li et al, 2013[32]	China	612	147	44	370	51	25 mAU/mL	ELISA	Unclear	Histopathology
Zhu et al, 2014[33]	China	328	115	18	174	21	25.5 mAU/mL	ELISA	Not described	Histopathology or clinical synthesis
Liu et al, 2012[34]	China	126	58	3	57	8	40 mAU/mL	ELISA	Unclear	Histopathology
Lu et al, 2009[35]	China	172	60	14	82	16	40 mAU/mL	ELISA	Unclear	Histopathology or clinical synthesis
Pu et al, 2014[36]	China	365	74	27	238	26	40 mAU/mL	ELISA	Unclear	Histopathology or clinical synthesis
Shi et al, 2014[37]	China	219	85	16	98	20	40 mAU/mL	ECL	Virus hepatitis, cirrhosis, ALD	Histopathology or clinical synthesis
Wan et al, 1994[38]	China	204	85	3	88	28	145 ng/mL	RIA	Unclear	Histopathology or clinical synthesis
Yan et al, 1998[39]	China	242	48	20	144	30	9.40 mIU/mL	Serum assay	Unclear	Histopathology or clinical synthesis
Yang et al, 2013[40]	China	130	22	7	73	28	37.5 ng/mL	ELISA	Unclear	Histopathology
Yin et al, 1988[41]	China	279	68	28	153	30	250 ng/mL	RREA	Unclear	Histopathology
Yin et al, 2001[42]	China	719	218	26	314	161	100 ng/mL	ELISA	Unclear	Clinical synthesis
Zhao et al, 2012[43]	China	110	36	4	76	14	37.5 ng/mL	ELISA	Unclear	Histopathology
Zhong et al, 2013[44]	China	398	92	71	211	24	27.8 mAU/mL	ELISA	Hepatitis B, Hepatitis C	Histopathology
Zhuang et al, 2014[45]	China	204	39	6	147	12	40 mAU/mL	ELISA	Unclear	Clinical synthesis

ALD = alcoholic liver disease, ECL = electrochemiluminescence, ELISA = enzyme-linked immunosorbent assay, FL = fatty liver, FN = false-negative value, FP = false-positive value, NALD = nonalcoholic liver disease, RIA = radio immunoassay, RREA = radiorocket electrophoresis autography, TN = true-negative value, TP = true-positive value.
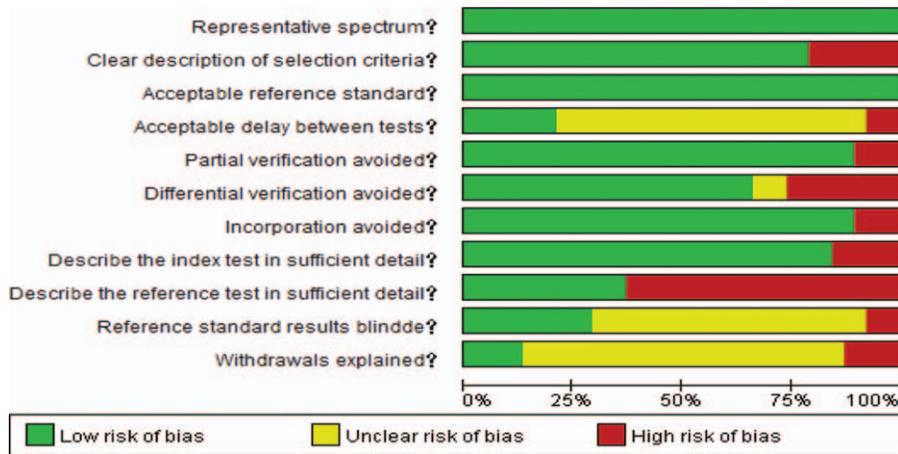
FIGURE 2. Methodological quality assessment chart showing the percentage of each item in the included studies.

