



Original Research

Prognostic value of alkaline phosphatase, gamma-glutamyl transpeptidase and lactate dehydrogenase in hepatocellular carcinoma patients treated with liver resection



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HIGHLIGHTS

- The prognostic value of alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT) and lactate dehydrogenase (LDH) have not been explored deeply and widely in surgically treated hepatocellular carcinoma (HCC) patients just like AFP.
- Our study was the first one to explore the prognosis value of ALP, GGT and LDH simultaneously in such patients and found that preoperative ALP, GGT and LDH could predict prognosis.
- We found that preoperative ALP, GGT and LDH could predict prognosis in such patients.

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ABSTRACT

Background: Alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT) and lactate dehydrogenase (LDH) are routinely tested before surgery and are easily obtained. They are also the most widely used tumor markers, which have a certain reference value in the diagnosis of hepatocellular carcinoma (HCC). The prognostic values of ALP, GGT and LDH have not been explored deeply and few studies have investigated the prognosis value of them in surgically treated HCC patients. Our study was performed to verify the prognostic significance of preoperative ALP, GGT and LDH in hepatitis B virus (HBV)-related HCC patients receiving curative hepatectomy.

Materials and methods: 469 pathologically confirmed HCC patients who received curative hepatectomy were retrospectively analyzed. Significant clinicopathological factors were collected and analyzed. Independent prognostic factors were identified by the multivariate analysis. Overall survival (OS) and recurrence-free survival (RFS) curves were analyzed and compared between different groups.

Results: Patients with low level of ALP, GGT and LDH have favorable OS and RFS, even in cirrhosis subgroup. ALP, GGT and LDH were also closely related to some important clinicopathological parameters. GGT and LDH were significant independent prognostic factors of both OS and RFS, while ALP was just a significant independent prognostic factor of OS, rather than RFS.

Conclusions: Preoperative ALP, GGT and LDH could predict prognosis in HBV-related HCC patients who received curative liver resection.

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1. Introduction

Hepatocellular carcinoma (HCC), the fifth most common malignancy with an increasing incidence, represents the commonest primary cancer of the liver [1]. The most important cause of HCC is

hepatitis B virus (HBV) in China and patients with HBV-related HCC usually have hepatic parenchymatous lesion and cirrhosis. At present, the most commonly used radical therapeutic options are liver resection and liver transplantation [2]. Although liver transplantation has become much more sophisticated in recently years, its application is limited in China due to short of donor and stiff price. Thus, hepatectomy is the optimal curative therapeutic option and is still widely used in developing countries. However, the postsurgical cumulative recurrence rate in HBV-related HCC

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patients is high and the long-term outcome of HCC patients is still dismal. Although prognostic factors have been widely investigated, their clinical application cannot be realized in a short time [3]. Thus, to explore simple and dependable predictors is essential to identify patients with poor prognosis.

Some serum liver enzymes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), hydroxybutyrate dehydrogenase (HBD) and α -fetoprotein (AFP), are routinely tested before surgery and are easily obtained. Of these, ALP, GGT and LDH are not widely used like AFP, which have a certain reference value in the diagnosis of HCC [4–10]. ALP, a hydrolase enzyme, can predict tumor patients' prognosis and is mainly found in the liver, bile duct, bone and so on [10]; Besides catalyzing the transpeptidation and hydrolysis of the glutamyl group of glutathione, GGT also participates in the biotransformation, nucleic acid metabolism and tumorigenesis [11]; LDH, a metabolic enzyme that in relation to anaerobic glycolysis, can also affect tumor initiation and progression [14]. Thus, in addition to being simply and easily obtained from preoperative routine tests, ALP, GGT and LDH also may predict prognosis in HCC patients [1,9–16]. Moreover, ALP is one of fundamental elements in the Chinese University Prognostic Index (CUPI) HCC staging system [17]. However, most of previous studies [1,9–16] focused on HCC patients who received non-surgical treatments, such as radio-frequency ablation (RFA), sorafenib, transcatheter arterial chemoembolization (TACE), etc. To the best of our knowledge, few studies have investigated the prognosis value of the three liver enzymes in surgically treated HCC patients. To date, the prognostic value of ALP, GGT and LDH have not been explored deeply and widely in such patients just like AFP.

Thus, our study was performed to verify the prognostic significance of ALP, GGT and LDH in surgically treated HBV-related HCC patients. We also investigated the relationship between clinicopathological parameters and the three liver enzymes in such patients.

