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Retrospective Study

Prognostic factors for disease-free survival in postoperative patients with hepatocellular carcinoma and construction of a nomogram model

HCC DFS and nomogram construction

Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is the most common type of liver cancer and has a high invasion and metastasis chance along with poor prognosis.

AIM

The goal of this study was to investigate the independent predictive markers for disease-free survival (DFS) in patients with HCC and establish a trustworthy nomogram.

METHODS

In this study, 445 patients who were hospitalized to The First Affiliated Hospital of Anhui Medical College between December 2009 and December 2014 were retrospectively examined. The survival curve was plotted using the Kaplan-Meier method and tested using the log-rank. To identify the prognostic variables, multivariate Cox regression analysis were carried out. To forecast the DFS in patients with HCC, a nomogram was created. C-indices and receiver operator characteristic (ROC) curves became used to evaluate the nomogram's performance. Decision curve analysis (DCA) was used to evaluate the clinical application value of the nomogram.

RESULTS

Longer DFS was observed in patients with the following characteristics: elderly, I-II stage, and no history of hepatitis B. The calibration curve showed that this nomogram was reliable and had a higher AUC value than the TNM stage. Moreover, the DCA curve revealed that the nomogram had good clinical applicability in predicting the 3- and 5-year DFS in HCC patients after surgery.

CONCLUSION

¹ Age, TNM stage, and history of hepatitis B infection were independent factors for HCC patients DFS, and a novel nomogram for HCC patients DFS was created and validated.

Key Words: hepatocellular carcinoma; DFS; prognosis; nomogram

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Core Tip: ² 1. Age, TNM stage, and hepatitis B history were shown to be independent predictors of DFS in individuals with HCC. Additionally, we developed and validated a brand-new ⁵ nomogram for estimating 3- and 5-year DFS in HCC patients. The calibration curves of the nomogram were reliable, and the new nomogram had a higher AUC value than the TNM stage. 2. We believe that our findings will be of interest to the readers of the *World Journal of Clinical Cases*.

INTRODUCTION

Many individuals with hepatocellular carcinoma (HCC) pass away each year all around the world, making it the fourth most prevalent cancer-related cause of death^[1,2]. Considerable improvements in examination and treatment methods have increased the 5-year survival rate of patients with early stage liver cancer to 70% after radical resection^[3]. However, the majority of HCC patients reach the middle or late stages when they are treated, and their 5-year survival rate is around 15%^[4].

The pathogenesis of HCC is controversial and complicated^[5], and viral hepatitis has been linked to liver cancer incidence^[6]. ¹ Radical hepatectomy is the first route for HCC patients, and chemotherapy is administered as required according to the postoperative pathological results^[7]. Clinical investigations have indicated that age, differentiation degree, HBsAg level, tumor size, AFP level, TNM stage, tumor number, GGT level, and other factors are important prognostic factors for HCC^[8-11]. According to Zheng et al.^[12],

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who noted that PLR and NLR represent new prognostic markers for HCC outcomes. The microvascular invasion, quantity of cancer nodules, margin positive and Child-Pugh status were discovered by Goh et al.^[13] to be independent predictors of overall survival. Furthermore, research has demonstrated that GGT and AST/ALT levels are prognostic factors for the OS of HCC patients^[14]. However, there haven't been many research done on DFS indicators in HCC patients. Therefore, this study aimed to identify clinical indicators that determine DFS in HCC patients.

MATERIALS AND METHODS

Patients

The First Affiliated Hospital of the Anhui Medical University treated 445 HCC patients with curative hepatectomy as part of this study's retrospective evaluation. The following were the inclusion requirements: 1) Histopathological confirmation of HCC in patients; 2) R0 resection of liver cancer; 3) availability of comprehensive clinical information; 4) follow-up data were available; and 5) absence of any further therapies, such as chemoradiotherapy and interventional therapy, ahead of surgery. The above were the exclusion requirements: 1) postoperative pathology revealed cholangiocarcinoma or metastatic liver cancer; 2) inadequate data were provided; 3) Child-Pugh grade C; 4) There was an inability to keep up with follow-up appointments. Based on the threshold for each indicator in the blood, patients were split into high and low groups. And the median NLR and PLR were used as cut-off values. All patients submitted written informed permission for this study, which was authorized by the First Affiliated Hospital of Anhui Medical university's ethics committee.