$P = 0.8638$, which indicated that the Moses-Littenberg model could be used to draw a symmetric SROC curve. The pooled SEN of serum DCP for the diagnosis of PHC was 0.66 (95% CI: 0.65–0.68; Figure 5A), the pooled SPE was 0.88 (95% CI: 0.87–0.90; Figure 5B), the pooled +LR was 7.13 (95% CI: 5.73–8.87; Figure 5C), the pooled −LR was 0.33 (95% CI: 0.29–0.38; Figure 5D), the pooled DOR was 23.69 (95% CI: 18.01–31.17; Figure 4), and the AUC was 0.9002 ($Q = 0.8315$; Figure 5E).

Regression Analysis

The heterogeneity among the studies was because of a nonthreshold effect. Thus, meta-regression was used to explore the sources of heterogeneity, which were primarily the complex variables (eg, population and methodology) of the studies. Depending on the study characteristics, the regression analysis included race, study year, detection method, and composition of the control group to calculate the correlation coefficient and the relative DOR. Heterogeneity was observed with respect to study
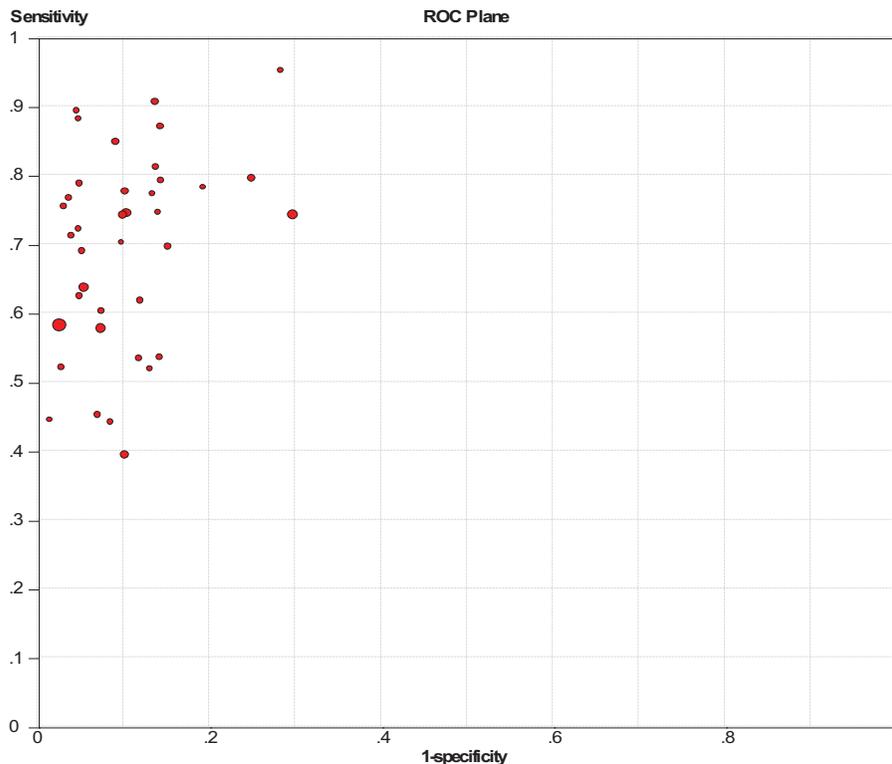
FIGURE 3. Receiver-operating characteristic curve planar scatter diagram of des-γ-carboxy-prothrombin for the diagnosis of hepatocellular carcinoma.

