Peer Review File

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Reviewer A:

Comment 1: The authors focused on the patients with high preoperative serum GGT levels because high GGT was associated with poor survival outcome. However, previous studies indicated many biomarkers associated with poor prognosis, such as neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, CRP-albumin-lymphocyte index, and alkaline phosphatase. (Peng Li, et al. Bioscience Reports 2019) (Iida H, et al. HPB 2021) (Ping S, et al. Medicine 2020) Why did the authors focus on the patients with high GGT level?

Reply 1: Thanks for your questions. The recurrence of hepatocellular carcinoma (HCC) after curative resection has been regarded as a major risk factor that affects patient survival. Therefore, more and more biomarkers, including tumor biomarkers, inflammatory biomarkers and so on, have been developed to predict tumor progression and prognosis. Complete blood counting and liver function tests which contain neutrophil-lymphocyte rate (NLR)(1-3), platelet-lymphocyte rate (PLR)(1,3,4), lymphocyte-monocyte rate (LMR)(1,3,5), C-reactive protein-albumin-lymphocyte index (CALLY index)(6), alanine aminotransferase (ALT), aspartate aminotransferase (AST)(7,8), alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT)(9-12), as routinely used clinical preoperative test indexes, were reported to be significantly associated with the prognosis in various cancers especially in HCC. These indicators can reflect the inflammatory reactions and nutritional status of the body, and HCC prognosis is related with not only tumor characteristics but also the host inflammatory response(13). In various studies, these indicators had been considered as independent risk factors for the prognosis of HCC, respectively(1,2,4-6,12). With reference to GGT, researchers found that it is a key enzyme in the process of biotransformation and nucleic acid metabolism. As an oxidative stress marker, GGT can give rise to the pro-oxidant reactions, and the latter can produce endogenous reactive oxygen species (ROS) in tumor cells and play an important role in tumor formation, cell proliferation and apoptosis(14). The expression of GGT was abnormal

in several human tumors(15), and GGT can lead to tumorigenesis and characterized as a marker for HCC(16). In view of the close relationship between GGT levels and the recurrence rate as well as poor prognosis of HCC, it is meaningful to establish a personalized and accurate recurrence prediction model for HCC patients with high preoperative serum GGT levels, which is conducive to identify the patients at high risks of recurrence after hepatectomy as soon as possible.

Indeed, the biomarkers mentioned by reviewers, including NLR, PLR, LMR, CALLY index and ALP, have been studied worldwide in recent years as predictors. The valuable comments of the reviewers gave us a lot of inspiration and we will try to establish recurrence prediction models related to these biomarkers in our future studies.

Changes in the text: We have supplemented our text as advised (see Page 5-6, line 75-88).

Comment 2: The authors developed the nomogram predicting overall recurrence after surgery. They concluded that the nomogram could provide treatment strategies including adjuvant therapy. However, postoperative recurrences are commonly divided into intrahepatic metastasis from the original tumor and multicentric development. Treatment strategy should be established based of the type of recurrence. Early recurrence is mainly derived from intrahepatic recurrence, and late recurrence is mainly derived from multicentric development. Therefore, they should divide the type of recurrence into early recurrence and late recurrence.

Reply 2: We are appreciative of the reviewer's suggestion. Currently, the treatment strategies for HCC recurrence mainly include local therapy (repeated hepatectomy, ablative, transcatheter arterial chemoembolization, etc.) and systemic therapy (targeted drugs, immune checkpoint inhibitors, systemic chemotherapy, etc.). The clinician can choose the appropriate treatment according to the indication. However, the clinical curative effect of these strategies for early and late recurrence of HCC is not ideal, and the monitoring of HCC recurrence are still key to prolonging survival. Therefore, it is very valuable to establish a prediction model for the population with high risk of HCC recurrence (such as the patients with high preoperative serum GGT levels), and this model can help clinicians predict the early and late recurrence of HCC patients with high risk of recurrence, and make clinical decisions accordingly.

