https://doi.org/10.1016/j.hpb.2018.03.019

HPB

REVIEW ARTICLE

Prognostic significance of preoperative prognostic nutritional index in hepatocellular carcinoma: a meta-analysis

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Abstract

Background: To date, epidemiological evidence of the association between preoperative prognostic nutritional index (PNI) and the prognosis of hepatocellular carcinoma (HCC) remains controversial.

Methods: A literature search was performed in the databases of PubMed, Embase, and Web of Science. Hazard ratio (HR), odds ratio (OR), and 95% confidence interval (CI) were extracted to estimate the association of preoperative PNI with overall survival (OS), disease-free survival (DFS), and postoperative recurrence of HCC, respectively. A random-effects model was used to calculate the pooled effect size.

Results: Thirteen studies with a total of 3,738 patients with HCC met inclusion criteria for this meta-analysis. It indicated that a lower level of preoperative PNI was a significant predictor of worse OS (HR = 1.82, 95%CI: 1.44-2.31) and DFS (HR = 1.49, 95% CI: 1.06-2.07). In addition, risk of postoperative recurrence was significantly higher in patients with a lower preoperative PNI (OR = 1.92, 95% CI: 1.33-2.76). Subgroup analysis based on therapeutic intent demonstrated a significant positive association between preoperative low PNI and worse OS for those patients undergoing surgical resection and for those undergoing TACE or non-surgical treatment.

Conclusion: The current meta-analysis demonstrates that preoperative PNI is a prognostic marker in HCC.

Received 24 January 2018; accepted 28 March 2018

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the second most frequent cause of death of cancer worldwide.[1] To date, surgical resection remains the main curative option for patients with HCC. However, due to the high risk of postoperative recurrence, prognosis of HCC remains unsatisfactory. Therefore, further efforts to identify the potential prognostic factors are critical to improve survival.

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Several factors have been reported to be associated with the prognosis of HCC, including tumor diameter, disease stage, alpha fetoprotein (AFP), vascular invasion, presence of cirrhosis, platelet count.[2–4] However, there is still no consensus on the best factor for predicting the outcome of patients with HCC. There is increasing evidence supporting the role of preoperative nutritional and immunological statuses as predictors of outcome in several malignant tumors including HCC.[5–7] As immunonutritional molecular biomarkers are not readily obtained in daily medical practice, several nutritional and immunological based scores derived from simple serum parameters have been proposed to serve as prognostic predictors for patients with malignancy.[8,9] Several meta-analyses further confirm that nutritional and immunological indices, such as neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and the Glasgow prognostic score, can function as prognostic factors for patients with HCC.[10,11]

The preoperative prognostic nutritional index (PNI) reflects both the nutritional and immunological conditions of tumor patient. It is calculated using the following formula: $10 \times$ ALB (g/dl) + $0.005 \times$ lymphocyte count (per mm^3).[12] A low (the optimal cut-off value ranged from 40 to 52) preoperative PNI has been shown to be independent adverse prognostic indicator for various malignancies, such as gastric cancer, colorectal cancer, cholangiocarcinoma, and HCC.[13–17] Zhao *et al.* conducted a meta-analysis of published studies to systematically review the association between the preoperative PNI and the prognosis of digestive system cancers.[18] With regard to HCC, the authors included four studies all of a small sample size. All the four studies showed significant association between preoperative PNI and HCC survival. Recently, several additional studies have reported that preoperative PNI is not significantly related to survival in HCC.[19–21] Therefore equipoise exists as to the usefulness of preoperative PNI in predicting prognosis for patients with HCC. Thus the aim of this study was to perform a meta-analysis of relevant studies regarding the association between preoperative PNI and the prognosis of HCC.

Materials and methods

Search strategy and selection criteria

Two investigators (Zhongran Man and Qing Pang) independently performed a comprehensive literature search through the databases of PubMed, Embase, and Web of Science up to November 30, 2017. The main search terms were (PNI OR prognostic nutritional index) AND (hepatocellular carcinoma OR liver cancer). Additionally, a manual search was performed of the cited the references of the relevant publications.

The eligible studies were screened on the basis of the following inclusion criteria: (a) designed as an observational study; (b) diagnosis of HCC was based on the pathological or clinical results; (c) assessed the effects of preoperative PNI in overall survival (OS), disease-free survival (DFS), or recurrence; (d) outcome measures could be extracted directly or calculated indirectly. No restrictions by stage or treatment were placed. If there were duplicated publications based on the same population, only the larger of the duplicate studies were included. Exclusion criteria included studies that: (a) only assessed the effect of preoperative PNI on the short-term complications; (b) involved individuals with metastatic liver cancer or recurrent HCC; (c) only reported postoperative PNI; (d) outcome measures could not be calculated; (e) mean or median follow-up time less than two years (or maximum less than four years) for radical therapy, or less than one year (or maximum less than two years) for non-radical therapy; (f) were reviews, conference abstracts, case reports, or correspondence.

Data abstraction

Two authors (Zhongran Man and Yong Wang) independently reviewed each eligible study and extracted the following data with a standardized data-collection protocol: first author, publication year, region of the study population, study period, method of therapy, mean or median age of patient, sample size, duration of follow-up, cut-off value of preoperative PNI, HR value (or OR, adjusted value in preference) and 95% CI. Mixed therapy was defined as various treatments and included both radical and non-radical therapy in the study. The research quality of each included study was assessed by Lei Zhou with the modified Newcastle–Ottawa Scale (NOS) scores. NOS scores of greater than or equal to 7 was defined as high quality. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline was used throughout the reporting of the current meta-analysis.

Statistical analysis

The outcomes observed included OS, DFS, and recurrence. Stata 12.0 software (StataCorp, Texas, USA) was used for the pooled analysis calculations. A random-effects model was uniformly adopted to calculate pooled effect size with the eligible studies. Between-study heterogeneity studies was assessed using the Q value and I^2 statistic values (25%, 50%, and 75% correspond to the cut-off values of low, moderate, and high degrees of heterogeneity, respectively). There was statistically substantial heterogeneity if P value less than 0.1 in Q statistic or I^2 >50%. Afterwards, according to the factors that might explain the potential source of heterogeneity, subgroup analyses and meta-regression were performed.

Studies were evaluated as to whether any single study could significantly influence the pooled effect size. A fixed-effects model to calculate the pooled effect sizes, and compared them with the results from a random-effects model. Finally, publication bias was determined by Begg's funnel plot. It was considered to be statistically significant if a P value was less than 0.05.

Results

The flow chart of the process of literature retrieval and screening is shown in Fig. 1. Agreement between the two authors was good on which studies to be included (kappa = 0.919).

Please cite this article in press as: Man Z, et al., Prognostic significance of preoperative prognostic nutritional index in hepatocellular carcinoma: a meta-analysis, HPB (2018), https://doi.org/10.1016/j.hpb.2018.03.019