	Diagnostic OR (95% CI)
Bachtiar2010 [8]	56.22 (19.22 - 164.49)
Beale2008 [9]	14.63 (5.26 - 40.64)
Choi2013 [10]	30.47 (10.22 - 90.87)
Cui2003 [11]	6.77 (3.40 - 13.48)
Durazo2008 [12]	38.53 (18.30 - 81.12)
Grazi1995 [13]	8.27 (4.22 - 16.18)
Ertel2013 [14]	28.74 (17.08 - 48.36)
Kuromatsu1997 [15]	10.48 (4.26 - 25.79)
Lok2009 [16]	17.40 (6.65 - 45.50)
Marrero2003 [17]	161.70 (47.02 - 556.10)
Marrero2009 [18]	6.64 (4.91 - 8.99)
Mittal2012 [19]	21.00 (5.05 - 87.37)
Morota2011 [20]	67.83 (27.24 - 168.89)
Nakamura2006 [21]	46.62 (24.63 - 88.25)
Okuda1998 [22]	18.00 (7.66 - 42.28)
Sassa1999 [23]	46.06 (5.99 - 354.34)
Sharma2010 [24]	46.67 (12.51 - 174.09)
Sterling2009	5.55 (3.06 - 10.08)
Wang2005 [26]	21.26 (8.46 - 53.47)
Young2009 [27]	34.87 (10.39 - 116.99)
Lisha Bu2000 [28]	57.88 (29.38 - 114.03)
Xiaohong Chen2002 [29]	6.95 (2.16 - 22.35)
Shui Fu2013 [30]	29.34 (12.97 - 66.37)
Miaohuan Kuang2010 [31]	38.34 (15.64 - 93.98)
Sheng Li2013 [32]	24.24 (15.51 - 37.87)
Yu Li2014 [33]	52.94 (27.03 - 103.68)
Chuanmiao Liu2012 [34]	137.75 (34.78 - 545.54)
Fenglin Lu2009 [35]	21.96 (9.96 - 48.43)
Juebiao Pu2014 [36]	25.09 (13.79 - 45.64)
Yaling Shi2014 [37]	26.03 (12.69 - 53.41)
Jun Wan1994 [38]	89.05 (26.10 - 303.86)
Huimin Yan1998 [39]	11.52 (5.99 - 22.14)
Guimin Yang2013 [40]	8.19 (3.15 - 21.31)
Zhengfeng Yin1988 [41]	12.39 (6.87 - 22.32)
Zhengfeng Yin2001 [42]	16.35 (10.44 - 25.62)
Yunsheng Zhao2012 [43]	48.86 (15.02 - 158.97)
Zhimin Zhong2013 [44]	11.39 (6.75 - 19.23)
Guohua Zhuang2014 [45]	79.63 (28.10 - 225.64)
Random Effects Model	
Pooled Diagnostic Odds Ratio = 23.69 (18.01 to 31.17)
Cochran-Q = 183.97; df = 37 (p = 0.0000)
Inconsistency (I-square) = 79.9%
Tau-squared = 0.5418

0.01 — 1 — 100.0
Diagnostic Odds Ratio

FIGURE 4. The diagnostic odds ratios of des-γ-carboxy-prothrombin for the diagnosis of hepatocellular carcinoma.

year and control group selection. However, no significant effect of race or detection method was observed (Table 2). Based on the above results, subgroup analyses were performed for the following: study year between 1988 and 2009; study year between 2010 and 2015; Asian group; European and American group; ELISA; other assay type; control group composed of individuals with chronic hepatitis; and control group composed of individuals with cirrhosis (Table 3). The DOR was higher for the study years 2010 to 2015 than for 1988 to 2009 (31.75 vs 20.37), which indicated that the diagnostic discrimination efficiency was good. The DOR was significantly higher in the chronic hepatitis group (control group) than in the liver cirrhosis group (20.37 vs 16.09). We also observed a higher diagnostic efficiency in the Asian and ELISA groups.

DISCUSSION

In this study, we analyzed the diagnostic efficiency of serum DCP levels for the diagnosis of PHC via a systematic evaluation of diagnostic testing methods, and we explored the factors that influenced study heterogeneity. A total of 38 studies and 11,124 research subjects were included in the analysis. The results of the included studies were evaluated with the QUADAS tool. Seven items (3, 4, 5, 6, 7, 11, and 14) were found to be bias-related, and only item 3 had a ''yes'' answer in 100% of the studies. This result indicates that the included studies featured acceptable criterion standards. Item 4 was ''unclear'' in 70% of the studies, which indicates that the possibility of disease progression bias was high in all of the included studies; however, there was no effect on the results after the stratified analysis. For 2 items (1 and 2) related to variability, there was high variability among the descriptions of the disease stage, age, sex and the inclusion criteria of the study population, whereas the variability in the description of the

exclusion criteria was low. The disease spectrum and the selection of the study population can affect the SEN and SPE of a diagnostic test and, hence, its popularization. Therefore, the description of the study population and the disease spectrum should be as detailed as possible. For the 2 items (8 and 9) related to the evaluation of study quality, the operating instructions for the evaluated test were substantially clear and reproducible in most studies, whereas the detailed operating instructions for the criterion-standard test were less clear.