In our study, we found that the recurrence rates of GGT-high group were obviously higher

than GGT-low group in both early and late postoperative period (Figure 2A) and the high preoperative serum GGT levels was determined as an independent risk factor for the post-operated recurrence of HBV-related HCC patients (Table S2), then, we constructed a nomogram for patients with high preoperative serum GGT levels to predict their recurrence. After considering this comment and the first comment given by reviewer B, we added a landmark analysis to assess recurrence rate at 2 years (early recurrence) and between 2 years and 5 years (late recurrence) (rFigure 1). Definitions of early and late recurrence were derived from the recent American Association for the Study of Liver Disease (AASLD) guidelines and previous studies(17,18). As can be clearly seen from the rFigure 1, both early ($P<0.001$) and late ($P=0.019$) recurrence rates of HBV-related HCC patients with high GGT were higher than those with low GGT. The Kaplan-Meier curves of early, late and overall recurrence were similar. In addition, we supplemented a Cox regression analyze for early recurrence in training cohort and the independent prognostic factors for 2-year recurrence-free survival (RFS) (rTable 1). Finally, the nomogram we constructed for HBV-related HCC patients with high GGT levels was just a personalized tool to predict the individual probability of 2-year (early recurrence), 3-year, and 5-year (late recurrence) recurrence after curative resection. We hope that the prediction results of this nomogram can provide some references for clinicians to make clinical decisions (see Page 17-18, line 343-350).

This study had completed the construction and validation of the prediction model, but the introduction of treatment strategies for early and late recurrence was not sufficient. We had revised our manuscript according to your comment (see Page 18, line 351-363).

Changes in the text: We have supplemented our text as advised (see Page 18, line 343-363) and added a figure (rFigure 1) and a table (rTable 1) in this response letter.

Comment 3: The benefit of this nomogram is unclear. The authors should describe how this nomogram helps surgeons in decision-making of treatment strategy for HBV-HCC patients.

Reply 3: We are appreciative of the reviewer's suggestion. There are several well-known prognostic staging systems for HCC, including the TNM (tumor node metastasis) staging system, the CLIP (Cancer of the Liver Italian Program) score, and the BCLC (Barcelona Clinical Liver Cancer) staging system, can help to divide HCC patients into different groups

with diverse outcomes, but these staging systems vary considerably and present controversial results, which patients will be divided into different prognostic results and therapeutic strategies groups by different staging systems. Notably, patients with high heterogeneity may be graded at the same stage but receive a different prognosis. In addition, the power of these criteria to predict RFS is controversial and they are not appropriate to predict recurrence of HCC in specific populations with high risks of recurrence, as these tools were not developed specifically for prognostic prediction. Nomogram models can provide a more individualized prediction based on a combination of variables, and have been used to predict the prognosis of many cancers, including intrahepatic cholangiocarcinoma, oesophagogastric adenocarcinoma, urothelial carcinoma, breast cancer, and lung cancer(19-22). Therefore, we constructed this nomogram to guide clinical follow-up for the high-risk population (HBV-related HCC patients with high preoperative serum GGT levels).

Firstly, the method of application about this nomogram was explained in figure 3 legend (see Page 27, line 542-551). For an individual patient with high GGT, we will record the values of the 5 clinical indicators, including AFP, HBV-DNA, Satellite nodules, Microvascular invasion and Tumor grade. Next, we can substitute the values of the 5 clinical indicators into rows 2 to 6 of the nomogram and draw a vertical line upward to intersect the scale (row 1) respectively, then, the score of each indicator will be obtained at row 1. The total point of the patient will be calculated by adding the scores of all 5 indicators, and this total point will be located on the total point axis (row 7). A vertical line will be drawn downward from the total point axis to the survival axes (row 8-10) to determine the likelihood of 2-, 3-, or 5-year RFS. Secondly, clinicians can make follow-up protocols and treatment strategies based on the individual probability of 2-, 3-, and 5-year HCC recurrence predicted by our nomogram. All in all, our nomogram integrated 5 variables which were easily available in clinical and exhibited increased accuracy for prognostic prediction compared with that of conventional staging systems. The predictions of this model can be used to guide routine follow-up for patients and patients given a high recurrence score by the nomogram should undergo more high-end imaging examinations, such as magnetic resonance imaging (MRI) or computed tomography (CT) exams, in addition, the interval time of follow up should be reduced, even if the most recent exam results after surgery indicated no causes for concern (see Page 18, line 346-350).

