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Invited critical review

Prognostic value of cytokeratin 19 in hepatocellular carcinoma: A meta-analysis

Da-wei Sun [a], Ying-yi Zhang [b], Xiao-dong Sun [a], Yu-guo Chen [a], Wei Qiu [a], Min Ji [a], Guo-yue Lv [a,*]

[a] Department of Hepatobiliary and Pancreatic Surgery, The First Hospital of Jilin University, Jilin University, Changchun 130021, Jilin Province, China
[b] Department of Oncology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

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ABSTRACT

Background: Although many studies have investigated the relationship between cytokeratin 19 (CK-19) and hepatocellular carcinoma (HCC), the prognostic value of CK-19 in HCC remains inconclusive.
Methods: Eligible studies were sought in PubMed, Embase, Web of Science, Cochrane Library and Wanfang databases. Pooled hazard ratios (HRs) and odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated.
Results: 17 studies with 2943 patients were included in this meta-analysis. Meta-analysis results showed that CK-19 over-expression was significantly associated with overall survival (OS) (HR = 1.60, 95% CI: 1.32–1.93, univariate analysis; HR = 2.25, 95% CI: 1.79–2.83, multivariate analysis) and disease-free survival (DFS) (HR = 1.68, 95% CI: 1.35–2.10, univariate analysis; HR = 1.97, 95% CI: 1.54–2.53, multivariate analysis). Meanwhile, CK-19 over-expression was also correlated with decreased 1-year OS rate (OR = 0.32, 95% CI: 0.21–0.50), 5-year OS rate (OR = 0.44, 95% CI: 0.14–0.87) and 1-year DFS rate (OR = 0.51, 95% CI: 0.34–0.76), but not with 5-year DFS rate (OR = 0.62, 95% CI: 0.35–1.10). These results suggested that CK-19 over-expression was significantly associated with poor survival rate and early tumor recurrence rate in HCC patients.
Conclusions: CK-19 can serve as an indicator of poor prognosis as well as a novel target for treatment in HCC.

Contents

* Corresponding author.
E-mail address: lvguoyue@sina.com (G. Lv).

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1. Introduction

According to the GLOBOCAN 2012, an estimated 782,500 new liver cancer cases and 745,500 deaths occurred worldwide during 2012, with China alone accounting for about 50% of the total number of cases and deaths [1]. Hepatocellular carcinoma (HCC), accounting for 70% to 90% of primary liver cancers [1], is the sixth most common type of cancer and the third most frequent cause of cancer-related deaths worldwide [2]. With the advancements in medicine, the treatment modalities for HCC have become diverse, including surgical resection, liver transplantation, local-regional therapies (alcoholization, radiofrequency ablation and chemoembolization) and systemic therapy (multikinase inhibitor sorafenib). Among these modalities, surgical resection serves as a predominantly and potentially curative treatment for HCC, but the recurrence rate after surgical resection is approximately 50% at 2 years and 75% at 5 years [3]. Besides, the 5-year survival rate for HCC patients after tumor resection only varies between 41% and 77% [4]. Therefore, it is essential to identify new molecular markers that can predict the prognosis or even serve as a novel target for treatment in HCC patients.

Cytokeratins (CKs) are keratin-containing intermediate filament proteins, forming the cytoskeleton of the epithelial cells. CKs are divided into two types: one is acidic type I (CK18-CK20), the other is basic or neural type II (CK7, CK8) [5]. As a typical acidic (type I) cytokeratin, cytokeratin 19 (CK-19) is the smallest keratin consisting of 399 amino acids. Besides, CK-19 lacks the carboxyterminal and non-α-helical tail domain, which is different from other CKs [6]. Nowadays, CK-19 is known as a biomarker of hepatic progenitor cells (HPCs) that are often found in HCC patients with poor prognosis [7–9]. However, the prognostic value of CK-19 expression in HCC remains inconclusive though many studies have tried to investigate the association between CK-19 expression and the prognosis of HCC patients.

Based on this background, we therefore conducted a meta-analysis to clarify the prognostic value of CK-19 expression in HCC patients by using available studies.