2. Materials and methods

2.1. Patients selection and data collection

During June 2007 and March 2013, 655 pathologically confirmed HCC patients who received curative hepatectomy at West China Hospital of Sichuan University were enrolled. Our inclusion criteria were as follows: (1) resectable primary HCC confirmed by pathological diagnosis; (2) positive for HBV and negative for hepatitis C virus (HCV) infection; (3) underwent hepatectomy as the initial therapy; (4) Child-Pugh grade A or B; (5) generally in good condition. Conversely, exclusion criteria were as follows: (1) HCC combined with other tumors; (2) negative for both HBV and HCV; (3) recurrent HCC; (4) lost to follow-up; (7) incomplete data. Thus, 186 were excluded. Finally, altogether 469 HBV-related HCC patients who received curative liver resection were included in our retrospective study.

Preoperative patients' demographics and clinical data, including age, gender, concomitant diseases, complete blood count, liver function test, ALP, GGT, LDH, AFP, imaging data, HBV and HCV markers were collected. Surgical details and postoperative pathological parameters were also recorded. All preoperative examinations, such as detailed medical history, physical examination, routine laboratory and imaging examinations were done two days before the surgery. All patients had signed the informed consent. We followed close to the Helsinki Declaration and our study was approved by the Ethics Committee of West China Hospital, Sichuan University.

2.2. Follow-up

All the patients were regularly followed at the first, third and sixth month after the surgery, every three months for the first three years, every six months thereafter. Basic physical examination, complete blood count, liver function test, AFP level, HBV markers, and abdominal ultrasound examination were performed at each visit. Imaging examinations, including abdominal enhanced computed tomography scan, magnetic resonance imaging, and hepatic artery angiography examination were selectively carried out depending on the actual situations when recurrence was suspected. Patients with confirmed recurrence were further treated with individualized projects (Table 1). The overall survival (OS) was defined as the interval from the date of surgery to the date of death or the last follow-up. The recurrence-free survival (RFS) was defined as the interval from the date of surgery to the date of confirmed HCC recurrence or the last follow-up. The last follow-up date was 26 February 2016.

2.3. Statistical analysis

Continuous data were presented as the median and the range, or mean \pm standard deviation (SD); Differences between the two groups were compared by the Mann-Whitney *U* test or the independent sample *t*-test, respectively. Categorical data were compared by the Pearson's chi-square analysis or the Fisher exact test. OS and RFS curves were analyzed using the Kaplan-Meier method and compared by the log-rank test. The best cut-off values of ALP, GGT and LDH were selected by the receiver operating characteristic (ROC) curve. Univariate and multivariate analysis of prognostic factors for OS and RFS were performed using the Cox proportional hazards model. A value of $p < 0.05$ was considered statistically significant (derived from two-tailed test). Statistical analyses were performed with SPSS software (version 17.0; SPSS Inc., Chicago, IL, United States).

3. Results

3.1. Patient baseline characteristics

A total of 469 HBV-related HCC patients who underwent curative liver resection were included in our retrospective analysis. During the follow-up period, 261 (55.7%) patients developed recurrence and 159 (33.9%) patients died during follow-up. The median duration of follow-up was 42 months (range: 2–99 months). The 1-, 3- and 5-year OS rates for all patients included in our study were 93.5%, 77% and 61.1%, respectively, and the 1-, 3- and 5-year RFS rates for all cases were 71.3%, 47.1% and 40.4%, respectively. Details of patient baseline characteristics are shown in Table 1.

3.2. Determination of the best cut-off value

The ROC curve analysis revealed a best cut-off of 136.5 IU/L for ALP (Fig. 1A), 81.5 IU/L for GGT (Fig. 1B) and 203.5 IU/L for LDH (Fig. 1C). Therefore, all 469 patients were divided into low ALP group ($ALP \leq 136.5$ IU/L, $n = 293$) and high ALP group ($ALP > 136.5$ IU/L, $n = 176$), or low GGT group ($GGT \leq 81.5$ IU/L, $n = 251$) and high GGT group ($GGT > 81.5$ IU/L, $n = 218$), or low LDH group ($LDH \leq 203.5$ IU/L, $n = 280$) and high LDH group ($LDH > 203.5$ IU/L, $n = 189$), respectively.

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