Follow-up and treatment

Calls and outpatient visits were used to gather patient follow-up data. The subsequent examinations were given at fix interval (follow-up began one week after discharge and occurred every 4 month after the one year). According to the inclusion criteria, we included a total of

445 postoperative HCC patients and excluded 14 patients who were lost to follow-up and 73 who were excluded. Finally, a cohort of 358 patients was analyzed.

15 Statistical analysis

7 SPSS software(version 19.0) was used to statistically evaluate all patients data. Investigating 14 categorical variables was done using the Fisher's exact test or the chi-squared test. DFS was analyzed using the Kaplan-Meier, and verified by log-rank. An elevated risk of mortality was indicated by HR >1.0. The R Project(3.5.5) was used to created nomogram.

RESULTS

Clinical characteristics of patients

344 HCC patients were enrolled in this research(Table 1). According to the age of 70, the patients were split into two groups: elderly, young. Patients with history of hepatitis B accounted for 25% of the total. In instance, 256 individuals had cirrhosis, while the majority of the 88 patients who did not have cirrhosis had abnormalities in their liver function, such fatty liver disease. The median NLR and PLR were respectively 2.19 and 97.67. The average follow-up period was 52 months. HCC patients had 1-, 3-, and 5-year DFS rates of 73.26%, 59.30%, and 44.48%, respectively.

Prognostic factors for DFS

Tables 2 and 3 present the univariate and multivariate regression analyses, respectively. Age, past hepatitis B infection history, and TNM stage were independent predictors of HCC patients DFS. The HR was 0.543 for patients under the age of 70 and 0.654 among those who haven't had hepatitis B.

DFS results according to the different age groups, TNM stage, and hepatitis B history

Young patients may have a higher recurrence risk or perhaps death within 6 months after surgery since the young group showed the most significant downhill trend in the first 6 months (Figure 1). The DFS outcomes for patients who had different TNM stages

and a history of hepatitis B are shown in Figures 2 and 3, respectively. As a result, the median DFS for stages III–IV was 12 months, it was 68 months for stages I–II.

To further explore the relationship of TNM stage and age, DFS results are displayed in Figure 4A–B. Figure 4A shows that, in stages I–II, patients who were older than 70 had a longer DFS than those who were younger than 70. However, no discernible alterations between phases III–IV were seen. In addition, we uncovered an association between age and various TNM stages (Figure 5A–B). According to the findings, individuals in stages I and II who were under 70 had a better prognosis. The relationship between the TNM stage and a history of hepatitis B was also examined (Figure 6A–B), but the difference was not statistically significant.

Development and validation of the prediction model

Age, TNM stage, and previous hepatitis B infection were utilised to create a nomogram (Figure 7). The C-index was calculated as 0.713 (95% CI: 0.660 – 0.767) using 1000 bootstrap resampling methods, which indicated that this nomogram had a strong level of predictability. The actual survival curve of the nomogram matched closely, based on calibration curves for the 3- and 5-year DFS (Figure 8A–B). We compared the nomogram's ROC against that of the TNM stage to further assess the performance of the model and discovered that the nomogram's AUC was greater than that of the TNM stage (Figure 9). The nomogram enhanced the capacity to predict DFS in patients with HCC throughout a large range of risk threshold probabilities, according to the 3- and 5-year DCA curves (Figure 10A–B).

DISCUSSION

HCC have a high incidence and fatality rate, and increasing attention has been focused on HCC prognostic factors^[15,16].

