Prognostic Factors of Disease-Free Survival in Postoperative Patients with Hepatocellular Carcinoma

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Research Article

Keywords: hepatocellular carcinoma, DFS, prognosis, nomogram

Posted Date: January 12th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-56060/v2>

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Abstract

Background

Hepatocellular carcinoma (HCC) is a primary malignancy of the hepatocyte with high risk of invasion, metastasis and poor prognosis, which leads to a high mortality rate in recent years. This study aims to investigate the independent prognosis factors of DFS(disease free survival) in primary hepatocellular carcinoma patients after radical hepatectomy and construct a nomogram prediction model.

Methods

This study retrospectively analyzed 358 patients admitted to the 1st Affiliated Hospital of Anhui Medical College from December 2009 to December 2014. Categorical variables were analyzed by chi-square test. The survival curve was plotted by kaplan-meier method and tested by log-rank method. Univariate and multivariate cox regression analyses were performed to determine the prognostic factors. A nomogram was constructed to predict the 3-year and 5-year DFS of HCC patients based on these factors. The performance of the nomogram was assessed with the C-indexes and calibration plot diagrams.

Results

Among the 344 patients with HCC, 298 cases (86.63%) are young patients (<70years), and 46 cases (13.37%) were elderly patients (≥ 70 years). The univariate and multivariate analyses showed that age, TNM stage, history of hepatitis B were the independent factors for DFS. The Kaplan-Meier curves indicated that elderly patients, TNM I-II stage and no history of hepatitis B had longer DFS. The C-index of the nomogram was 0.604(95%CI:0.561-0.647), and the Calibration curve showed that the actual DFS curve of the nomogram fits the predicted DFS curve.

Conclusions

Our findings suggested that age, TNM stage, history of hepatitis B were independent factors for predicting DFS of HCC patients. Patients older than 70 years had a better prognosis than young patients. Patients with early TNM stage and no history of hepatitis B had longer DFS. We constructed and validated a new nomogram for predicting DFS in HCC patients.

Introduction

On the basis of global cancer statistics, primary liver cancer ranks fifth among all types of cancer, and ranks fourth in cancer-related death worldwide. According to recent WHO data, as many as 781,631 people die of liver cancer every year in the world ^{1,2}.

With helical computed tomography (CT), magnetic resonance imaging (MRI) examination and the level of treatment methods have been greatly improved, patients with early liver cancer underwent radical surgical resection, the 5-year survival rate can reach 70%³. However, most liver cancer patients who come to the hospital due to dull pain in the upper abdomen or other symptoms are already in the middle and late stages of the disease, the 5-year survival rate is less than 15%⁴. Therefore, it is urgent to study the prognostic factors of HCC.

The factors and pathogenesis of HCC are controversial comprising of multiple genetic, epigenetic alterations, chromosomal aberrations and gene mutations⁵. It has been reported that the occurrence of liver cancer is related to viral hepatitis, especially hepatitis B⁶. At present, radical hepatectomy is the first choice for the treatment of HCC patients. After the operation, the necessary and appropriate chemotherapy regimen should be given⁷.

Up to date, many clinical studies have been performed to identify the corresponding markers that can accurately predict the prognosis of HCC. Unfortunately, no clear prognostic factors for HCC patients have been identified. A great deal of clinical investigations indicated that factors affecting overall survival of HCC patients include age, HBsAg, alcohol consumption history, TNM stage, differentiation degree, tumor number, tumor size, AFP, GGT, NLR and so on⁸⁻¹¹.

Jun Zheng et al¹² suggested NLR and PLR, which were SIR (Systemic inflammatory response) indexes, were new prognostic markers for predicting the prognosis of HCC. Increased NLR or PLR was found to be an independent predictor of higher recurrence and poor survival in HCC patients receiving curative or palliative therapy. Brian K. P. Goh et al.¹³ showed number of cancer nodules (more than three nodules), Child-Pugh status, margin positivity and presence of microvascular invasion, but not tumor size, were independent negative predictors of OS (overall survival). In addition, in the retrospective study of 414 patients with liver cancer over a period of 7 years, our team found that serum gamma-glutamyltransferase levels and AST/ALT play an important role in the prediction of OS in patients with primary hepatic carcinoma. Low GGT group and low AST/ALT group have a better prognosis¹⁴. Our group has studied the prognostic factors of OS in patients with liver cancer, but no further study has been conducted on DFS in liver cancer patients, especially hepatocellular carcinoma patients.

The purpose of this study was to explore the clinical factors affecting DFS in patients with HCC after radical resection, so as to take appropriate therapeutic measures for maximizing these patients DFS.