Changes in the text: We have modified our text as advised (see Page 7, line 103-108 and Page 18, line 346-350) and the method of application about this nomogram was explained in figure 3 legend (see Page 27, line 542-551).

Comment 4: The authors should clarify why they set 60 U/L as the cut-off value of GGT.

Reply 4: Thanks for your questions. We are so sorry that we did not explain this important parameter in our manuscript. Many studies have adopted the upper limit of the GGT normal values tested by their center's laboratory as the cutoff value of GGT(16,23), so we used the upper limit of the normal values (10- 60 U/L) in Eastern Hepatobiliary Surgery Hospital as the cutoff values of GGT (see Page 9, line 162-163).

Changes in the text: We have modified our text as advised (see Page 9, line 162-163).

Reviewer B:

Comment: There were two previous nomogram studies (Pubmed PMID 30671793 and 30327670) in HBV related HCC after hepatectomy, and the risk factors were not specific except HBV-DNA load. It is necessary to compare the risk factors of the above mentioned studies and this one in the part of discussion.

Reply: Thanks for your valuable comments. We have carefully studied the 2 researches you mentioned and compared the risk factors of them with our study in the part of discussion (see Page 15-16, line 283-306). In this article (Pubmed PMID 30671793), the risk factors for predicting HCC recurrence were **ALP**, **albumin**, protein induced by vitamin K absence/antagonism-II (**PIVKA-II**), **multiple tumors**, **tumor hemorrhage**, portal vein tumor thrombosis (**PVTT**), **intrahepatic metastasis** and **tumor-free resection margin(24)**. And in our study, the independent prognostic factors (Table S2) predicting RFS in the same population (HCC patients positive for HBsAg) were **gender**, **albumin**, **GGT**, **tumor number**, **tumor diameter** and **microvascular invasion**. Further, we took the high-GGT population as the research object, analyzed independent prognostic factors of RFS and established the nomogram. By comparing the two studies, we found that the independent prognostic factors were similar to some extent on the same population (HCC patients positive for HBsAg). Although the clinicopathologic variables of the two studies both included preoperative serum indexes and

postoperative pathological characteristics, the laboratory indicators of different centers were different, for example, GGT was not included in their study and PIVKA-II was not routinely tested in our center before 2011. In the other article you mentioned(25), we have learned that HBV-related peritumoral inflammatory score (HBV-PIS) can reflect both the status of liver dysfunction and the tumor biology, and HBV-related ALBI score (HBV-ALBI) is a newly emerging alternative to the conventional Child-Pugh (C-P) score for grading liver function. They developed a nomogram comprising HBV-PIS and HBV-ALBI with different HBV-DNA loads for patients who underwent curative resection. Comparatively, although the variables of our nomogram were more easily obtained and commonly used, their variables can more comprehensively evaluate status of liver dysfunction, liver inflammation and tumor biology. We will refer to their experience in future studies.

Changes in the text: We have modified our text as advised (see Page 15-16, line 283-306).

Major comment 1: Until about 2 years, recurrence occurred more frequently in the GGT-high group, and after that, it increases in parallel with the GGT-low group. What do you think is the specific reason for this point?

Reply 1: Thanks for your questions. After considering your and the second comment of reviewer A, we added a landmark analysis using R version 3.5.1 software (http://www.r-project.org/) with the *survival* package to assess recurrence rate at 2 years and between 2 years and 5 years (rFigure 1). The landmark method has been used extensively in medical research to correct for the bias inherent in the analysis of time-to-event outcome between groups determined during study follow-up(26-28). A potential limitation of landmark analyses was the fact that events, in particular recurrence rate, that occurred before the landmark would not be included in the analysis beyond the landmark(28). In this study, the landmark analysis that discriminated between recurrence rate of up to 2 years and recurrence rate from 2 years up to 5 years. Recurrence rates before and after 2 years of follow-up were both significantly higher in the GGT-high group than GGT-low group (HR 1.410, 95%CI 1.154-1.724, $p<0.001$ and HR 1.352, 95%CI 1.050-1.740, $p=0.019$). Thus, due to the inherent bias of Kaplan-Meier analysis that early recurrences were a competing event for late recurrences (Those patients who relapsed early would not have the event of late recurrence), the recurrence rates after 2 years in our

original Kaplan-Meier curve (Figure 2A) seemed like a parallel increase in two groups.