The meta-analysis revealed that the pooled SEN and SPE of serum DCP for the diagnosis of PHC were 66% and 88%, respectively, indicating that the false-negative and false-positive diagnostic rates were 34% and 12%, respectively. The Q-value of the SROC curve for the maximum polymerization spot of SEN and SPE was 183.97, and the AUC was 0.9002. These results indicate that the total accuracy of DCP for the diagnosis of PHC was high. The DOR is an independent indicator of the accuracy of a test, and it illustrates the probability that positive results are multiples of negative results; furthermore, it reflects the degree of correlation between the results of the diagnostic test and the presence of the disease. DOR values range from 0 to infinity, and a greater value indicates a higher discriminatory ability of the diagnostic method (ie, the method has high accuracy). If the DOR value is 1, the diagnostic method is not satisfactory for discriminating patients from nonpatients. The DOR value in this meta-analysis was 23.69, which indicates that DCP has a high accuracy for the diagnosis of PHC. Because the LR is more practical and more easily explains the results than the SROC curve and DOR, we also summarized the +LR and −LR in this study. The +LR explains the increased likelihood of a positive test result in patients compared with individuals without the disease
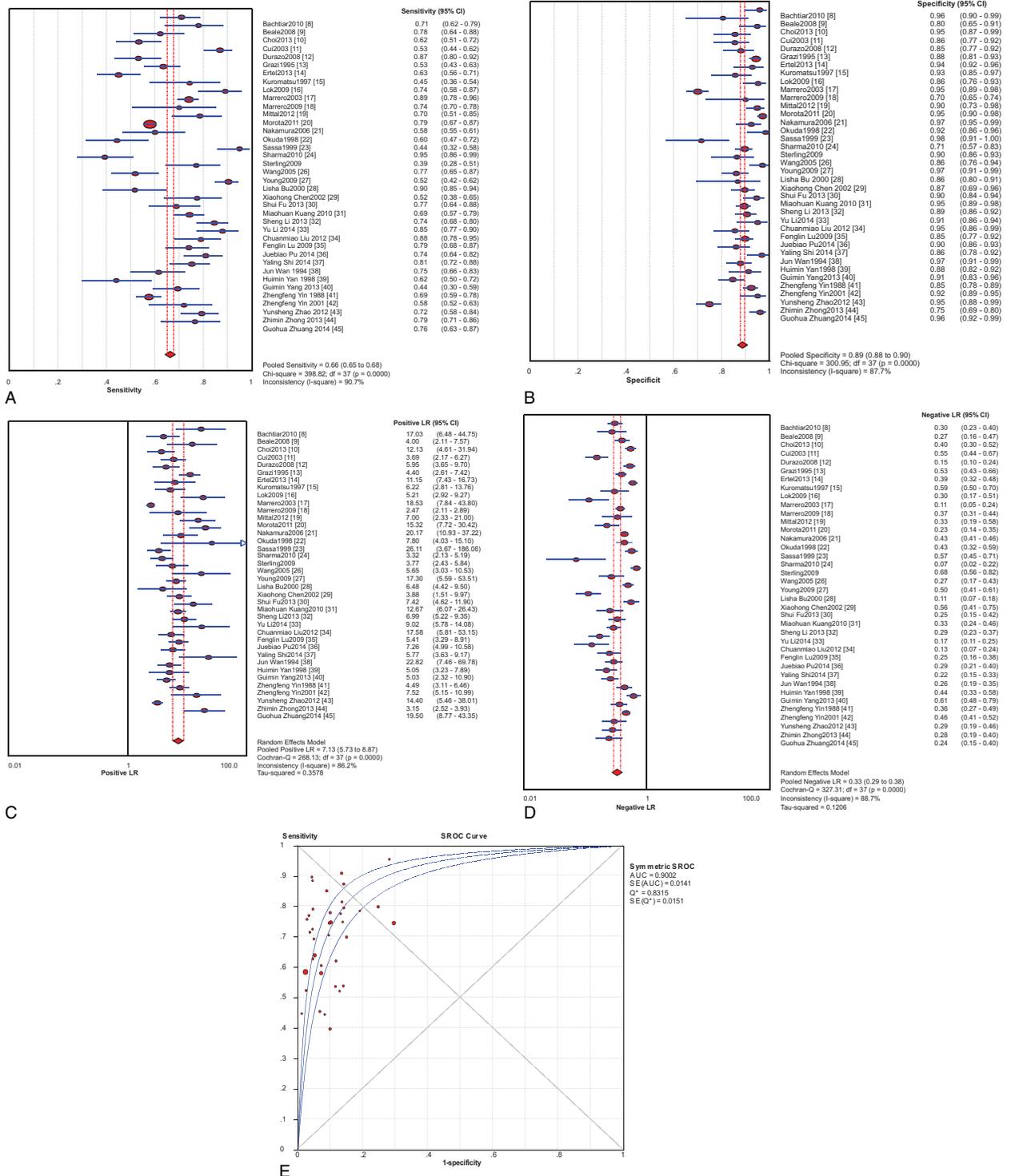
FIGURE 5. (A) Sensitivity forest plot of des-γ-carboxy-prothrombin for the diagnosis of hepatocellular carcinoma. (B) Specificity forest plot of des-γ-carboxy-prothrombin for the diagnosis of PHC. (C) Positive likelihood ratio forest plot of des-γ-carboxy-prothrombin for the diagnosis of hepatocellular carcinoma. (D) Negative LR forest plot of des-γ-carboxy-prothrombin for the diagnosis of hepatocellular carcinoma. (E) SROC curve of des-γ-carboxy-prothrombin for the diagnosis of hepatocellular carcinoma.

