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Original Article

Diagnostic value of C-reactive protein in hepatocellular carcinoma: a meta-analysis

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Abstract: Early diagnosis of hepatocellular carcinoma (HCC) is crucial for the treatment of patients. In the current study, our purpose was to appraise the diagnostic value of C-reactive protein (CRP) for HCC in both the normal population and patients with liver cirrhosis (LC). Multiple databases were searched for literature retrieval. Diagnostic meta-analysis was conducted to determine the namely sensitivity, specificity, diagnostic odds ratio (DOR), negative predictive value (NPV), positive predictive value (PPV), the area under receiver operating characteristic (AUROC), likelihood ratios, positive post-test probability (PPP) and negative post-test probability (NPP). In the normal population, the pooled sensitivity and specificity were 0.99 and 0.79, respectively, with favorable results of NPV and PPV (NPV = 0.97; PPV = 0.74); the DOR and AUROC were 530 and 0.90, respectively; the positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were 4.6 and 0.01, respectively; with the predefined pre-test probability of disease (PPD), the PPP and NPP were 69% and 0%, respectively. In patients with LC, the pooled sensitivity and specificity were 0.59 and 0.63, respectively; the NPV and PPV were 0.57 and 0.58, respectively; the DOR and AUROC were 2 and 0.64, respectively; the PLR and NLR were 1.6 and 0.65, respectively; with the predefined PPD, the PPP and NPP were 44% and 24%, respectively. Our diagnostic meta-analysis suggests that CRP can be considered as a biomarker for the diagnosis of HCC with high diagnostic accuracy in the normal population, whereas the diagnostic value of CRP for HCC in LC patients is extremely low.

Keywords: HCC, CRP, normal population, LC patients, meta-analysis

Introduction

Hepatocellular carcinoma (HCC), accounting for over 90% of primary liver cancers, is the fifth most common malignancy and the third leading cause of cancer-related death worldwide [1-3]. With its increasing incidence, HCC becomes a major global health problem [1]. A number of risk factors have been reported to be associated with HCC including liver cirrhosis (LC), hepatitis B virus infection (HBV), hepatitis C virus infection (HCV), co-infection of HBV and HCV, aflatoxin intoxication, drinking water contamination, alcohol drinking, tobacco smoking, oral contraceptives, tea or coffee consumption, obesity, diabetes mellitus (DM) and so on [4-7]. Among all the risk factors, the HBV infection is responsible for about 54% of HCC cases, while HCV infection leads to 31%, with other factors resulting in the remaining 15% [2].

Currently, the median survival of patients with HCC ranges from 6 to 20 months after diagnosis [8]. For patients with early-stage HCC, the curative therapies such as surgical resection, liver transplantation and radiofrequency ablation (RFA) are considered to be effective, and the 5-year survival rate for these patients is approximately 40% to 70% [9, 10]. For individuals with advanced-stage HCC, the oral multitargeted kinase inhibitor sorafenib becomes the recommended treatment, and the median survival is less than 1 year and 5-year survival is no more than 10% [11, 12]. So the early diagnosis of HCC is imperative because the early intervention is more effective in the context of small lesions.

C-reactive protein (CRP) is an acute-phase reactant that has a key role in the process of inflammation [13, 14]. The elevated level of CRP is correlated with the occurrence of systemic infections, trauma and malignancies [13]. Ohishiet al. performed a nested case-control study and reported that no systematic relation-

ship was detected between HCC risk and the elevated serum levels of CRP [15]. However, there are contradictory results. A relevant study, published in 2015, documented that the serum CRP level could serve as a diagnostic biomarker for HCC [16]. The aim of the present study was therefore to comprehensively estimate the diagnostic performance of CRP on HCC. The diagnostic value of CRP for HCC was evaluated in both the normal population (healthy individuals) and patients with LC.

Methods

Literature search

We conducted a systematic search in PUBMED (1966~2016), the Web of science (1945~2016) and Embase (1980~2016) for studies assessing the diagnostic value of CRP for HCC. Our search strings combined "HCC" synonyms with synonyms for "CRP". And the search term was "Hepatic carcinoma" OR "liver cancer" OR "liver carcinoma" OR "Hepatic cancer" OR "Hepatocellular carcinoma" OR "Hepatocellular cancer" OR "HCC" OR "Hepatoma" AND ("serum" OR "blood" OR "plasma") AND ("C-reactive Protein" OR CRP) AND (diagnosis OR Indicate) AND (healthy OR control OR "liver cirrhosis" OR hepaticsclerosis). The last update of literature retrieval was onJanuary 25, 2016.

