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Original Research

The predictive value of integrated inflammation scores in the survival of patients with resected hepatocellular carcinoma: A Retrospective Cohort Study

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HIGHLIGHTS

- The study firstly combined general inflammation scores and HBV infection in HCC.
- Integrated inflammation scores were longitudinally measured before and after tumor resection.
- Preoperative integrated inflammation scores possess prognostic value for HCC.
- Dynamic changes of integrated inflammation scores harbor prognostic potential in HCC.
- Preoperative and dynamic changes of coCRP/ALB-PLR present consistently prognostic value for HCC.

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ABSTRACT

Background: Evidence supports the predictive potential of inflammatory marker-derived scores (inflammation scores) and hepatitis B virus (HBV) infection on prognosis of patients with hepatocellular carcinoma (HCC). However, no study has longitudinally assessed the predictive values of inflammation scores combined with hepatitis B virus status on survival of these patients. Therefore, a study was designed to evaluate the prognostic capacity of preoperative, dynamic changes in integrated scores, through a combination of general inflammation scores and HBV infection status, on HCC patients undergoing tumor resection.

Methods: The clinicopathological data of 247 patients with primary HCC who underwent liver resection were collected. Inflammation-related laboratory examinations were performed 1 week before operation, and 1 week, 1 month, 3months, and 6months after operation. The prognostic values of preoperative and dynamic changes in integrated inflammation scores were studied using the Cox regression models.

Results: Elevated preoperative integrated inflammation scores, including co-Glasgow prognostic score (coGPS), co-modified Glasgow prognostic score (comGPS), co-C reactive protein to albumin ratio (coCRP/ALB), co-prognostic index (coPI), co-neutrophil to lymphocyte ratio (coNLR), co-lymphocyte to monocyte ratio (coLMR), coNLR-PLR and coCRP/ALB-PLR, were associated with decreased overall survival (OS). Dynamic changes in coGPS, comGPS, coCRP/ALB, coPI, coPLR, coNLR, coSII, coNLR-PLR, and coCRP/ALB-PLR were independent prognostic factors of OS. coCRP/ALB-PLR was significantly associated with disease free survival.

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Conclusions: Preoperative and dynamic changes in integrated inflammation scores, particularly for coCRP/ALB-PLR were important and stable prognostic markers in HCC.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer morbidity and mortality on a global scale [1]. Despite improvements in diagnosis and treatment, the prognosis of primary HCC remains poor due to high rates of local relapses or metastasis after resection [2]. Practical prognostic biomarkers are required to provide better clinical treatment strategies.

78% of HCC cases are attributed to infection, mainly caused by hepatitis B virus (HBV) and hepatitis C virus (HCV) [3]. The infection of hepatitis virus can induce chronic inflammation, which exerts a carcinogenic effect by promoting proliferation and migration of malignant cells and inhibiting adaptive immune responses [4]. Increased emphasis has been placed on inflammation-based factors and their role in progression of HCC. Among these factors, the C-reactive protein (CRP) related indices such as the Glasgow prognostic score (GPS) [5] and modified Glasgow prognostic score (mGPS) [6] have been widely recognized as having prognostic values in patients with HCC. Furthermore, circulating blood cell related indices such as the neutrophilto lymphocyte ratio (NLR) [7], platelet to lymphocyte ratio (PLR) [8], systemic immune-inflammation index (SII) [9], and prognostic index (PI) [10], were also reported as predictive indicators for prognosis of HCC. Recently, several investigations showed that the derived neutrophil to lymphocyte ratio (dNLR) [11], lymphocyte to monocyte ratio (LMR) [12], and CRP to albumin ratio (CRP/ALB) [13] exhibited prognostic potential in cancers, including HCC. However, the inflammation scores were mainly derived from preoperative biomarkers. Several studies have explored the prognostic value of inflammation scores in HCC by analyzing postoperative changes in PLR, NLR, and SII [14–16]. Although hepatitis virus plays an important role in the induction of inflammation-related HCC, few studies correlating inflammation scores with hepatitis virus infection status have been conducted.