Methods

Patients

This study retrospectively recruited 344 cases of hepatocellular carcinoma patients that received curative hepatectomy during the department of gastrointestinal surgery at the First Affiliated Hospital of Anhui Medical College. The inclusion criteria were: 1) All patients with HCC were confirmed histo-pathologically;

2) Resection of liver cancer was necessary; 3) The clinical data of the patients were complete and correct; 4) The survival of patients could be followed up; 5) no other treatment, such as chemoradiotherapy and interventional therapy before surgery. Exclusion of patients criteria were: 1) Postoperative pathology: bile duct cell carcinoma or metastatic liver cancer; 2) Incomplete data; 3) Child-pugh grading of liver function was grade C; 4) Inability to follow up or loss of follow-up. We collected information of patients through the record room of our hospital, including patients gender, age, personal history (smoking history, alcohol use history), BMI, presence of basic diseases (hypertension, diabetes, history of hepatitis B), presence of liver cirrhosis, tumor number, tumor size, differentiation degree, TNM stage, number of cancer nodules, AFP, portal vein thrombosis, ascites, routine peripheral blood examination (neutrophils, lymphocytes and platelets) and anticoagulation test (prothrombin time, fibrinogen), liver function test (ALB(albumin-bilirubin), TBIL(total bilirubin), TC(total cholesterol), ALT(alanine aminotransferase), AST(aspartate aminotransferase), GGT(gamma-glutamyltransferase)). In our study, the patients were divided into a High group and normal group based on their thresholds levels of serum ALB, TBIL, TC, TG, ALT, AST and GGT. In addition, the median of NLR and PLR were used as cutoff value, respectively. This study was approved by the ethics committee of the 1st Affiliated Hospital of Anhui Medical College, and all patients signed the preoperative informed consent.

Follow-up and treatment

The follow - up information of the patients was obtained through telephones and outpatient visit. The follow – ups carried out in normal intervals (follow-up began one month after the surgery, each 3 months within two years, and each 6 months from the third years to fifth year, and once a year after the fifth year). Routine peripheral blood examination, liver function test, liver ultrasound or CT were performed at each follow-up patient after hepatectomy.

Statistical analysis

All patient data were statistically described using spss 19.0 software. Chi-square test or Fisher exact test were used to investigate categorical variables. Univariate analysis was performed for all variables, and then the variables of $P < 0.05$ were selected for multivariate Cox regression analysis. The kaplan-meier method was performed to analyze DFS and survival curves were compared using the log-rank test in each group. Cox proportional hazards regression were utilized to assess the relationship between different groups and DFS in patients. The hazard ratio (HR) and 95% confidence interval (95% CI) were used to show the risks. $HR > 1.0$ showed an increased risk of death. The R Project for Statistical Computing 3.5.5 software and RMS program package were used to construct the DFS prognostic nomogram model. P value < 0.05 was considered statistically significant.

Results

Clinical characteristics of patients

A total of 344 HCC patients were included in this study, among whom 279 cases were males and 65 cases were females, accounting for 81.10% and 18.90% respectively. Details of patients' information were shown in table 1. The patients were divided into two groups according to their age, namely the elderly group with age ≥ 70 years old and the young group with age < 70 years old. 258 (75%) patients had a history of hepatitis B, only 86 (25%) cases did not. Most patients had no history of hypertension or diabetes (76.74% and 88.08%). Nearly half of the patients (45.93%) had a BMI more than 23. Moreover, the patients who had liver cirrhosis were 256 (74.42%), 88 patients without liver cirrhosis, nevertheless, most of them had abnormal liver function, such as hepatitis and fatty liver. 44 (12.79%) cases had ascites, unfortunately, two of them had bloody ascites. The TNM stage of I-II and III-IV were 300 (87.21%) cases and 44 (12.79%) cases. The median of NLR and PLR was 2.19 (inter-quartile range: 1.64-3.31) and 97.67 (72.10-138.17), respectively. The median follow-up time for this study was 52.00 (10.00-78.75) months. During the follow-up period, the 1-year, 3-year and 5-year DFS of the patients were 73.26%, 59.30% and 44.48%, respectively.

Correlation between different age groups and clinicopathological characteristics of patients

The results of the correlation between clinical and pathological indicators in the elderly group and the young group were shown in Table 2. Patients without hypertension and diabetes appeared to be less common in elderly patients than in the young group (45.65% vs. 81.54% and 80.43% vs. 89.26%). As for hematological index, the age was significantly connected with HbsAg, AST, ALB, PLR ($P < 0.05$). However, there were no statistical differences between the two groups with regard to smoking, alcohol intake, BMI, tumor number, tumor diameter, differentiation degree, TNM stage, AFP, TBIL, TC, ALT, GGT and NLR.