2. Materials and methods

2.1. Search strategy

Relative literatures were sought in PubMed, Embase, Web of Science, Cochrane Library and Wanfang databases updated to June 2015. Key words used in the search process were ("Cytokeratin 19" or "Keratin 19" or "cytokeratin 19-fragments" or "CK-19" or "CK19") and ("Hepatocellular carcinoma" or "Liver cancer" or "HCC"). The search strategy used in PubMed is the following: "(((((((keratin 19) OR K19) OR cytokeratin 19) OR CK-19) OR cytokeratin 19-fragments) OR CYFRA 21-1)) AND (((HCC) OR Liver cancer) OR Hepatocellular carcinoma)". The reference lists of identified articles were also screened to further identify potential studies.

2.2. Inclusion and exclusion criteria

All studies included in this meta-analysis should meet the following criteria: (1) cohort or case control study; (2) confirming HCC by pathological methods; (3) detecting CK-19 expression in HCC tissue rather than serum; (4) investigating the prognostic value of CK-19 expression in HCC, e.g. overall survival (OS) and/or disease-free survival (DFS); (5) providing available information for hazard ratio (HR) with 95% confidence interval (CI). Articles were excluded if they met any item of the following criteria: (1) comment letters, case reports, duplications, or review articles; (2) studies based on cell lines or animals; (3) detecting CK-19 expression in serum; and (4) without sufficient data to calculate the HR and 95% CI. There was no limitation on language or the minimum of patients in every single study. When multiple studies from the same medical center were identified, only the most complete or recent study was included.

2.3. Data extraction

Two investigators (Da-wei Sun and Ying-yi Zhang) performed the data extraction independently and discrepancies were resolved by consensus. For each included study, the following items were extracted, including the first author's name, year of publication, origin of population, study sample size, tumor stage, methods for detecting CK-19 expression, cut-off value for CK-19 expression, treatments, study endpoints, HR with corresponding 95% CI, data source and follow-up period.

When the hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were given explicitly in the articles, we used the crude ones. If these above variables were not provided directly, the total numbers of observed deaths/cancer recurrences and the numbers of samples in each group were extracted to calculate HRs [10]. If the prognosis was only plotted as a Kaplan–Meier curve in some articles, the software Engauge Digitizer version 4.1 (http://digieizer.sourceforge.net/) was applied to digitize and extract the data. Then estimation of the HR was performed as described before [10]. On the other hand, we only extracted the 1/5-year OS/DFS rate results which are directly provided in the article.

2.4. Statistical analysis

In this meta-analysis, combined HRs with corresponding 95% CIs were used to assess the prognostic impact of CK-19 expression on OS and DFS, and combined ORs with their 95% CIs were used to assess the prognostic impact of CK-19 expression on 1/5-year OS/DFS rate. An observed HR > 1 indicated a worse prognosis in patients with CK-19 over-expression and HR < 1 suggested a better prognosis. In contrast, an observed OR < 1 indicated a worse 1/5-year OS/DFS rate in patients with CK-19 over-expression, and an observed OR > 1 suggested a better survival rate.

Cochrane Q test (assessing the P value) and I^2 statistic were used to assess the heterogeneity between eligible studies [11]. If the P value was <0.1 or/and I^2 >50%, indicating the presence of heterogeneity, a random-effects model was used; otherwise, the fixed-effects model was used. All statistical calculations were performed using STATA 10. Potential publication bias was examined by Begg's and Egger's tests [12,13]. In addition, funnel plots were used to describe the distribution of included studies' results. All P values were two-sided, and $P < 0.05$ was considered statistically significant.

2.5. Quality assessment

Two investigators (Xiao-dong Sun and Yu-yuo Chen) independently assessed the quality of the potentially included studies according to the Newcastle–Ottawa Scale (NOS) criteria [14]. The NOS criteria is scored based on three aspects: (1) subject selection, based on "representativeness of the exposed cohort", "selection of the non-exposed cohort", "ascertainment of exposure" and "absence of interest outcome before study"; (2) comparability of subject, based on the study design or analysis; (3) outcome (cohort studies) or exposure (case control), based on "assessment of outcome", "long enough for follow-up time" and "adequacy of follow-up patients' number". For quality assessment, one score for each sub-item with the exception of the main item related to comparability that allows the assignment of 2 scores. Therefore, scores ranged from 0 (lowest) to 9 (highest), and studies with scores ≥6 were rated as high quality. During this process, studies with scores less than 6 were excluded in this meta-analysis and discrepancies were resolved by consensus (Table 1).