Inclusion and exclusion criteria

Studies satisfying the following inclusion criteria were considered potentially eligible: (1) studies pertaining to the CRP level in patients with HCC or/and LC and healthy individuals; (2) studies investigating the utility of CRP for the diagnosis of HCC; (3) CRP level was measured using biochemical methods such as turbidimetric latex agglutination method and ELISA; (4) literatures in which the relevant data could be used to construct a 2 × 2 contingency table. Studies were excluded from the analysis if (1) studies regarding to other malignancies rather than HCC; (2) studies performed on animals or cells; (3) studies focusing on the change of CRP level between pre- and post-treatment; (4) studies in which the raw data were unavailable; (5) duplicated literatures.

Data extraction

Information of each included study was collected independently by two reviewers. We obtained data on studies, enrolled subjects and CRP levels. Studies characteristics comprised the first author and the publication year. Enrolled subjects characteristics included the age, the male ratio and the number of HCC patients, LC patients and healthy controls (HC). CRP levels characteristics involved the methods for CRP detection, sample source, display method of CRP levels, cut-off value and the diagnostic criteria.

Outcomes of interest

To evaluate whether CRP can be used as a diagnostic marker for HCC, we calculated the namely sensitivity, specificity, diagnostic odds ratio (DOR), negative predictive value (NPV) and positive predictive value (PPV). The summary receiver operating characteristic (ROC) curve was plotted and the area under ROC (AUROC) was computed. We also designed a Fagan nomogram to assess the clinical value of the index test with the positive likelihood ratio (PLR), negative likelihood ratio (NLR), positive post-test probability (PPP) and negative post-test probability (NPP) obtained.

Statistical analysis

For included studies, data were extracted for theconstruction of 2 × 2 contingency tables of true positive, false positive, true negative and false negative values. Data synthesis was conducted within the bivariate random-effects model. The STATA software version 12 (STATA Corp, College Station, Texas) was applied for the bivariate meta-analysis. To graphically reveal the sensitivity and specificity measurements, the forest plots were constructed. The source of heterogeneityfor sensitivity and specificity was analyzed in the meta-regression. The 95% confidence intervals (CIs) for sensitivity, specificity, DOR, AUROC, PLR, NLR, NPV and PPV were also computed in the analysis.

For DOR, a higher value indicates a better discriminatory test performance. When its value ranges from 10 to 80, a diagnostic test with an adequate performance is considered, whereas that higher than 80 is regarded as an indicator of excellent test [17]. With respect to the AUROC, when its value is between 0.5 and 0.7, the accuracy of diagnostic system is considered low; the value between 0.7 and 0.9 signifies a moderate accuracy of the diagnostic system; the value ranged from 0.9 to 1 implies a high accuracy of the diagnostic system [18]. The value of NPV suggests the probability of getting a negative test result for a healthy sub-

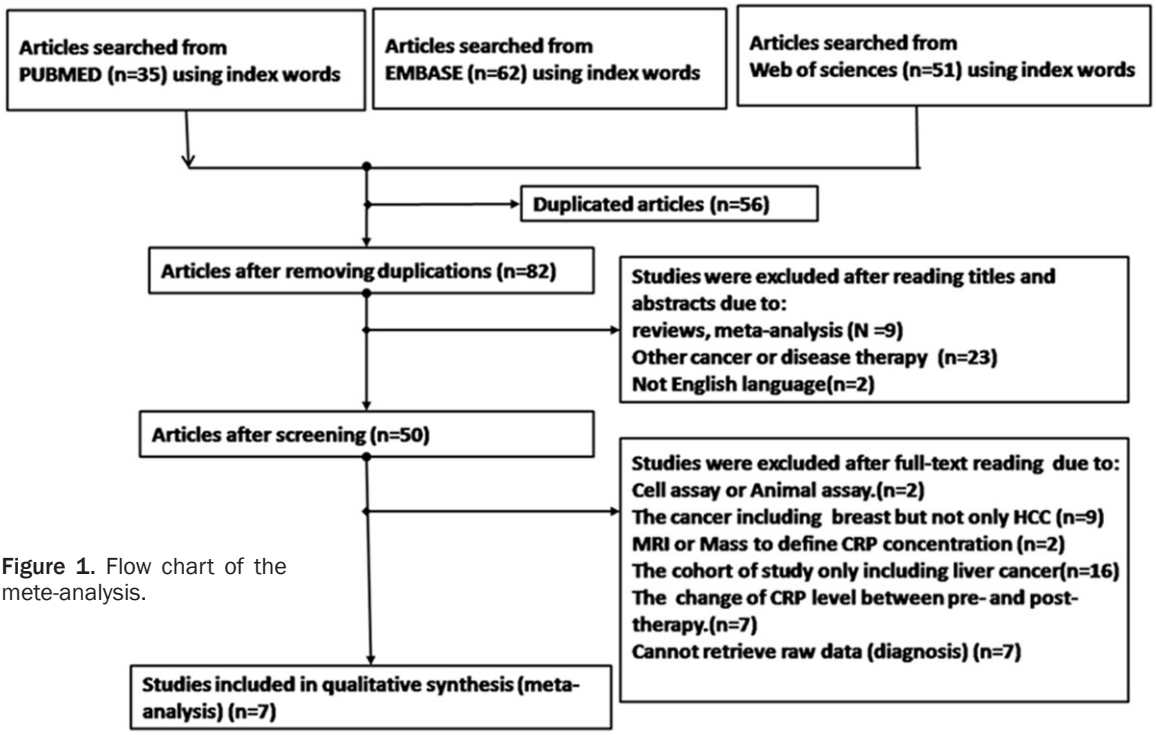

Figure 1. Flow chart of the mete-analysis.

ject; the value of PPV infers the probability of getting a positive test result for a diseased subject [19].

