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ORIGINAL ARTICLE

Diagnostic accuracy of osteopontin plus alpha-fetoprotein in the hepatocellular carcinoma: A meta-analysis

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Summary
Objective: Osteopontin (OPN) has been reported as a potential biomarker for diagnosis of hepatocellular carcinoma (HCC) in many inconsistent results. This study demonstrates a systematic meta-analysis for the evaluation on diagnostic accuracy of serum or plasma OPN and alpha-fetoprotein (AFP) alone and combined assays for HCC.
Methods: Relevant literatures were searched in PubMed up to August 2016. The quality of each study was evaluated by QUADAS-2 (quality assessment for studies of diagnostic accuracy). Statistical analysis was performed by Meta-Disc 1.4 and Stata 12.0. The random-effect models were used to estimate pooled sensitivity, specificity and other diagnostic indicators of OPN and/or AFP in HCC.
Results: A total of 14 case-control literatures (15 studies) met the inclusion criteria in this meta-analysis. The respective pooled diagnostic sensitivity and specificity were 0.71 (95% CI: 0.69—0.74) and 0.80 (95% CI: 0.78—0.82) for OPN; 0.61 (95% CI: 0.58—0.63) and 0.92 (95% CI: 0.91—0.94) for AFP; 0.82 (95% CI: 0.79—0.84) and 0.77 (95% CI: 0.74—0.80) for OPN plus AFP. Their area under the curve (AUC) values were 0.8786, 0.8718 and 0.9005, respectively.
Conclusion: Combination of OPN and AFP was better than OPN or AFP alone in diagnosis of HCC.

Abbreviations: AFP, alpha-fetoprotein; CLD, cirrhosis/chronic liver disease; HCC, Hepatocellular Carcinoma; HBV, chronic hepatitis B virus; HCV, chronic hepatitis C virus; OPN, Osteopontin; AFP-L3, lectin-bound AFP; DCP, des-γ-carboxy prothrombin; GPC-3, glypican-3; DKK-1, Dickkopf-1; GP73, Golgi protein 73.

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Introduction

Hepatocellular carcinoma (HCC) is the sixth common malignant tumor and the third cause of cancer-related death worldwide [1]. Cirrhosis, which results from chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections, alcohol abuse or accumulation of fat referred as non-alcoholic steatohepatitis, is a major cause of HCC (over 90%) [2—4]. The high-risk patients were recommended to detect the concentration of serum alpha-fetoprotein (AFP) and liver ultrasound every 6 to 12 months for HCC screening by the 2012 National Comprehensive Cancer Network (NCCN) in USA [5]. Unfortunately, most of HCC patients are still diagnosed at terminal stage. Due to the fact that most therapies are only effective at early stage [6], the prognosis of HCC patients is very poor. The 5-year survival rate is less than 5% [7]. Therefore, the early diagnosis of HCC is eagerly required.

Although AFP is widely used for HCC screening, the result is not satisfactory because of its low sensitivity, particularly in detection of early-stage HCC [8—11]. Therefore, new serum biomarkers with high accuracy are urgently needed. A number of studies have reported many serum biomarkers for HCC detection, such as lectin-bound AFP (AFP-L3), des-γ-carboxy prothrombin (DCP), glypican-3 (GPC-3), Dickkopf-1 (DKK1), and Golgi protein 73 (GP73), etc. [12—14]. Up to now, only the AFP-L3 and DCP have been used for HCC diagnosis and prognosis in Japan [15]. Nevertheless, some recent reports showed that none of them showed better performance characteristics than AFP, especially for the early stage of HCC [16—18].

In 1979, osteopontin (OPN) was first reported as a transformation-associated protein in the epithelial cells [19]. It is an arginine-glycine-aspartate (RGD)-containing acidic member of the small integrin-binding ligand N-linked glycoprotein (SIBLING) family of proteins [12]. Many studies have showed that OPN and AFP are both potential diagnostic biomarkers to distinguish HCC and cirrhosis/chronic liver disease (CLD) [20—22]. Wan et al. [23] reported the diagnostic value of serum OPN was superior to AFP. However, we found that the diagnostic value of serum/plasma OPN or AFP was similar. Moreover, there are still some disputes about whether the combination of OPN and AFP is better than OPN or AFP alone in diagnosis of HCC. The aim of this study, therefore, is to perform a systematic meta-analysis for evaluating the diagnostic accuracy of serum/plasma OPN + AFP for HCC.

Materials and methods

Literature search

Relevant literatures were searched in PubMed up to August 2016. Our search was based on the random combination of the two key words: ''liver cancer or hepatocellular carcinoma or HCC'' and ''osteopontin or OPN.'' Publication date was not limited in this meta-analysis. The references of the included studies were also browsed in order not to miss any data about the literature.

Inclusion and exclusion criteria

Eligible selection criteria in this meta-analysis were required as follows:

- the literature should be written in English;
- they should be used for evaluating the diagnostic value of serum/plasma OPN and AFP for HCC in human beings;
- HCC diagnosis should be based on histopathology or appropriate diagnostic criteria defined by accepted guidelines;
- the indicators for HCC diagnosis should be directly or indirectly extracted or calculated, which included sensitivity, specificity, the true positive (TP) value, false positive (FP) value, false negative (FN) value, true negative (TN) value.

The exclusion criteria were employed as follows:

- non-experimental studies such as case reviews, case reports and letters were excluded for they did not provide the indicators of serum/plasma OPN and AFP for diagnosis of HCC;
- the study was conducted on animal models;
- the sample type of the study was not serum or plasma.

All the literatures were selected in two steps by two independent researchers. First, literatures were browsed based on titles and abstracts, and then, the full texts of potentially qualified literatures were strictly screened for further assessment. Any discrepancies were settled by discussion.

Data extraction and quality assessment

Some key data were extracted from the eligible studies: authors, year of publication, study design, sample size, control group of patients, etiology of the HCC, country of the patients, assay type of the biomarkers, cut-off value and the indicators for HCC diagnosis. To ensure the veracity of data extraction, two researchers independently extracted them. If there was any discrepancy in the final result, the third researcher was invited to extract the data again. The quality assessment for studies of diagnostic accuracy (QUADAS-2) tool was often used to evaluate the quality of the eligible studies [24]. The answer to each items was ''yes'', ''no'' or ''unclear''.

Statistical analysis

The diagnostic accuracy for each biomarker was estimated by pooled sensitivity, pooled specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and summary receiver operator characteristic (SROC) curve. The Meta Disc 1.4 software was used to evaluate the sensitivity, specificity, PLR, NLR and SROC of OPN and AFP in diagnosis of HCC. The threshold effect was measured by Spearman correlation coefficients and P-value < 0.05 suggested the threshold effect existed. I-squared was used to estimate the presence of heterogeneity. When I-squared > 50% was found, it indicated that there was heterogeneity and the random-effect model was chosen to combine effect size. Meta-regression was performed to find the sources of heterogeneity. Stata