The prognostic factors for DFS

The results of univariate regression analysis were expressed in Table 3, and Table 4 showed the multivariate analysis of DFS which included the significant factors obtained from Table 3. Multivariable Cox regression analysis revealed that age, history of hepatitis B and TNM stage were independent factors for predicting disease-free survival rate of HHC patients. Besides, the hazard rate (HR) was 0.543 (95%CI:0.328-0.898) for patients older than 70, 0.654 (95%CI:0.472-0.907) for patients without history of hepatitis B, and 0.585 (95%CI :0.423-0.810) for patients with TNM stage of I-II.

Results of DFS in different age groups, AJCC stage and with or without history of hepatitis B

As shown in Figure 1, the DFS of the different age groups were compared with Kaplan–Meier plot. The results indicated that patients with age ≥ 70 have a longer DFS ($P < 0.05$). As can be seen from the Kaplan–Meier curves, the survival rate in the young group showed the most significant downward trend in the first 6 months of follow-up, suggested that the patients in the young group had a greater risk of recurrence or even death within 6 months after surgery. Figures 3 and 5 showed DFS at different TNM stage and with or without a history of hepatitis B, respectively. From the figures, we found that the median DFS of the stage I-II group was 68 months, and the median DFS of the stage III- IV group was 12 months. patients with TNM stage of I-II and no history of hepatitis B had longer DFS ($P < 0.05$).

In order to investigate the association between TNM stage and the different age groups further, we performed survival analysis and results were shown in Figure 2A and Figure 2B. Figure 2A showed that in TNM stage of I-II, the elderly group possessed a longer DFS than the young group. However, there was no significant difference in TNM stage of III-IV. In addition, we also investigated the association between age and different TNM stage groups through Figure 4A and Figure 4B. The results suggested that the young group also had a better prognosis in TNM stage of I-II. In contrast, the difference was not statistically significant in the elderly group. Furthermore, the association between TNM stage and with or without history of hepatitis B was analyzed, however, no statistically significance was found. The association between TNM stage and with or without history of hepatitis B was analyzed in Figure 6A and Figure 6B, and no statistically significance was found.

The establishment and validation of prediction model

Based on the cox regression model, we used independent prognosis factors such as age, TNM stage, history of hepatitis B to establish a nomogram in Figure 7. Each clinicopathological feature of the patient was projected upward to obtain the corresponding score, which was then added to obtain the total score points. The predicted survival rate was correlated with the total points by drawing a vertical line from the Total Points scale to the 3-year or 5-year DFS scale. The C-index of this prediction model was calculated to be 0.604(95%CI:0.561-0.647) through 1000 times of bootstrap resampling method for internal validation, which suggested that this nomogram had good predictive value. The 3-year and 5-year DFS Calibration curve(Figure 8A and Figure 8B) show that the actual survival curve of the nomogram fits the predicted survival curve, indicating the model is reliable.

Discussion

Primary liver cancer is one of the most common gastrointestinal malignancies. Because there are usually no typical symptoms in the early stage, the diagnosis of some patients is delayed¹⁵. Hepatocellular carcinoma (HCC) has a high incidence rate and a high mortality rate. As a result, more and more attention has been put to the research of HCC prognostic factors¹⁶.

Our current research retrospectively analyzed the Clinico-pathological information of 344 patients with HCC admitted to the First Affiliated Hospital of Anhui Medical College from December 2009 to December 2014. The results of univariate and multivariate cox regression analysis indicated that age, history of hepatitis B and TNM stage were independent factors of DFS in patients with HCC($P<0.05$). NLR was calculated using the formula absolute neutrophil count (number of neutrophils/ml) divided by absolute lymphocyte count (number of lymphocytes/ml), PLR was calculated as absolute platelet count (number of platelets/ml) divided by absolute lymphocyte count (number of lymphocytes/ml)¹⁷. Many studies had shown that NLR, AFP and fibrinogen were related to liver cancer patients OS^{18,19}. In our study, we used the median of NLR and PLR as their cutoff values, the values were similar to that previously reported^{20,21}. To our surprise, hematological indicators such as NLR, PLR and AFP were not prognosis factors of patients DFS. It demonstrates that the levels of NLR, PLR and AFP are reliable indicators for

predicting the OS of patients with HCC. However, these indicators are probably not play a role in HCC patients DFS.