In terms of likelihood ratio (LR), its value implies the predictive accuracy of the diagnostic system [20]. PLR above 10 or NLR below 0.1 indicates a high predictive efficacy; PLR between 5 and 10 or NLR between 0.1 and 0.2 signifies a moderate predictive efficacy; PLR between 2 and 5 or NLR between 0.2 and 0.5 implies a very small predictive efficacy [21-23].

Publication bias

We used the Deeks'funnel plot to detect publication bias. An asymmetrical funnel shape infers the presence of publication bias.

Results

Study retrieval

The original search generated 35 literatures from PUBMED, 62 from Embase and 51 from Web of sciences. We eliminated 56 duplicates, leaving 82 literatures for further assessment. We then excluded 32 literatures after reading titles and abstracts. The remaining 50 literatures were screened through full-text reading. Finally, there were 7 eligible studies for the analysis, and **Figure 1** displayed the literature inclusion and exclusion process. The main characteristics of each included study were summarized in **Table 1**.

Pooled diagnostic performance

We incorporated data pertaining to the diagnostic value of CRP for HCC, performed the relevant analysis, and the results were shown in **Table 2**. For the prediction of the presence of HCC in the normal population, the CRP demonstrated a sensitivity of 0.99 (95% CI: 0.84-1.00, **Figure 2A**) and a specificity of 0.79 (95% CI: 0.70-0.85, **Figure 2A**). For that in patients with LC, the sensitivity was 0.59 (95% CI: 0.50-0.66, **Figure 2B**) and the specificity was 0.63 (95% CI: 0.50-0.75, **Figure 2B**). The results of sensitivity and specificity suggested that pooled sensitivity and specificity for the diagnostic accuracy of CRP for HCC in healthy individuals were higher than those in patients with LC.

The Fagan plot was generated to investigate the clinical utility of CRP for HCC in both healthy individuals and LC patients, and the results were recorded in **Table 2**. For the prediction of the presence of HCC in the normal population, the value of PLR was 4.6 (95% CI: 3.2-6.6, **Figure 3A**), and the value of NLR was 0.01 (95% CI: 0.00-0.24, **Figure 3A**). We believed that the CRP had a high predictive efficacy for HCC in

Table 1. Characteristics of the studies included in the analysis

First author, year	Methods for CRP detection	Age	Male (%)	HCC:LC:HC	Sample source	Display method of CRP levels	Cut-off value	Diagnostic criteria
Fabris 1994	Particle-enhanced nephelometry (NA Latex (CRP Reagents, Behring, Germany)	53.7+14.4	59.65%	38:45:33	Blood	Scatter plot	5 mg/l	Hepatocellular carcinoma was diagnosed on the basis of positive diagnostic imaging and/or high (>400 ng/ml) levels of serum cqfetoprotein; it was always confirmed histologically by percutaneous liver biopsy or at necropsy.
Fabris 1996	Particle-enhanced nephelometry (NA Latex CRP Reagents, Behring, Germany)	53.1±15.0	56.06%	24:32:33	Blood	Scatter plot	5 mg/l	Hepatocellular carcinoma was diagnosed on the basis of suggestive diagnostic imaging andfor high (>400 ng/ml) levels of serum alfetoprotein and always confirmed by J13 percutaneous liver biopsy or at necropsy.
Kong 2012	Enzyme-linked immunosorbent assay	-	-	29:25:25	Serum	Box plot	-	-
Omran 2015	Turbidimetric latex agglutination method (Biosystems SA, Barcelona, Spain).	25-70	59.15%	53:20:15	Serum	ROC curve	5 mg/l	Liver Diseases (AASLD) Practice Guidelines
She 2015	Human CRP ELISA Kit (ab99995)	-	-	60:70:40	Plasma	-	2.36182 mg/l	Asian Pacific Association for study of the liver (APASL) the European Association for the study of the Liber (EASL) the American Association for the study fo Liver Dieases (AASLD)
Ohishi 2014	Autoanalyzer (Hitachi 7180, Hitachi, Tokyo, Japan) and a high-sensitivity assay kit (Nissui Pharmaceutical, Tokyo, Japan)	-	60.25%	224:0:644	Serum	Table	0.96 mg/l	Hiroshima Tumor and Tissue Registry and Nagasaki Cancer Registry
Li 2000	Nephelometric analysis (array TM protein, system, Beckman Instruments, Fullertom, CA, USA)	62 (24-89)	63.93%	56:76:0	Serum	Scatter plot	6 mg/l	Ultrasonographically guided percutaneous aspiration cytology or biopsy

HCC: Hepatocellular carcinoma; HC: healthy control; LC: liver cirrhosis; -: not mentioned.

