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Diagnosis Accuracy of Serum Glypican-3 in Patients with Hepatocellular Carcinoma: A Systematic Review with Meta-analysis

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Background and Aims. The diagnostic value of serum GPC3 in patients with hepatocellular carcinoma (HCC) remains controversial. Thus, we performed a systematic review and meta-analysis to assess the diagnostic accuracy of serum GPC3 for HCC.

Methods. A systematic search was performed for the related studies. Sensitivity, specificity and other measures regarding the accuracy of serum GPC3 and alpha-fetoprotein (AFP) in the diagnosis of HCC were pooled using random-effects models. Summary receiver operating characteristic curve (sROC) analysis was used to summarize the overall test performance.

Results. Nineteen studies were included in this meta-analysis. Pooled sensitivity, specificity and 95% confidence interval (CI) of serum GPC3 for the diagnosis of HCC were 55.2% (52.9−57.4%) and 84.2% (82.2−86.0%), respectively. When combining GPC3 with AFP, pooled sensitivity, specificity, and 95% CI were 75.7% (71.8−79.4%) and 83.3% (79.6−86.6%), respectively. The area under sROC (AUC) and 95% CI for AFP combined with GPC3 were 0.762 (0.649−0.875). For diagnosis of early HCC, pooled sensitivity and specificity of serum GPC3 were 55.1% (47.9−66.2%) and 97.0% (95.2−98.2%), respectively. The AUC of GPC3 for early HCC was 0.793 (0.668−0.917).

Conclusions. This meta-analysis indicates that serum GPC3 has a comparable accuracy to AFP for the diagnosis of HCC, and there is an elevation in the sensitivity of diagnosis when GPC3 was combined with AFP. Diagnostic accuracy of serum GPC3 for early HCC is still unsatisfactory.

Key Words: Hepatocellular carcinoma, Serum, Glypican-3, Diagnostic accuracy.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignant neoplasm and the third leading cause of cancer-related death worldwide (1). Due to lack of effective and timely diagnostic methods, patients with HCC are often correlated with a poor prognosis, which has a 5-year overall survival of $<15\%$ across all countries (2). Therefore, early diagnosis is extremely important to improve clinical outcomes. At the present time, α-fetoprotein (AFP) combined with ultrasonography or computed tomography is widely used in clinical practice for diagnosis of HCC. However, sensitivity of AFP is only 25−65% at the commonly used cutoff of 20 ng/mL. In addition, many patients with chronic hepatitis, liver cirrhosis and other liver disease or gastrointestinal cancer also have elevated serum levels of AFP (3). Therefore, novel and reliable makers to complement AFP are needed to improve the diagnostic accuracy of HCC.

Glypican-3 (GPC3) belongs to the glypican family of glycosyl-phosphatidyl-inositol anchored heparan sulfate proteoglycans and plays an important role in cellular growth, differentiation and migration (4). Many studies have reported that GPC3 was absent in normal human tissues but highly expressed in fetal liver and HCC tissues (5−8). Studies have reported the potential value of GPC3

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as a promising serum marker for the diagnosis of HCC, but a conflict remains about the diagnostic accuracy of serum GPC3 for HCC, especially when compared with AFP. In the present review, we systematically selected the studies evaluated the diagnostic accuracy of serum GPC3 for HCC, aiming to assess the diagnostic value of serum GPC3, especially when compared and combined with AFP. In addition, we also evaluated the diagnostic performance of serum GPC3 for early HCC.

Methods

Literature Search Strategy

A comprehensive electronic search in PubMed, Embase, Web of Science, and Cochrane Database of Systematic Reviews was performed by two independent investigators (Xiaobo Jia and Jiao Liu) for related articles. The latest search was updated on January 26, 2014. Keywords used in the search process were as follows: a) HCC: HCC, hepatocellular carcinoma, primary liver cancer, hepatic carcinoma; b) serum, blood; and c) GPC3: GPC3, glypican 3, glypican-3, OCI 5, MXR 7. No restriction was set on the time of the publication, study design and published status, but the publication language was set for English. In addition, we hand searched the relevant articles to make sure not miss relevant information.

Inclusion and Exclusion Criteria

The systematic review generated complete databases from published articles assessing the diagnosis value of serum GPC3 for HCC. The included articles had to meet the following criteria: a) The experimental group had a proven diagnosis of HCC; b) protein concentration of GPC3 is tested in serum samples; c) studies analyzed the diagnosis accuracy of serum GPC3.

Exclusion criteria were as follows: a) letters, reviews without original data, case reports, conference abstracts, editorials, and expert opinions were excluded; b) studies lacking control groups or experiments on animals and cells, or receiving therapy before samples were taken were excluded; c) studies that evaluated serum maker levels by messenger RNA, DNA or DNA polymorphisms were excluded; d) studies with no usable data were excluded. Different articles with the same authors were checked to avoid duplication and the most recent or the most complete study was included.

Data Extraction

Data were extracted by two independent investigators (Xiaobo Jia and Jiao Liu) from the articles that met the inclusion and exclusion criteria. The following data were extracted from the included studies: first author's name and country, year of publication, journal, study design, reference standard, number of patients, age, type of the sample, assay type of the marker, cutoff values and raw data for the assessments of sensitivity and specificity (the number of true positive, false negative, true negative and false positive results). Any disagreements in data extraction were resolved by the third independent investigator (Yingtang Gao).

Assessment of Methodological Quality

Quality assessments of included studies were performed by two independent investigators with Quality Assessment of Studies of Diagnostic Accuracy II (QUADAS-2) included in systematic reviews checklist recommended by the Cochrane Collaboration (9). Each of the signaling questions included to assist in judgments about risk of bias were labeled as ''yes'', ''no'', or ''unclear''. Each of the items that assessed risk of bias and concerns regarding applicability was labeled as ''high'', ''low'', or ''unclear''. For studies that set healthy controls, if the data of healthy controls could not be removed from the final analysis, the study was regarded as a case-control design, and the risk bias of the patient selection domain was labeled as ''high risk''. Any disagreements in quality assessment were resolved by the third independent investigator (Yingtang Gao).

Statistical Analysis

Statistical analyses were performed by Review Manager 5.2 (http://www.cochrane.org) and Meta-Disc 1.4 software (10). The recommended standard methods for meta-analyses of diagnostic tests evaluations were used according to Cochrane DTA Handbook. Cochran Q-test and I^2 value were used to estimate heterogeneity among the included studies. Spearman approach was applied to verify whether the heterogeneity could be explained by a threshold effect. Meta-regression analysis was performed to explain the observed heterogeneity. Factors such as race, age, sex, agent and methods used might be the source of heterogeneity. Pooled sensitivity, specificity, diagnostic odds ratio (DOR) and positive (PLR) and negative likelihood ratio (NLR) were obtained by a random-effects model. Forest plots were used to depict the overall diagnostic sensitivity, specificity and the corresponding 95% CI. The AUC of the sROC were used to depict the overall diagnostic performance of each marker. The bivariate model was used for data synthesis and test comparison.

Results

Characteristics of Included Studies

A flow diagram of included studies was shown in Figure 1. A total of 132 articles were found, and 30 articles were