This study was designed to extensively investigate the prognostic values of preoperative and dynamic changes in integrated indicators using a combination of general inflammation-related scores and HBV infection in HCC patients.

2. Materials and methods

2.1. Patients

Patients with pathologically confirmed primary HCC who underwent curative liver resection in our institution from January 2007 to December 2014 were enrolled. Patients were excluded if their clinicopathological data were unavailable or if there was evidence of a history of inflammatory disease other than hepatitis. Finally, 247 patients were included in this study. The research was approved by the Institutional Review Board. Written informed consent was obtained from all participants.

2.2. Data collection

The clinical and pathological data of all patients were extracted from medical records, including age, sex, complete blood counts, alpha-fetoprotein (AFP), albumin (ALB), CRP, hepatitis B surface antigen (HBsAg), history of cirrhosis, Child-Pugh score, as well as TNM classification (UICC/AJCC Seventh Edition), tumor size, number of tumor nodules, vascular invasion, and tumor differentiation [12]. The inflammation-related laboratory examinations were performed 1 week before operation, and also 1 week, 1 month, 3months, and 6months after tumor resection. Peripheral blood was collected in tubes containing ethylenediaminetetraacetic acid (EDTA). Biochemical analyses were carried out using the Cobas 6000 modular equipment (Roche, Basel, Switzerland). Blood cell counts were detected by the Sysmex XE-2100 Automated Hematology System (Kobe, Japan).

2.3. Definitions of integrated inflammation scores

A range of integrated inflammation scores, namely coGPS, comGPS, coCRP/ALB, coPI, coPLR, coNLR, codNLR, coSII, coLMR, coNLR-PLR, and coCRP/ALB-PLR, before and after tumor resection, were used in this study. The integrated preoperative inflammation scores were constructed by combining the HBV surface antigen status and the original systematic inflammation scores (GPS, mGPS, CRP/ALB, PI, PLR, NLR, dNLR, SII, LMR, NLR-PLR, and CRP/ALB-PLR) tested at 1 week before tumor resection. For the original preoperative systematic inflammatory scores, GPS, mGPS, PI, and PLR were calculated and categorized with the widely accepted thresholds [10,17]; NLR, dNLR, SII, LMR, and CRP/ALB were dichotomized by the optimal thresholds with the highest Youden Indices (specificity + specificity − 1) derived from the receiver operating characteristic (ROC) curves. The NLR-PLR and CRP/ALB-PLR were constructed by the combination of two corresponding scores, respectively. The integrated postoperative inflammation scores were developed by the combination of hepatitis B virus surface antigen status and changes in the original systematic inflammation scores before and after tumor resection. For the postoperative original systematic inflammation scores, changes in GPS, mGPS, and PI were dichotomized as normalization vs. persistent abnormality after operation [18]. Normalization was defined as a decreased score (i.e. change from 2 to 1, 2 to 0 or 1 to 0), or a stable score of 0 before and after operation, whereas persistent abnormality meant an increased score, or a stable score of 1 or 2. The normalization group was assigned a score of 0, and the persistent abnormality group was assigned a score of 1. Changes in the continuous variables CRP/ALB, PLR, NLR, dNLR, SII, and LMR were dichotomized by the optimal cutoff points from the ROC curves. If the changes in the above indices were greater than the corresponding cutoff points, the postoperative scores of CRP/ALB, PLR, NLR, dNLR, and SII were marked as 1 point, and that of LMR was assigned as 0 points. Otherwise, the postoperative scores of CRP/ALB, PLR, NLR, dNLR, and SII were marked as 0 points, and that of LMR was assigned a score of 1. The postoperative scores of NLR-PLR and CRP/ALB-PLR were constructed by the summation of the corresponding single scores. Furthermore, all the original systemic inflammation scores were combined with HBsAg to generate the co-inflammation scores by assigning one additional point to the original systemic inflammation score for patients with positive HBV surface antigen. The construction of the original inflammation scores was presented in Supplemental Tables 1 and 2. The definition of the integrated inflammation scores was summarized in