Table 2. Summary table of the meta-analysis

Study	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)	AUROC (95% CI)	PPD	PLR (95% CI)	NLR (95% CI)	PPP	NPP	NPV (95% CI)	PPV (95% CI)
HCC vas HC	0.99 (0.84, 1.00)	0.79 (0.70, 0.85)	530 (20, 14084)	0.90 (0.87, 0.92)	33%	4.6 (3.2, 6.6)	0.01 (0.00, 0.24)	69%	0%	0.97 (0.92, 1.00)	0.74 (0.70, 0.78)
HCC vas LC	0.59 (0.50, 0.66)	0.63 (0.50, 0.75)	2 (1, 4)	0.64 (0.59, 0.68)	68%	1.6 (1.2, 2.2)	0.65 (0.53, 0.81)	44%	24%	0.57 (0.51, 0.63)	0.58 (0.52, 0.63)

HCC: Hepatocellular carcinoma; HC: healthy control; LC: liver cirrhosis; PLR: Positive Likelihood Ratio; NLR : Negative Likelihood Ratio; DOR: Diagnostic Odds Ratio; PPD: Pretest Probability of Disease; PPP: positive post-test probability; NPP : negative post-test probability; NPV: negative predictive value; PPV: Positive predictive value.

the normal population. When the pre-test probability of disease (PPD) was estimated at 33%, it appeared that the PPP was 69% and the NPP was 0% (**Figure 3A**). The finding indicated that in the normal population, if one had a CRP level above the predefined threshold, he had 69% chance to be diagnosed with HCC (successful test), whereas the chance would be 0% if the CRP level below the threshold. For the prediction of the presence of HCC in patients with LC, the value of PLR was 1.6 (95% CI: 1.2-2.2, **Figure 3B**), and the value of NLR was 0.65 (95% CI: 0.53-0.81, **Figure 3B**), which signified that the CRP had no predictive efficacy for HCC in LC patients. When the PPD was predefined at 68%, it appeared that the PPP was 44% and the NPP was 24% (**Figure 3B**). The results demonstrated that if a LC patient had a CRP level above the predefined threshold, he had 44% chance to be diagnosed with HCC (successful