TABLE 2. Results of Meta-regression of the Study Characteristics

Regression Analysis	Regression Coefficient	*P*	OR (95% CI)
Study year (1988–2009 vs 2010–2015)	0.595	0.0301	1.81 (1.06–3.09)
Race (Asian vs European and American)	−0.476	0.1938	0.62 (0.32–1.21)
Detection (ELISA vs other)	−0.486	0.1583	0.62 (0.31–1.22)
Control group (chronic hepatitis vs cirrhosis)	−0.340	0.0315	0.71 (0.52–0.97)

CI = confidence intervals, OR = odds ratio.

(ie, controls). This indicator is stable and is not susceptible to changes in disease prevalence. A higher +LR or a lower −LR indicates a greater diagnostic value for the test results. This study had a high +LR (7.13) and a low −LR (0.33), indicating that serum DCP is equally effective at diagnosing PHC in individuals with the disease and at excluding PHC in individuals without the disease. These results are similar to those of a newly published meta-analysis by Gao et al.[46]

A heterogeneity analysis is an important part of a meta-analysis. Based on the characteristics of the study subjects, we used meta-regression to determine the potential causes of heterogeneity. We also used the method introduced by Deville et al[7] to screen and remove studies with obvious heterogeneity to perform subgroup analyses. We determined that differences in the control groups and in the study year were the main sources of heterogeneity and were statistically significant. The studies that were published in 2010 to 2015 had a higher diagnostic efficiency than those published in 1988 to 2009. Our additional analysis implies that this difference may be related to recent improvements in detection methods and testing instruments because of the rapid development of biotechnology, leading to corresponding increases in diagnostic SEN and SPE. We also observed higher SEN, SPE, +LR, and DOR values but a lower −LR for the control group that included individuals with chronic hepatitis compared with the control group that included individuals with cirrhosis. These differences may be related to the courses and characteristics of these diseases. Kim et al[47] detected the serum DCP