In our study, the definition of elderly group in hepatocellular carcinoma patients was age of 70 or over based on previous published studies^{22,23}. Age ≥ 70 patients with HCC had longer DFS. In order to further understand the influence of age on patients DFS under different AJCC stages, we analyzed the DFS of patients in different age groups under stages I-II and III-IV, respectively. Patients aged ≥ 70 at stage I-II also had a better prognosis compared to the young group. Interestingly, in study of Atsuko Sakakibara et al.²⁴, they divided the age groups into the young group and the old group at the age of 40, it was observed that despite the older adult group having a higher proportion of advanced cancer patients, the overall survival rate of stage IIB patients in the young group at the 3-year follow-up was significantly lower, This result was similar to what we found in this study. Beside, The similar results were also found in the study of Liying Zhao et al.²⁵, this retrospective cohort study included a total of 995 patients with CRC suggested the patients aged 35 years and younger have specific clinicopathological characteristics that tend to a worse prognosis. On the contrary, W. Faber et al.²⁶ retrospectively studied 141 patients with liver cirrhosis after curative resection, and found out prognosis of patients less than 70 years old was significantly better. The 5-year survival rate reached about 50%, which was significantly higher than that of the elderly group. The most likely reason for these two completely opposite conclusions is that different researchers have different research priorities and parameter Settings, resulting in different results. Therefore, it is necessary to further study the mechanisms by which age affects cancer prognosis and the relationship between age of surgery and DFS in HCC patients. It is generally known that the stage of tumor can greatly affect the prognosis of patients, the more advanced the stage, the worse the prognosis. In this study, we found that regardless of the patients age, the prognosis of patients of TNM stage I-II was significantly better than that of patients with stage III-IV. The results were the same as that of a decade-long and population-based Analysis by Lu Wu et al.²⁷. For patients at the early stage, radical surgery should firstly be considered, this may prolong the DFS and help prevent metastasis.

As is known to own, hepatitis B virus (HBV) is a leading causing factors of HCC. HBV infection is a global health problem and roughly 30% of the world's population shows serological evidence of current or past HBV infection, especially in China. China is a big country with hepatitis B, although the success of neonatal vaccination since 1992, which had achieved a great reduction²⁸, there are still great challenges, HBV infection affects at least 2 billion people worldwide, and 97 million people are HBV carriers and at least 20 million of them still suffer from active or chronic HBV infection in China²⁹. Lian Li et al.³⁰ suggested the HBV DNA level was an independent prognostic factor for patients with OS and DFS, in addition, HBV DNA level of 2000 IU/ml or greater before operation indicated a poorer prognosis. As for the pathogenesis of liver cancer caused by HBV, on the one hand, HBV virus gene fragments can be inserted directly into the genomes of normal hepatocytes, causing gene mutations that induce normal cells to transform into tumor cells, especially in patients with high HBV-DNA levels. on the other hand, HBx is a protein encoded by HBV with trans-activation activity which can dysregulate cell transcription and proliferation control and sensitize liver cells to carcinogenic factors³¹. History of hepatitis B was

associated with DFS in HCC patients in this study, this may emphasize that we should pay attention to the history of hepatitis B when we ask the history of HCC patients in the course of clinical practice.

As a visual prediction tool, the nomogram has been widely used in the prognostic research of primary liver cancer, breast cancer, cervical cancer and other malignant tumors. It can integrate multiple predictive variables in a weighted manner and intuitively show the influence of variables on individual predictive values³². In this study, we first attempt to develop a prognostic nomogram which combined serum markers (i.e., age, inflammatory markers and tumor markers) and clinicopathology characteristics for predicting the probability of HCC patients 3-year and 5-year DFS. The calibration curve and C-index(concordance index) were used to assess the accuracy of the nomogram, the results showed that the nomogram had great predictive ability.

The main advantage of this study was that the analyzed factors are relatively comprehensive and can effectively reduce residual confounding.

There were several limitations of our study such as the number of patients in the elderly group was small and single-center retrospective design. Hence, Increasing the sample size and replacing the single center with a multi-center prospective study could make the results more convincing and representative.

Conclusions

In conclusion, we found that age, TNM stage and history of hepatitis B were independent prognostic factors for patients DFS after radical hepatectomy. Furthermore, the patients older than 70 years old, earlier TNM stage and no history of hepatitis B were associated with a better prognosis. Moreover, we constructed and validated a new nomogram for predicting postoperative DFS in patients with type II and III AEG. The prediction model showed accurate and reliable prediction efficiency, which may help clinical workers to formulate personalized treatment plans.