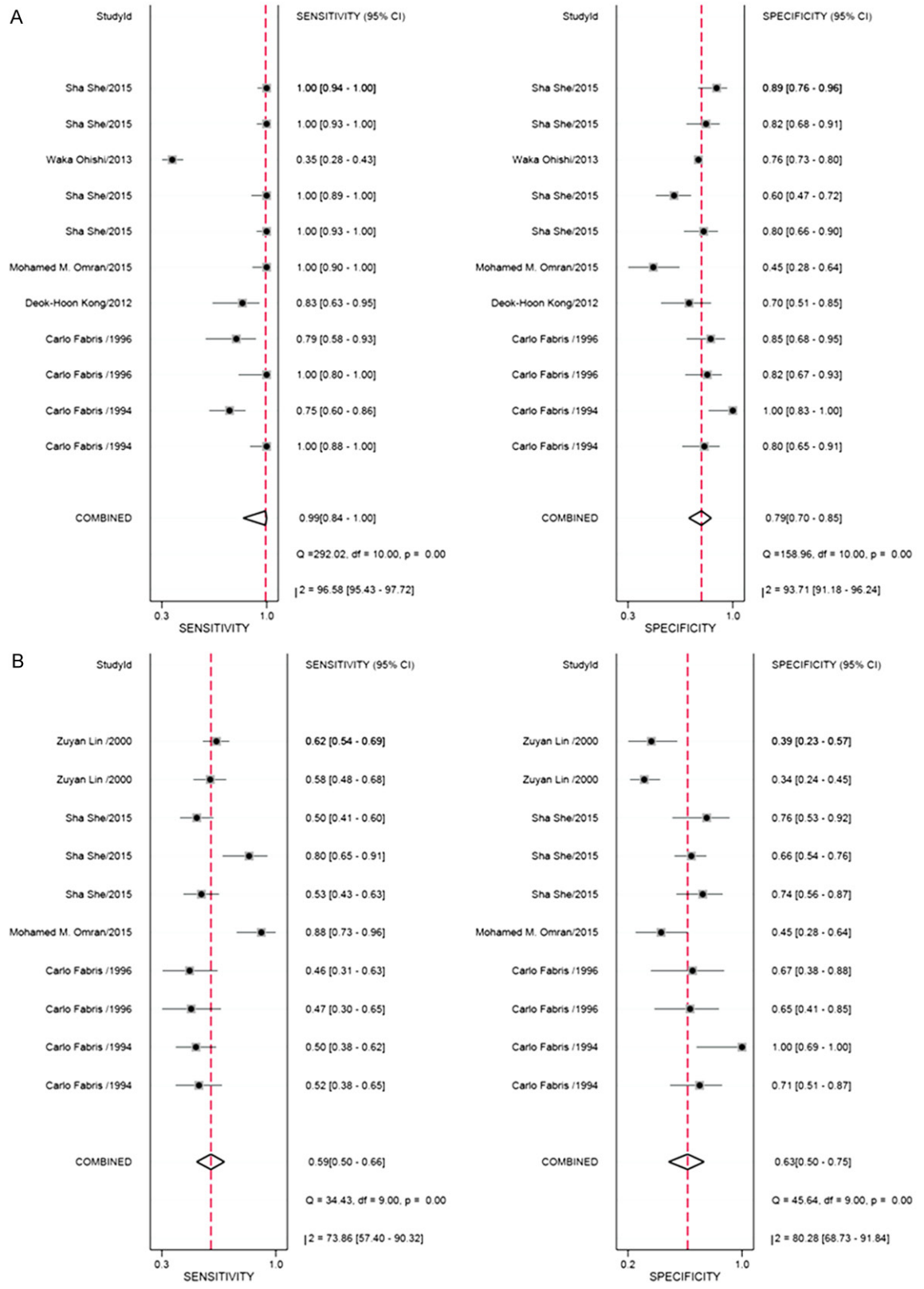

Figure 2. Forest plots of pooled sensitivity and specificity estimates and corresponding 95% CIs for studies in both the normal population (A) and the LC patients (B).

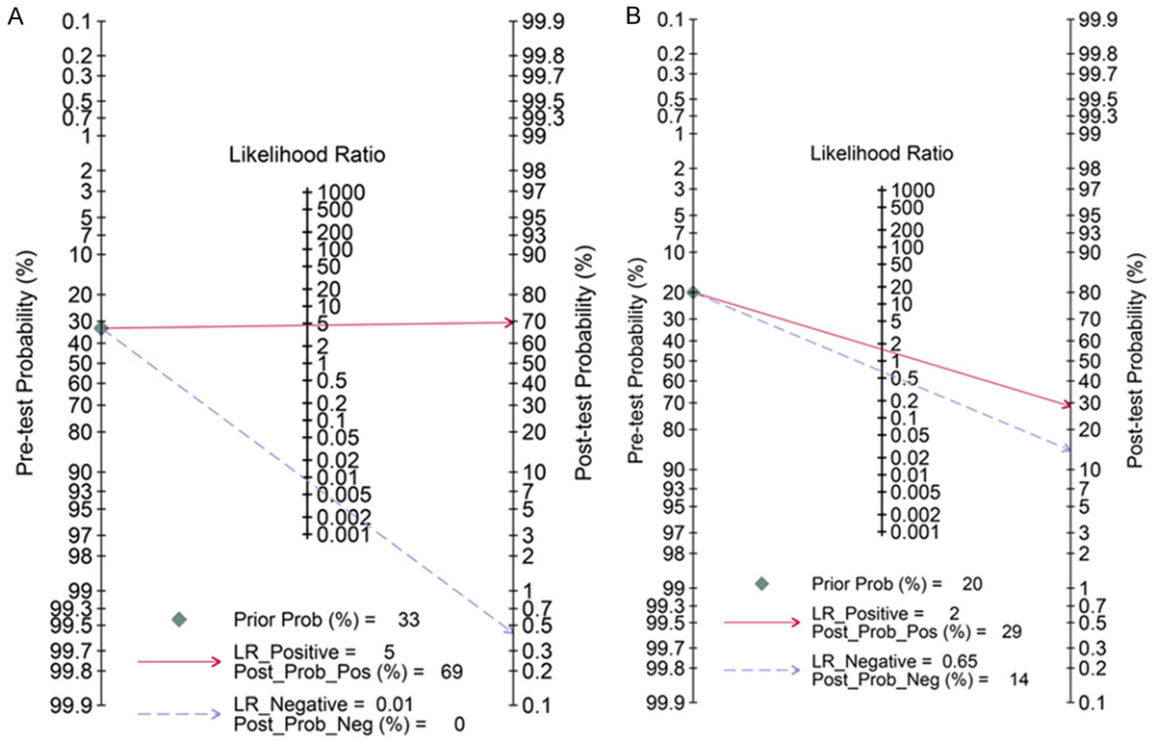

Figure 3. Fagan plots of evaluating the clinical utility of CRP for HCC in both the normal population (A) and the LC patients (B).