Recently, nomograms have been widely used as diagnostic and prognostic tools for various cancers^[17]. We attempted to develop a prognostic nomogram that combines most of the important serum markers and clinicopathological characteristics. Many studies have shown that CA-199 and AFP are related to OS of patients with HCC^[18,19], and the

NLR and PLR levels found in the current investigation were similar with earlier results^[20,21]. However, we discovered that haematological markers like NLR, and AFP were not predictive of DFS.

Based on earlier published studies, the elderly group of HCC patients in our research was classified as those who were older than 70^[22,23]. We examined the DFS of patients aged ≥ 70 and < 70 in stages I-II and III-IV of TNM to further understand how age affects DFS in patients with various TNM stages. Sakakibara *et al.*^[24] used 40 years as the cutoff between young and old patients, and found that the 3-year OS of stage IIB patients in the young group was considerably lower than that of the old group, which is comparable to our results. Similar findings were made by Zhao *et al.*^[25], who retrospectively selected 995 CRC patients aged 35 years and discovered that they had a poorer prognosis. Faber *et al.*^[26], on the other hand, retrospectively examined 141 individuals and reported that those under the age of 35 often had a considerably better prognosis. Regardless of age, we discovered that stages I and II had a much favorable survival than stages III and IV, which is in line with Lu Wu *et al.*^[27] results.

HBV, which affects 30% of people globally and is particularly widespread in China^[28], is the main culprit of HCC. As according Li *et al.*^[29], preoperative HBV DNA levels over 2000 IU/mL were associated with a poorer prognosis and were strongly correlated with OS and DFS. In terms of the pathogenesis of HCC brought on by HBV, the integration of HBV DNA into the host genome triggered changes in gene protrusions, leading to the occurrence of liver cancer. In contrast, HBV-associated proteins, such as HBsAg, HBcAg, and HBx, can mediate oxidative stress in cells^[30]. Hence, for patients with HCC, more attention should be paid to a history of HBV in clinical practice.

This study had certain limitations, including an insufficient number of elderly patients and inclusion of only a single center. A limited relationship is observed between hepatitis B and HCC in Western countries; therefore, this study failed to collect clinical information from more patients (including foreign patients) through SEER and other databases to develop a more comprehensive and convincing nomogram model.

CONCLUSION

Age, TNM stage, and a history of hepatitis B infection were independent predictive variables in HCC patients DFS. We constructed and validated an accurate and reliable nomogram that has great reference value for evaluating the prognosis of patients and guiding treatment.

ARTICLE HIGHLIGHTS

Research background

The most prevalent form of liver cancer is hepatocellular carcinoma (HCC), which also has a poor prognosis and a serious risk of invasion and metastasis.

Research motivation

The objective of this study was to develop a valid nomogram and explore the independent prognostic markers for DFS in HCC patients.

Research objectives

The First Affiliated Hospital of Anhui Medical University treated 445 HCC patients with curative hepatectomy.

Research methods

Survival curve was plotted using the Kaplan–Meier method and tested using the log-rank. To identify the prognostic variables, multivariate Cox regression analysis were carried out. To forecast the DFS in patients with HCC, a nomogram was created. C-indexes and receiver operator characteristic (ROC) curves became used to evaluate the nomogram's performance. Decision curve analysis (DCA) was used to evaluate the clinical application value of the nomogram.

Research results

A longer DFS period was observed in patients with the following characteristics: elderly, I-II stage, and no history of hepatitis B. The calibration curve showed that this nomogram was reliable and had a higher AUC value than the TNM stage. Moreover, the DCA curve revealed that the nomogram had good clinical applicability in predicting 3- and 5-year DFS in HCC patients after surgery.

Research conclusions

We created and tested a brand-new nomogram to forecast DFS in HCC patients, and it is accurate and reliable.

Research perspectives

We constructed and validated an accurate and reliable nomogram that has great reference value for evaluating the prognosis of patients and guiding treatment.

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