concentration in patients with liver cancer, cirrhosis, and chronic hepatitis and determined that the concentration of DCP was higher in the serum of patients in the liver cancer group (5420.3 ± 3960.0 mAU/mL) than in those in the cirrhosis group (26.3 ± 7.2 mAU/mL). The difference was even more significant between patients in the liver cancer group and patients in the chronic hepatitis group (16.1 ± 2.0 mAU/mL), similar to the results of our study. DCP, which is produced and released into the blood by hepatocellular carcinoma cells, likely exerts an additional stimulatory effect on the growth of hepatocellular carcinoma cells. DCP may also promote the formation of tumor microvessels, which become part of the autocrine pathway that stimulates the growth of hepatocellular carcinoma cells. In addition, some clinical data[48,49] have indicated that the DCP expression level is closely related to liver cancer lesion size and number, degree of invasion, and intrahepatic and extrahepatic metastasis. However, these types of data were not reported in the studies included in this meta-analysis, and thus, the roles of these factors could not be analyzed herein.

The advantages of the present study are as follows. We included a large number of studies, developed a robust search strategy, screened the literature according to strict selection criteria, and used meta-regression for the hierarchical analysis of heterogeneity. However, our study also has the following limitations:

1. The language of the included studies was limited to English and Chinese, which may have led to the omission of relevant studies in other languages.
2. Of the 38 included studies, 32 were retrospective studies, and only 6 were prospective studies. Retrospective studies may overestimate or underestimate diagnostic efficacy, which may decrease the reliability of our results.
3. The case group of liver cancer patients was smaller than the control group, which may have affected the SEN of the test.
4. Owing to the lack of relevant data, the correlations between the serum DCP level and liver cancer etiology, lesion size, and tumor stage could not be analyzed.
5. DCP levels are strongly influenced by warfarin, alcohol abuse, and vitamin K absence, but these studies did not analyze these factors.
6. Subgroup and SEN analyses were performed in the included studies, but this study is a secondary study, and therefore, heterogeneity cannot be completely eliminated.

In conclusion, the results of this meta-analysis indicate that serum DCP has high diagnostic efficiency and high SPE, which

TABLE 3. Results of Subgroup Analyses of the Study Characteristics

Sub-group	N	Sen (95% CI)	Spe (95% CI)	+LR (95% CI)	−LR (95% CI)	DOR (95% CI)	AUC
1988–2009	21	0.63 (0.62–0.65)	0.88 (0.87–0.89)	6.27 (4.63–8.48)	0.38 (0.33–0.44)	18.34 (12.55–26.79)	0.8817
2010–2015	17	0.74 (0.72–0.76)	0.90 (0.89–0.91)	8.37 (6.13–11.42)	0.28 (0.24–0.34)	31.75 (23.38–43.11)	0.9133
Asian	30	0.65 (0.64–0.67)	0.90 (0.89–0.91)	7.61 (6.11–9.46)	0.33 (0.29–0.36)	25.79 (19.81–33.56)	0.9058
European and American	8	0.70 (0.68–0.73)	0.85 (0.83–0.87)	5.45 (3.30–9.00)	0.33 (0.24–0.46)	17.07 (8.76 -33.25)	0.8902
ELISA	30	0.67 (0.66–0.68)	0.89 (0.88–0.90)	7.39 (5.68–9.61)	0.31 (0.26–0.36)	26.32 (19.08–36.00)	0.9078
Other methods	8	0.62 (0.59–0.66)	0.8 (0.87–0.91)	5.90 (4.32–8.07)	0.42 (0.34–0.52)	15.59 (9.61–25.28)	0.8000
Chronic hepatitis	6	0.65 (0.61–0.69)	0.90 (0.87–0.92)	6.67 (5.07–8.78)	0.36 (0.24–0.53)	20.37 (11.19–37.09)	0.9246
Cirrhosis	11	0.61 (0.60–0.63)	0.87 (0.85–0.88)	6.31 (3.67–10.85)	0.43 (0.36–0.51)	16.09 (8.79–29.44)	0.8434

n+LR = positive likelihood ratio, AUC = area under the curve, CI = confidence intervals, DOR = diagnostic odds ratio, −LR = negative likelihood ratio, SEN = sensitivity, SPE = specificity.

are helpful for obtaining a definitive diagnosis. However, the results of this analysis were influenced by race, etiology, the composition of the control group, the test equipment, and the detection method. Therefore, additional high-quality studies are needed to further define the utility of serum DCP for diagnosing PHC.

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