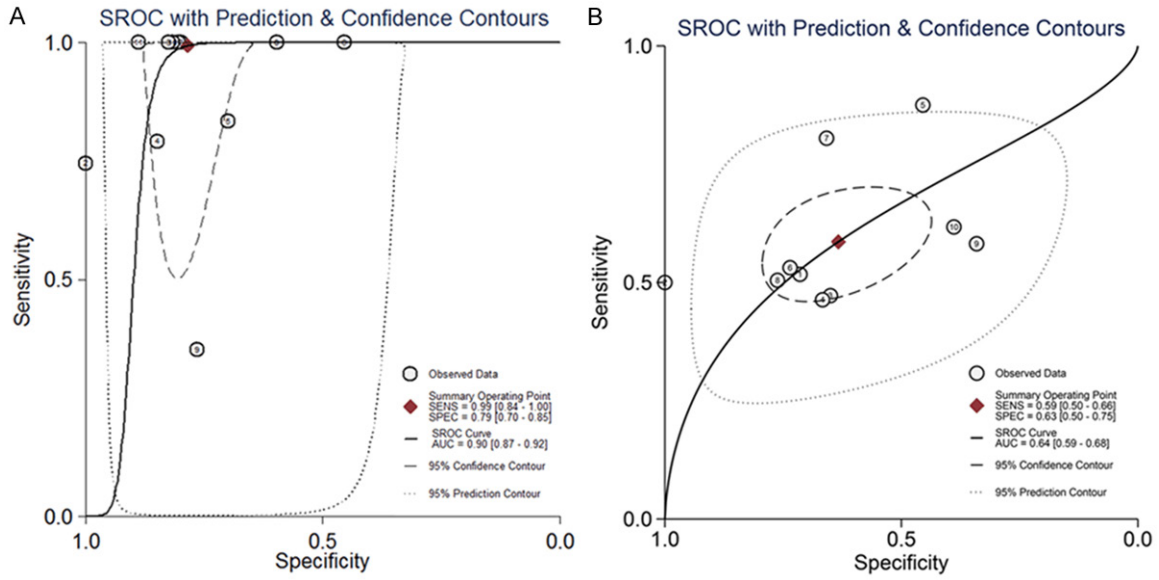

Figure 4. Summary receiver operating characteristic (SROC) curves for studies in both the normal population (A) and the LC patients (B).

test), whereas the chance would be 24% if the CRP level below the threshold.

The pooled DOR of CRP in predicting HCC in the normal population was calculated at 530 (95% CI: 20-14084), and the value in LC patients was computed at 2 (95% CI: 1-4). The results implied that the CRP could be considered as an excellent biomarker for the diagnosis of HCC in the normal population, whereas the CRP had a very

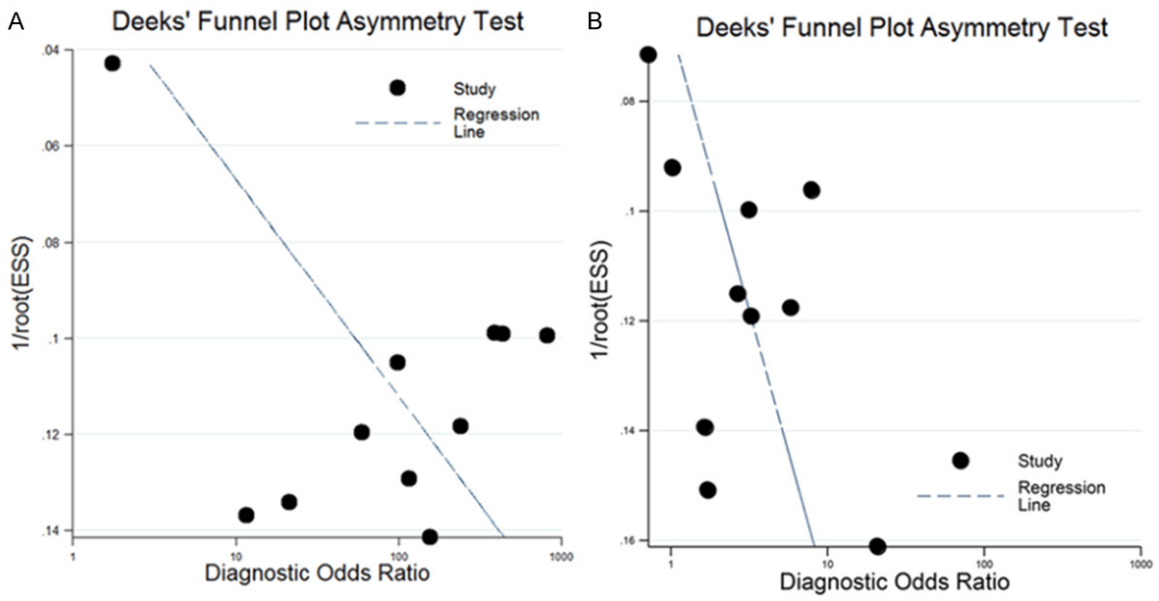

Figure 5. The Deeks' funnel plots for the analyses in both the normal population (A) and the LC patients (B).

small diagnostic value for HCC in patients with LC. The AUROC of CRP for the prediction of HCC in the normal population was 0.90 (95% CI: 0.87-0.92, **Figure 4A**), and the value in LC patients was 0.64 (95% CI: 0.59-0.68, **Figure 4B**). Results of this part signified that the CRP had a high diagnostic accuracy for HCC in the normal population, while the diagnostic accuracy of CRP for HCC in LC patients was considered low.