Abbreviations

BMI
body mass index
TNM
Tumor-Node-Metastasis
HBs Ag
hepatitis B surface antigen
AFP
alpha-fetoprotein
ALB
albumin-bilirubin
TBIL

total bilirubin
TC
total cholesterol
AST
aspartate aminotransferase
ALT
alanine aminotransferase
GTT
gamma-glutamyltransferase
NLR
neutrophil-to-lymphocyte ratio
PLR
platelet-to-lymphocyte ratio.

Declarations

Availability of data and materials

The data used and/or analyzed during the current study were obtained from the Department of Gastrointestinal Surgery, the First Hospital of Anhui University. The data are available from the corresponding author on reasonable request.

Ethics declarations

Ethics approval and consent to participate

The present study was reviewed and approved by Ethics Committee of The First Hospital of Anhui University (Hefei, China). Informed consent for use of the medical data in this study was obtained from the patients. I confirm that all methods were performed in accordance with the relevant guidelines and regulations in declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that there are no competing interests associated with the manuscript.

Acknowledgements

None.

Funding

Contributions

PQL collected the clinical information of patients, performed the statistical analysis, and completed the writing of the manuscript; LXZ and BCD assisted in collecting the patients' clinical information and writing the manuscript; CL and BCZ helped them.; AMX and WZJ designed the main study and critically revised the manuscript. All authors read and approved the final manuscript.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424.
2. Feng RM, Zong YN, Cao SM, Xu RH. Current cancer situation in China: good or bad news from the 2018 Global Cancer Statistics? *Cancer Commun (Lond)*. 2019;39(1):22.
3. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol*. 2018;69(1):182-236.
4. Ilikhan SU, Bilici M, Sahin H, et al. Assessment of the correlation between serum prolidase and alpha-fetoprotein levels in patients with hepatocellular carcinoma. *World J Gastroenterol*. 2015;21(22):6999-7007.
5. Fransvea E, Paradiso A, Antonaci S, Giannelli G. HCC heterogeneity: molecular pathogenesis and clinical implications. *Cell Oncol*. 2009;31(3):227-233.
6. Maucort-Boulch D, de Martel C, Franceschi S, Plummer M. Fraction and incidence of liver cancer attributable to hepatitis B and C viruses worldwide. *Int J Cancer*. 2018;142(12):2471-2477.
7. Schlachterman A, Craft WW, Jr., Hilgenfeldt E, Mitra A, Cabrera R. Current and future treatments for hepatocellular carcinoma. *World J Gastroenterol*. 2015;21(28):8478-8491.
8. Bucci L, Garuti F, Camelli V, et al. Comparison between alcohol- and hepatitis C virus-related hepatocellular carcinoma: clinical presentation, treatment and outcome. *Aliment Pharmacol Ther*. 2016;43(3):385-399.
9. Yamakado K, Miyayama S, Hirota S, et al. Subgrouping of intermediate-stage (BCLC stage B) hepatocellular carcinoma based on tumor number and size and Child-Pugh grade correlated with prognosis after transarterial chemoembolization. *Jpn J Radiol*. 2014;32(5):260-265.
10. Liao R, Du CY, Gong JP, Luo F. HBV-DNA Load-Related Peritumoral Inflammation and ALBI Scores Predict HBV Associated Hepatocellular Carcinoma Prognosis after Curative Resection. *J Oncol*. 2018;2018:9289421.
11. Zhang H, Yu X, Xu J, Li J, Zhou Y. Combined hepatocellular-cholangiocarcinoma: An analysis of clinicopathological characteristics after surgery. *Medicine (Baltimore)*. 2019;98(38):e17102.