Changes in the text: We made few modifications in the manuscript (see Page 11, line 204) and explained your question in detail in this response letter.

Major comment 2: What is the basis for the cut-off values of GGT, AFP and HBV-DNA load used in this study?

Reply 2: Thanks for your questions. We are so sorry that we did not explain these important parameters in our manuscript. Many studies have adopted the upper limit of the GGT normal values tested by their center's laboratory as the cutoff value of GGT(16,23), so we used the upper limit of the normal values (60 U/L) in Eastern Hepatobiliary Surgery Hospital as the cutoff values of GGT. In addition, according to the research experience of our center(29,30), HBV-DNA load ⩾ 2000 IU/mL was defined as high level, and HBV-DNA load < 2000 IU/mL was defined as low level, and 400 ng/ml was considered as the cutoff of AFP between the high and low levels (see Page 9, line 159-166)

Changes in the text: We have modified our text as advised (see Page 9, line 159-166).

Major comment 3: Why was the nomogram evaluated by classifying the high GGT group separately? Is it because you know that there are other specific factors associated with recurrence in this group, or is it possible to make pathogenetic inferences? Do you think that the HBV-DNA load is not specific in low GGT group?

Reply 3: Thanks for your questions.

(1) Previous studies have found that the abnormal expression of GGT was found in several human tumors(15), and GGT play an important role in tumor formation, cell proliferation and apoptosis(14). Over the last few years, more and more researchers have begun to pay attention to the close relationship between GGT levels and the recurrence rate as well as poor prognosis of HCC(16,31). HBV-related HCC patients that were detected with high preoperative serum GGT levels tend to relapse early, which leads to an unsatisfied long-term survival (Figure 2). In order to overcome the major challenge of high postoperative recurrence rate of HBV-related HCC with high preoperative GGT levels, patients at high risks of recurrence after hepatectomy should be identified as soon as possible, which could

help determine the further management strategies. Thus, we established a predictive nomogram model for the high-GGT group.

(2) We did not know in advance that there were other specific factors related to the recurrence in the high-GGT group. However, during the study, GGT was found to be an independent risk factor for the recurrence of HBV-related HCC patients (Table S2), and it was also reported in the literature that GGT was closely related to the prognosis of HCC. Therefore, we believed it was meaningful to establish a personalized recurrence prediction model for this high-risk group, and we have done so and validated the model.

(3) This does not make pathogenetic Inferences. It can only be said that there was a strong correlation between high GGT and HCC recurrence, which did not conform to all the requirements of etiological inference, and we chose this high-risk population as the research object based on the existence of this correlation.

(4) This is a very meaningful and interesting question. Previous studies have reported that high HBV viral loads may affect the prognosis of HBV-related HCC patients and may be a driving force of active necroinflammation and HBV mutants, which promote the invasive ability and metastatic potential of HCC(32). After being combined with HBV-DNA loads, both PIS and ALBI showed better predictive powers for OS and RFS of HCC patients after curative resection, revealing the ongoing impact of HBV on the liver tissues (such as liver local inflammation/immune response and hepatic function damage, et al) and subsequently becoming a major contributor in hepatocarcinogenesis to affect the prognosis of tumor hosts(25,33,34). Thus, we believe that the HBV-DNA load is specific for recurrence of HBV-related HCC patients with regardless of high GGT or low GGT. Based on our current data, we cannot answer this question accurately and we will explore it in the subsequent studies.

Changes in the text: We have modified our text according to the suggestions (see Page 6, line 87-89 and Page 7, line 103-108).

Major comment 4: Have you not analyzed the very high group in the high GGT group as well? Or applied the continuous variables for GGT?

Reply 4: Thanks for your interesting questions. According to your opinion, we specifically

performed a Cox regression analyze for the very high GGT group (rTable 2). There was no clear definition of the very high group in previous studies, so we selected patients with GGT values in the top third of the high group (n=201) as the very high group. However, due to the large number of independent variables of our study, the sample size of the very high group was insufficient. And we would like to expand the sample size in future studies to investigate the characteristics of the very high group.

