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Prognostic value of the platelet to lymphocyte ratio change in liver cancer

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ABSTRACT

Background: There is limited evidence concerning the postoperative platelet to lymphocyte ratio change (ΔPLR) in relation to the prognosis of hepatocellular carcinoma (HCC). This study was designed to evaluate the prognostic value of ΔPLR in patients with hepatitis B virus (HBV)-related small HCC who underwent liver resection.

Materials and methods: We retrospectively reviewed 219 patients with HBV-related small HCC who underwent liver resection between February 2007 and April 2013. The patients were divided into two groups as follows: group A (ΔPLR $\geq$2.875, $n = 94$) and group B (ΔPLR $<$2.875, $n = 125$), according to receiver operating characteristic analysis. Demographic, clinical, and follow-up data were analyzed, and multivariate analysis was used to identify prognostic factors.

Results: The 1-, 3-, and 5-y overall survival (OS) rates were 90.5%, 72.3%, and 42.1%, respectively, in group A and 98.1%, 89.5%, and 86.4%, respectively, in group B ($P < 0.001$). Correspondingly, the 1-, 3-, and 5-y recurrence-free survival (RFS) rates were 57.5%, 36.1%, and 22.8%, respectively, in group A and 84.3%, 62.4%, and 55.4%, respectively, in group B ($P < 0.001$). Multivariate analysis showed that ΔPLR was an independent prognostic factor for both OS ($P < 0.001$, hazard ratio = 5.452, 95% confidence interval 2.592–11.467) and RFS ($P < 0.001$, hazard ratio = 2.191, 95% confidence interval 1.4611–3.288).

Conclusions: ΔPLR was an independent prognostic factor for OS and RFS in patients with HBV-related small HCC who underwent liver resection.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers and the third leading cause of cancer death worldwide [1,2]. The commonly known etiologies of HCC cover chronic infections with hepatitis B or C virus (HBV or HCV), aflatoxin B exposure, alcohol consumption, and drug abuse. Among them, chronic infection with HBV is the main etiologic factor for most HCC cases in China [3]. Although many therapeutic options have been developed, liver resection remains one of the standard treatment methods for small HCC patients who meet the Milan criteria [4,5]. Despite the advances in surgical techniques and perioperative management, recurrence rates remain high and survival rates remain poor in HCC patients [6]. Prognostic factors mainly comprise tumor morphology, tumor histopathology, and the general condition of the patient. A variety of prognostic factors can affect survival after liver resection in HCC patients, including tumor size and number,

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vascular invasion, satellite lesions, positive margins, histologic grade, hepatic functional reserve, age, and so forth [7–11].

The pathogenesis of HCC is mainly based on inflammation, as 70%–90% of HCC develops on a background of chronic liver inflammation [12]. Recently, there is increasing evidence correlating the presence of systemic inflammation with poor outcomes in several human cancers, including HCC [13–16]. The systemic inflammatory response is thought to cause an aberrant release of proinflammatory cytokines and inflammatory mediators, predisposing the tumor to proliferate and metastasize through the promotion of angiogenesis, damage to DNA, and inhibition of apoptosis [17–19]. Generally, various markers such as C-reactive protein levels, absolute blood neutrophil or lymphocyte counts, the neutrophil to lymphocyte ratio, and the platelet to lymphocyte ratio (PLR) can be used to evaluate systemic inflammation [20–22]. The PLR has been shown to correlate with the recurrence and survival rates of patients with HCC [22,23]. However, these studies only focused on the preoperative PLR, whereas the postoperative PLR change (ΔPLR), which represents the dynamic change of the PLR between the preoperative to postoperative periods, has been rarely studied in patients with HCC who underwent liver resection.

This study was designed to evaluate the prognostic value of ΔPLR in patients with HBV-related small HCC who underwent liver resection.

2. Material and methods

2.1. Patients

The study was approved by the Ethics Committee of West China Hospital, Sichuan University. Between February 2007 and April 2013, 346 newly diagnosed small HCC patients meeting Milan criteria underwent liver resection in the Department of Liver Surgery and Liver Transplantation Center of West China Hospital, Sichuan University. All medical records were prospectively collected. The preoperative diagnosis of small HCC meeting Milan criteria was made when either two types of imaging examination showed the typical features of HCC or positive findings were found on one imaging examination together with an alpha fetoprotein (AFP) level >400 ng/mL. Finally, the diagnosis of HCC was confirmed by postoperative histopathologic examination. We selected samples that were HBV positive but HCV negative according to serology tests and infection histories. The following data were retrieved from our prospectively maintained database: oncological data, including the size and number of lesions, presence of microvascular invasion, and AFP levels; hematological tests, including blood cell counts and differentiation assessments; liver function tests; HBV markers; imaging examinations, including ultrasound, computed tomography, or magnetic resonance imaging; and recurrence and survival data.

Because patients with large HCC were recommended to receive transcatheter arterial chemoembolization (TACE) according to Barcelona Clinic Liver Cancer staging system and chronic infection with HBV is the main etiologic factor for most HCC cases in China, in the present study, our inclusion criteria were as follows: (1) primary small HCC (solitary tumor <5 cm in diameter or ≤3 nodules that were ≤3 cm in diameter); (2) receiving liver resection as the initial treatment; (3) HBV positive but HCV negative; and (4) appropriate liver reserve function (Child–Pugh grade A) and renal function (serum creatinine, 124 mmol/L).

Exclusion criteria included the following: (1) recurrent HCC; (2) loss to follow up within 3 mo after liver resection; (3) clinical symptoms or signs of sepsis or infection at the time of blood sampling for PLR; (4) splenectomy and hepatectomy at the same time; and (5) poor data integrity.

Based on these criteria, a total of 127 patients were excluded from this study. Among them, 20 had recurrence after curative resection, 11 had Child–Pugh grade B, 12 had a history of therapy, including radiofrequency ablation or TACE, before curative resection, 9 were HBV negative, 17 had infections, 18 were lost to follow up within 3 mo after the liver resection, 16 underwent splenectomy and hepatectomy at the same time, and 25 had data of poor integrity. Finally, 219 patients were included and evaluated in the present study.

2.2. Definition of PLR

All preoperative blood cell counts and differential counts were taken 2 d before the operation. The PLR was calculated from the differential count by dividing the absolute platelet count by the absolute lymphocyte count. Some patients may choose to receive traditional Chinese medicine therapy and/or restoratives 1-mo later after operation, which we do not recommend or forbid. We believe traditional Chinese medicine therapy or restoratives may have an effect on PLR. Patients were regularly followed up at the outpatient department at the first month after operation; traditional Chinese medicine therapy would not be chosen in this period because liver function did not get back to normal shortly. So postoperative PLR was obtained at the first follow-up visit, 1 mo after the operation. ΔPLR was calculated by subtracting the preoperative PLR from the postoperative PLR.

2.3. Follow-up visits

All the 219 patients were regularly followed up at the first, third, and sixth months in the first half year after the operation, every 3 mo throughout the following 3 y, and every 6 mo in subsequent years.

Physical examination, blood cell and differential counts, AFP levels, liver function tests, HBV markers and HBV-DNA levels (if the patient was diagnosed with HBV infection), and imaging examinations in specific situations were included in the follow-up examinations. Tumor recurrence was determined from imaging findings. Overall survival (OS) time was defined as the interval between the operation and death or the last follow up. Recurrence-free survival (RFS) was defined as the time interval between the operation and the first incidence of detectable recurrence. The last follow-up date was the end of April 2014.

2.4. Statistical analysis

Statistical analysis was conducted with SPSS software, version 21.0 (SPSS Company, Chicago, IL). Categorical data