12. Zheng J, Cai J, Li H, et al. Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio as Prognostic Predictors for Hepatocellular Carcinoma Patients with Various Treatments: a Meta-Analysis and Systematic Review. *Cell Physiol Biochem*. 2017;44(3):967-981.
13. Goh BK, Chow PK, Teo JY, et al. Number of nodules, Child-Pugh status, margin positivity, and microvascular invasion, but not tumor size, are prognostic factors of survival after liver resection for multifocal hepatocellular carcinoma. *J Gastrointest Surg*. 2014;18(8):1477-1485.
14. Zhang LX, Lv Y, Xu AM, Wang HZ. The prognostic significance of serum gamma-glutamyltransferase levels and AST/ALT in primary hepatic carcinoma. *BMC Cancer*. 2019;19(1):841.
15. Orcutt ST, Anaya DA. Liver Resection and Surgical Strategies for Management of Primary Liver Cancer. *Cancer Control*. 2018;25(1):1073274817744621.
16. Llovet JM, Zucman-Rossi J, Pikarsky E, et al. Hepatocellular carcinoma. *Nat Rev Dis Primers*. 2016;2:16018.
17. Diem S, Schmid S, Krapf M, et al. Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. *Lung Cancer*. 2017;111:176-181.
18. Chan MY, She WH, Dai WC, et al. Prognostic value of preoperative alpha-fetoprotein (AFP) level in patients receiving curative hepatectomy- an analysis of 1,182 patients in Hong Kong. *Transl Gastroenterol Hepatol*. 2019;4:52.
19. Dai T, Peng L, Lin G, et al. Preoperative elevated plasma fibrinogen level predicts tumor recurrence and poor prognosis in patients with hepatocellular carcinoma. *J Gastrointest Oncol*. 2019;10(6):1049-1063.
20. Yang YT, Jiang JH, Yang HJ, Wu ZJ, Xiao ZM, Xiang BD. The lymphocyte-to-monocyte ratio is a superior predictor of overall survival compared to established biomarkers in HCC patients undergoing liver resection. *Sci Rep*. 2018;8(1):2535.
21. Fu H, Zheng J, Cai J, et al. Systemic Immune-Inflammation Index (SII) is Useful to Predict Survival Outcomes in Patients After Liver Transplantation for Hepatocellular Carcinoma within Hangzhou Criteria. *Cell Physiol Biochem*. 2018;47(1):293-301.
22. Cucchetti A, Sposito C, Pinna AD, et al. Effect of age on survival in patients undergoing resection of hepatocellular carcinoma. *Br J Surg*. 2016;103(2):e93-99.
23. Hsu KF, Yu JC, Yang CW, et al. Long-term outcomes in elderly patients with resectable large hepatocellular carcinoma undergoing hepatectomy. *Surg Oncol*. 2018;27(3):595-601.
24. Sakakibara A, Matsui K, Katayama T, Higuchi T, Terakawa K, Konishi I. Age-related survival disparity in stage IB and IIB cervical cancer patients. *Journal of Obstetrics and Gynaecology Research*. 2019;45(3):686-694.
25. Zhao L, Bao F, Yan J, et al. Poor prognosis of young patients with colorectal cancer: a retrospective study. *Int J Colorectal Dis*. 2017;32(8):1147-1156.
26. Faber W, Stockmann M, Schirmer C, et al. Significant impact of patient age on outcome after liver resection for HCC in cirrhosis. *Eur J Surg Oncol*. 2014;40(2):208-213.

27. Wu L, Tsilimigras DI, Farooq A, et al. Management and outcomes among patients with sarcomatoid hepatocellular carcinoma: A population-based analysis. *Cancer*. 2019;125(21):3767-3775.

28. Cui F, Shen L, Li L, et al. Prevention of Chronic Hepatitis B after 3 Decades of Escalating Vaccination Policy, China. *Emerg Infect Dis*. 2017;23(5):765-772.

29. Wang FS, Fan JG, Zhang Z, Gao B, Wang HY. The global burden of liver disease: the major impact of China. *Hepatology*. 2014;60(6):2099-2108.

30. Li L, Li B, Zhang M. HBV DNA levels impact the prognosis of hepatocellular carcinoma patients with microvascular invasion. *Medicine (Baltimore)*. 2019;98(27):e16308.

31. Levrero M, Zucman-Rossi J. Mechanisms of HBV-induced hepatocellular carcinoma. *J Hepatol*. 2016;64(1 Suppl):S84-S101.

32. Ohori Tatsuo G, Riu Hamada M, Gondo T, Hamada R: Nomogram as predictive model in clinical practice. *Gan to kagaku ryoho Cancer & chemotherapy* 2009, 36(6):901-906.

Tables

Table 1 Clinicopathological characteristics of the 344 patients

Characteristics	Median(25th–75th percentile) or no. (%)
Gender	
male	279(81.10%)
female	65(18.90%)
Age	
≥70 year	46(13.37)
<70 year	298(86.63)
Smoking history	
Yes	151(43.90%)
No	193(56.10%)
Alcohol consumption history	
Yes	133(38.66%)
No	211(61.34%)
History of hepatitis B	
Yes	86(25.00%)
No	258(75.00%)
Hypertension	
Yes	80(23.26%)
No	264(76.74%)
Diabetes	
Yes	41(11.92%)
No	303(88.08%)
BMI	
<18.5	26(7.56%)
≥18.5,<23	160(46.51%)
≥23	158(45.93%)
Liver cirrhosis	
Yes	256(74.42%)