Changes in the text: We have explained this problem in this letter, and there were no relevant changes in the original text.

Major comment 5: You divided the training set and validation set in entire cohort. Let me know the detailed process of random.

Reply 5: We are appreciative of the reviewer's suggestion. The patients in GGT-high group were divided into the training cohort (n=393) and validation cohort (n=210) using a random number table (see Page 10, line 171-172).

Changes in the text: We have modified our text as advised (see Page 10, line 171-172).

Minor comment 1: Abbreviation of RFS was not explained in your manuscript.

Reply 1: We are so sorry that we neglected this point, and we have modified it in the revised manuscript (see Page 7, line 104, recurrence-free survival (RFS)).

Changes in the text: We have modified our text as advised (see Page 7, line 104).

Minor comment 2: p14, 267 error: 2-, 3-, and 5-years

Reply 2: We would like to apologize for this mistake and we have modified it in the revised manuscript (see Page 15, line 299).

Changes in the text: We have modified our text as advised (see Page 15, line 299).

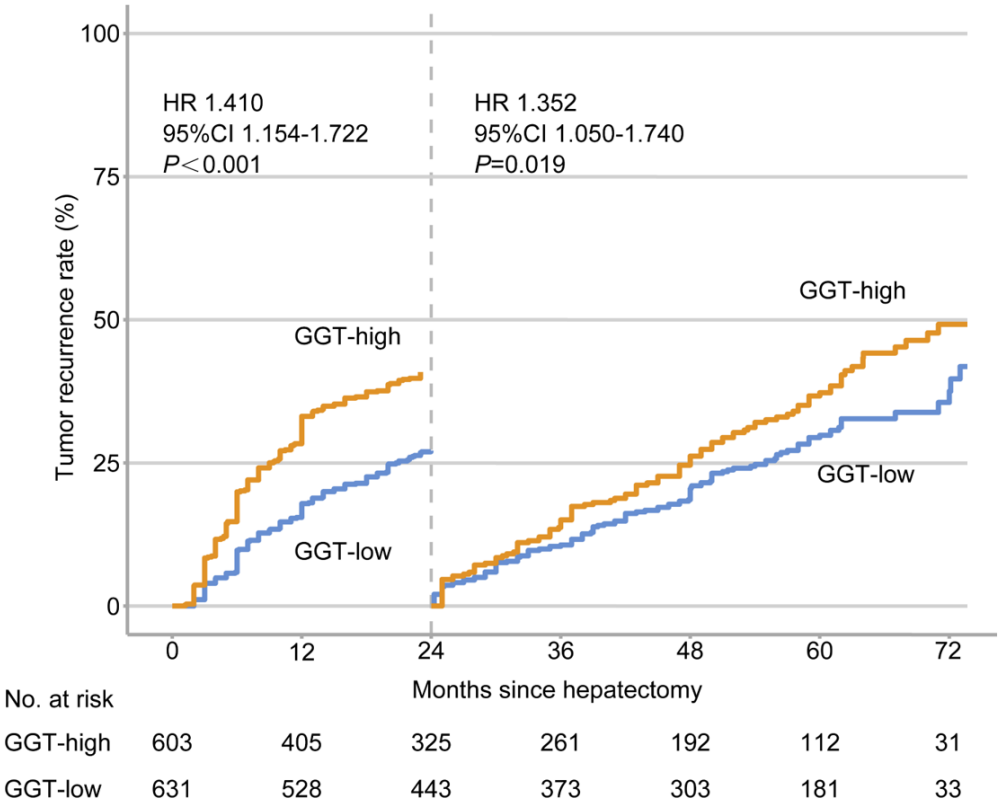

Figure 1. Kaplan-Meier curves of tumor recurrence rates for the HBV-related HCC patients. Landmark analyze discriminated between recurrence rate of up to 2 years and recurrence rate from 2 years up to 5 years. Abbreviations: γ-glutamyl transpeptidase (GGT), hazard ratio (HR), confidence interval (CI).

rTable 1. Independent prognostic factors predicting 2-year RFS in training cohort (n=214).