Furthermore, the diagnostic accuracy of CRP for HCC was also estimated with NPV and PPV as measures. In the normal population, the NPV was 0.97 (95% CI: 0.92-1.00), and PPV was 0.74 (95% CI: 0.70-0.78), suggesting in that population, the probability of a healthy subject getting a negative test result (diagnosed with no HCC) was 97%, while the probability of an individual with HCC getting a positive test result (diagnosed with HCC) was 74%. In LC patients, the NPV was 0.57 (95% CI: 0.51-0.63), and PPV was 0.58 (95% CI: 0.52-0.63), demonstrating that the probability of a LC patient without HCC getting a negative test result (diagnosed with no HCC) was 57%, while the probability of a patient with LC and HCC getting a positive test result (diagnosed with HCC) was 58%.

Publication bias

The Deeks' funnel plot was constructed to examine the publication bias, and the results were illustrated in **Figure 5A** and **5B**. There was no obvious asymmetry in the funnel plots, indicating that no significant publication bias was found in the analysis.

Discussion

In the present study, there were 7 eligible studies incorporated for the analysis. We not only assessed the diagnostic value of CRP for HCC in the normal population, the diagnostic value was also appraised in patients with LC. In the normal population, although the results of PPP and NPP, which is largely affected by the set value of PPD, showed a low diagnostic efficacy of CRP for HCC, the values of sensitivity, specificity, DOR, AUROC, NLR, NPV and PPV signified a high diagnostic accuracy of CRP for HCC. So we still believed that the CRP could be used as a biomarker for the diagnosis of HCC in the normal population, and the CRP had a high diagnostic accuracy for HCC in the normal population. In patients with LC, all the relevant data implied that the diagnostic accuracy and efficacy of CRP for HCC were extremely low, and CRP had little diagnostic value for HCC in LC patients.

HCC, the most prevalent liver cancer, is the fifth and seventh most common cancer in men and women in the world [24]. Because of the high prevalence of chronic viral hepatitis B, approximately 75% of cases occur in Asia [3]. Review studies based on the Indian and Thai popula-

tions proposed that for HCC, the HBV infection, liver cirrhosis attributed to alcohol drinking, HBV infection accompanied by aflatoxin exposure, viral infection and alcohol consumption resulting in LC with viral infection were the major risk factors [25, 26]. The early-stage HCC patients usually have no specific symptoms, and over 60% of HCC patients have tumor metastasis when first diagnosed, which partly leads to the poor prognosis of HCC [27]. In our study, we performed the current diagnostic meta-analysis and found that the CRP was a useful biomarker for the early diagnosis of HCC in the normal population.

LC, causing damage on the blood flow and organ's vital functions, is widely accepted as a prelude to HCC regardless of the underlying etiology [28, 29]. And the concept that LC is regarded as the premalignant condition is introduced to explain the etiological association between LC and HCC to some extent [30]. It is documented that the cumulative 5-year risk of developing HCC is between 5% to 30% for LC patients, which is correlated with the characteristics of patients including the age, gender, ethnicity, stage of cirrhosis and the duration of exposure to other risk factors of HCC [31]. Our results showed that the CRP was a valuable biomarker for the early diagnosis of HCC in the normal population, whereas the CRP had no obvious diagnostic value for HCC in patients with LC.

CRP, firstly discovered in 1930, is reported to be considered as a biomarker and a mediator of inflammation in clinical practice [32]. CRP has the property of responding to cytokines released from leucocytes in the cancer microenvironment, and for breast cancer patients CRP is a promising biomarker for the survival in the prognosis [33]. For HCC, a previous meta-analysis, published in 2013, was to explore the prognostic value of CRP for HCC patients and found that high serum CRP expression indicated a poor prognosis [34].

In the present study, subgroup analyses of sensitivity and specificity were conducted in both the normal population and patients with LC to detect the sources of heterogeneity. For the normal population, the publication year, sample size, detection method and guideline of the HCC diagnosis in each included study were not exactly the same, which was responsible for the large heterogeneity in sensitivity (Supplementary Figure 1A); while the large heterogeneity in specificity was attributed to the difference in sample source and guideline of the HCC diagnosis among all the incorporated studies (Supplementary Figure 1A). For patients with LC, the subgroup meta-regression analysis demonstrated that the difference in sample source and guideline of the HCC diagnosis among all the eligible studies resulted in the large heterogeneity in specificity (Supplementary Figure 1B).