No	88(25.58%)
Ascites	
Yes	44(12.79%)
No	300(87.21%)
Cancer nodules	
Single	299(86.92%)
Multiple(≥ 2)	45(13.08%)
Capsule	
Yes	290(84.30%)
No	54(15.70%)
Tumor diameter	
≥ 5 cm	163(47.38%)
<5cm	181(52.62%)
Differentiation grade	
Low	85(24.71%)
Moderate and High	259(75.29%)
TNM stage	
I	262(76.16%)
II	38(11.05%)
III	40(11.63%)
IV	4(1.16%)
Portal vein thrombus	
Yes	13(3.78%)
No	331(96.22%)
HbsAg	
Positive	268(77.91%)

Negative	76(22.09%)
Operation method	
proximal stomach	86(25.00%)
Full stomach	258(75.00%)
5-year survival	
Yes	162(47.09%)
No	182(52.91%)
Prothrombin time	13.80(13.30-14.50)s
Fibrinogen	2.91(2.41-3.54)g/L
ALB	40.45(37.23-43.78)g/L
TBIL	10.00(8.00-15.00)μmol/L
TC	4.35(3.62-4.86)mmol/L
ALT	34.50(24.00-49.00)U/L
AST	36.00(27.00-52.00)U/L
GTT	55.50(34.00-122.75)U/L
NLR	2.19(1.64-3.31)
PLR	97.67(72.10-138.17)

Abbreviations: BMI, body mass index; TNM, Tumor-Node-Metastasis; HBs Ag, hepatitis B surface antigen; AFP, alpha-fetoprotein; ALB, albumin-bilirubin; TBIL, total bilirubin; TC, total cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GTT, gamma-glutamyltransferase; NLR, neutrophil-to-lymphocyteratio; PLR, platelet-to-lymphocyte ratio.

Table 2 Association between different age groups and clinicopathological characteristics in AEG patients

Patient-related factors	Age (year)		χ^2 value	P value
	≥ 70 n=46	≥ 70 n=298		
Gender			0.872	0.350
male	35	244		
female	11	54		
Smoking history			0.490	0.484
Yes	18	133		
No	28	165		
Alcohol use history			0.065	0.798
Yes	17	116		
No	29	182		
History of hepatitis B			5.655	0.017*
Yes	18	68		
No	28	230		
Hypertension			28.762	0.000*
Yes	25	55		
No	21	243		
Diabetes			6.188	0.013*
Yes	9	23		
No	37	266		
BMI			0.967	0.617
<18.5	5	21		
$\geq 18.5, < 23$	22	138		
≥ 23	19	139		
Liver cirrhosis			13.802	0.000*
Yes	24	232		
No	22	66		

Ascites			1.008	0.315
Yes	8	36		
No	38	262		
Cancer nodules			0.228	0.633
Single	5	40		
Multiple(≥ 2)	41	258		
Tumor volume			0.489	0.485
$\geq 5\text{cm}$	24	139		
$< 5\text{cm}$	22	159		
Capsule			0.283	0.595
Yes	40	250		
No	6	48		
Differentiation grade			0.755	0.385
Low	9	76		
Moderate and High	37	222		
AJCC stage			0.798	0.372
I- II	42	258		
III- IV	4	40		
Portal vein thrombus			0.039	0.843
Yes	1	12		
No	45	286		
HbsAg			24.027	0.000*
Positive	23	245		
Negative	23	53		
AFP			0.836	0.360

≥400ng/ml	9	77		
<400ng/ml	37	221		
Fibrinogen			3.225	0.073
>4g/L	12	46		
≤4g/L	34	252		
Prothrombin time			0.283	0.595
Normal	7	55		
Abnormal	39	243		
ALB			4.400	0.036*
≥40g/L	18	166		
<40g/L	28	132		
TBIL			0.032	0.857
>20.5μmol/L	5	35		
≤20.5μmol/L	41	262		
TC			0.631	0.427
>5.2mmol/L	6	53		
≤5.2mmol/L	40	245		
ALT			2.809	0.094
>50U/L	6	72		
≤50U/L	40	226		
AST			4.875	0.027*
>40U/L	12	129		
≤40U/L	34	169		
GTT			0.326	0.568
>60U/L	24	142		
≤60U/L	22	156		

5-year survival			2.869	0.090
Yes	27	135		
No	19	163		
NLR			3.614	0.057
≥2.19	29	143		
<2.19	17	155		
PLR			6.424	0.011*
≥97.67	31	141		
<97.67	15	157		

The * represented $P < 0.05$.

Table 3 Univariate analysis of different factors associated with Disease-free Survival in AEG patients

Characteristics	HR value (95% CI)	P value
Gender [male/ female]	0.840(0.574,1.230)	0.371
Age[≥70/<70]	0.577(0.350,0.951)	0.031*
Smoking history [Yes /No]	1.031(0.770,1.381)	0.839
Alcohol use history [Yes /No]	0.813(0.601,1.101)	0.182
History of hepatitis B [Yes /No]	1.392(1.008,1.921)	0.044*
Hypertension [Yes/ No]	0.684(0.471,0.993)	0.046*
Diabetes[Yes/ No]	0.816(0.513,1.298)	0.390
BMI[≥23/<23]	0.912(0.682,1.221)	0.537
Liver cirrhosis[Yes/ No]	1.321(0.930,1.876)	0.120
Ascites[Yes/ No]	1.172(0.774,1.776)	0.453
Cancer nodules [Single/ Multiple]	1.668(1.140,2.497)	0.013*
Capsule[Yes/ No]	1.349(0.925,1.966)	0.120
Tumor diameter[≥5cm/<5cm]	1.350(1.010,1.804)	0.043*
Differentiation grade (Low/ Moderate and High)	1.291(0.932,1.787)	0.124
TNM stage(I- II/ III- IV)	1.692(1.224,2.340)	0.001*
Portal vein thrombus(Yes /No)	2.862(1.508,5.432)	0.001*
HbsAg(Positive/ Negative)	1.107(0.774,1.582)	0.579
AFP(≥400ng/ml/<400ng/ml)	0.958(0.683,1.345)	0.805
Fibrinogen(>4g/L/≤4g/L)	1.494(1.037,2.152)	0.031*
Prothrombin time(Normal/ Abnormal)	0.836(0.565,1.236)	0.369
ALB(≥40g/L/<40g/L)	0.988(0.746,1.335)	0.457
TBIL(>20.5μmol/L/≤20.5μmol/L)	1.180(0.762,1.827)	0.457
TC(>5.2mmol/L/≤5.2mmol/L)	1.401(0.980,2.003)	0.065
ALT(>50U/L/≤50U/L)	1.049(0.743,1.481)	0.786
AST(>40U/L/≤40U/L)	1.055(0.785,1.416)	0.724
GTT(>60U/L/≤60U/L)	1.279(0.957,1.709)	0.097
NLR(≥2.19/<2.19)	0.988(0.740,1.321)	0.938

PLR($\geq 97.67 / < 97.67$)

0.956(0.715,1.277) 0.759

The * represented $P < 0.05$.

Table 4 Multivariate analysis of different factors associated with Disease-free Survival in AEG patients

Characteristics	HR value (95% CI)	P value
Age $\geq 70 / < 70$	0.543(0.328,0.898)	0.017*
History of hepatitis B Yes / No	0.654(0.472,0.907)	0.011*
Hypertension Yes/ No	0.754(0.510,1.114)	0.156
Cancer nodules Single/ Multiple	1.009(0.579,1.757)	0.975
Tumor diameter $\geq 5\text{cm} / < 5\text{cm}$	1.125(0.817,1.548)	0.471
TNM stage(I- II/ III- IV)	0.585(0.423,0.810)	0.001*
Portal vein thrombus(Yes /No)	1.784(0.885,3.597)	0.106
Fibrinogen($> 4\text{g/L} / \leq 4\text{g/L}$)	1.304(0.872,1.951)	0.196

The * represented $P < 0.05$.

Figures

Figure 1

Kaplan-Meier curve for Disease-Free Survival according to age groups.

Figure 2

Kaplan-Meier curves for Disease-Free Survival in different age groups based on
(A) stage I-II and (B) stage III-IV.

Figure 3

Kaplan-Meier curve for Disease-Free Survival according to stage groups.

Figure 4

Kaplan-Meier curves for Disease-Free Survival in different stage groups based on (A) age ≥ 70 and (B) age < 70 .

Figure 5

Kaplan-Meier curve for Disease-Free Survival according to history of hepatitis B groups.

Figure 6

Kaplan-Meier curves for Disease-Free Survival in different history of hepatitis

B groups based on (A) stage I-II and (B) stage III-IV.

Figure 7

Nomogram for predicting DFS of HCC patients after curative resection.

Figure 8

Calibration curves of the prognostic nomogram for the (A)3-year DFS and (B)5-year DFS of HCC patients.