Other biomarkers for the early diagnosis of HCC have been reported in previous studies. Several review studies exhibited that biomarkers such as alpha-fetoprotein, Golgi protein-73, Insulin-like Growth Factor, Dickkopf-1, heat shock proteins, glypican-3 and so on were potential indicators for the early diagnosis of HCC [27, 35, 36].

This meta-analysis has some limitations. Firstly, the sample sources of all the incorporated studies are not exactly the same, which may pose bias for our results. And with more relevant studies available, meta-analysis based on the same sample source should be made. Secondly, there is difference in the cut-off value of CRP levels among included studies, which may also cause bias in our results. Additionally, we have not taken the unpublished studies into consideration.

In summary, the current diagnostic meta-analysis suggests that CRP has a high diagnostic accuracy for HCC in the normal population, whereas the diagnostic value of CRP for HCC in LC patients is extremely low. And CRP can be regarded as a biomarker for HCC in the normal population clinically.

Disclosure of conflict of interest

None.

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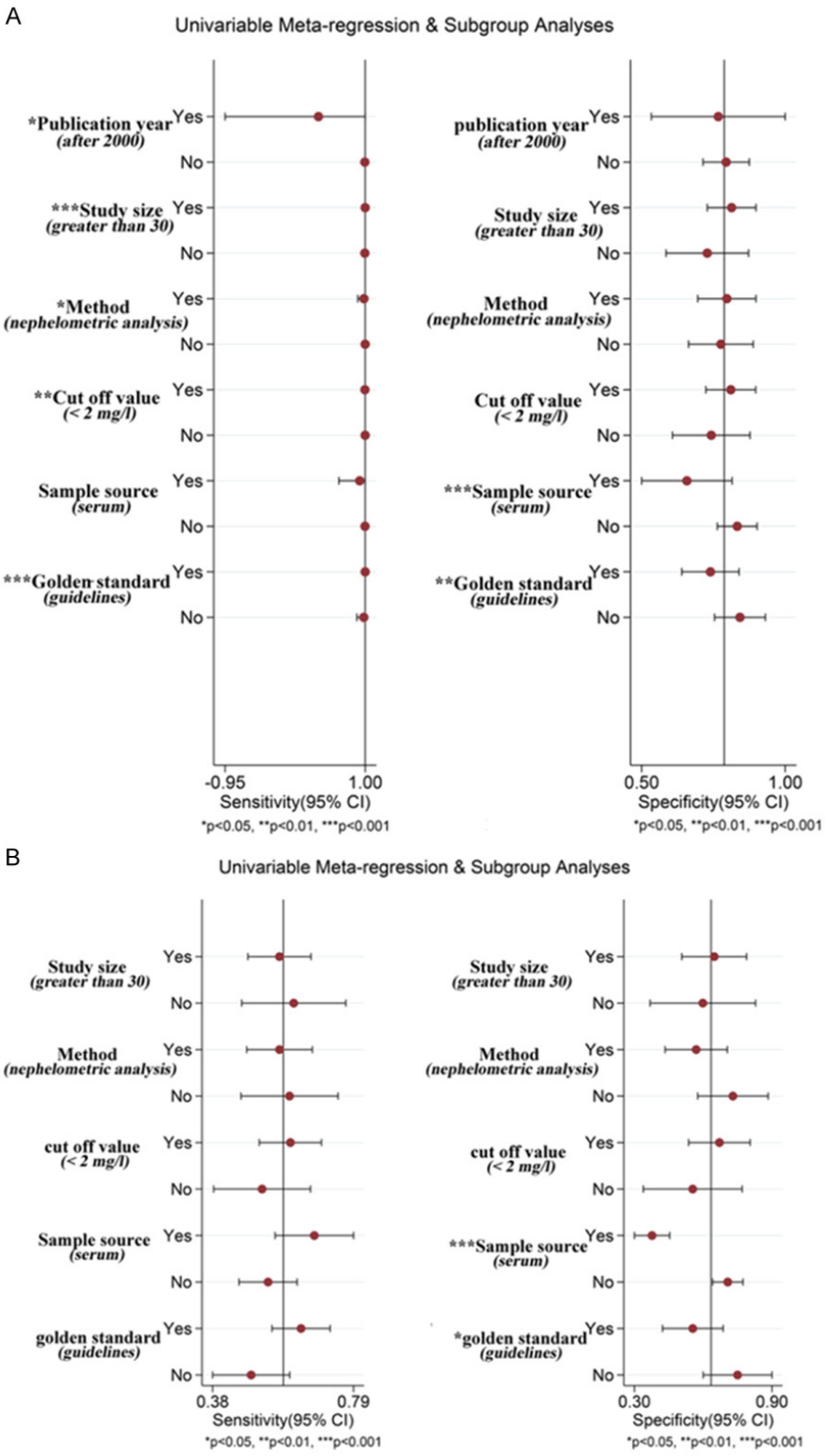

Supplementary Figure 1. The meta-regression analysis to identify possible sources of heterogeneity in sensitivity and specificity in both the normal population (A) and the LC patients (B).