Characteristics	Univariate			Multivariate analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age >50 years	0.730	0.550-0.980	**0.039**	0.950	0.700-1.300	0.759
Gender Male	1.010	0.640-1.600	0.961	NA	NA	NA
HBV-DNA >2000 IU/ml	1.260	0.930-1.720	0.139	NA	NA	NA
TBil >17.1 μmol/L	0.970	0.660-1.440	0.890	NA	NA	NA
Albumin <3.5 g/dl	1.100	0.810-1.490	0.560	NA	NA	NA
ALT >44 U/L	0.990	0.740-1.330	0.965	NA	NA	NA
AST >40 U/L	1.280	0.950-1.730	0.100	NA	NA	NA
Child-Pugh B	0.650	0.160-2.600	0.539	NA	NA	NA
AFP >400 ng/ml	2.850	2.000-4.070	**< 0.001**	1.450	0.980-2.160	0.065
Nonanatomical hepatectomy	127.960	61.690-265.410	**< 0.001**	62.220	27.010-143.340	**< 0.001**
Surgical margin <1 cm^	655.090	151.390-2834.720	**< 0.001**	58.830	13.190-262.290	**< 0.001**
Tumor number >1^	2.160	1.480-3.150	**< 0.001**	0.780	0.520-1.190	0.250
Tumor diameter >5 cm^	2.300	1.690-3.120	**< 0.001**	0.780	0.540-1.130	0.192
Bilateral tumor distribution^	87.250	48.090-158.280	**< 0.001**	12.490	6.900-22.600	**< 0.001**
Satellite nodules^	1.990	1.470-2.680	**< 0.001**	1.030	0.740-1.440	0.863
Microvascular invasion	3.710	2.750-4.980	**< 0.001**	1.120	0.780-1.600	0.554
Edmondson-Steiner grade III-IV	8.430	4.790-14.850	**< 0.001**	3.580	1.940-6.630	**< 0.001**
Cirrhosis^	0.890	0.640-1.230	0.487	NA	NA	NA

Abbreviations: total bilirubin (TBil), albumin, alanine aminotransferase (ALT), glutamate

aspartate aminotransferase (AST), Child-Pugh score, a-fetoprotein (AFP), recurrence-free survival (RFS).

^ Post-operative parameter.

Table 2. Independent prognostic factors predicting RFS in the very high GGT group (n=201).

Characteristics	Univariate			Multivariate analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age >50 years	0.760	0.590-0.970	**0.028**	0.720	0.560-0.930	**0.013**
Gender Male	0.850	0.570-1.280	0.445	NA	NA	NA
HBV-DNA >2000 IU/ml	1.150	0.890-1.480	0.289	NA	NA	NA
TBil >17.1 μmol/L	1.170	0.850-1.610	0.325	NA	NA	NA
Albumin <3.5 g/dl	1.040	0.810-1.340	0.758	NA	NA	NA
ALT >44 U/L	1.010	0.790-1.300	0.915	NA	NA	NA
AST >40 U/L	1.290	1.000-1.650	**0.049**	1.210	0.920-1.580	0.172
Child-Pugh B	1.120	0.500-2.510	0.786	NA	NA	NA
AFP >400 ng/ml	1.530	1.170-2.000	**0.002**	1.110	0.830-1.480	0.485
Nonanatomical hepatectomy	43.690	29.880-63.890	**< 0.001**	22.580	13.850-36.800	**< 0.001**
Surgical margin <1 cm^	48.090	32.520-71.130	**< 0.001**	5.100	3.170-8.210	**< 0.001**
Tumor number >1^	2.240	1.630-3.080	**< 0.001**	1.340	0.930-1.950	0.121
Tumor diameter >5 cm^	2.230	1.720-2.890	**< 0.001**	1.250	0.900-1.730	0.179
Bilateral tumor distribution^	102.400	60.850-172.340	**< 0.001**	16.620	9.790-28.190	**< 0.001**
Satellite nodules^	1.990	1.550-2.560	**< 0.001**	1.100	0.830-1.440	0.518
Microvascular invasion	2.340	1.820-3.010	**< 0.001**	0.910	0.690-1.200	0.500

Edmondson-Steiner grade III-IV	2.870	1.880-4.360	**< 0.001**	1.710	1.090-2.680	**0.020**
Cirrhosis^	0.890	0.670-1.170	0.405	NA	NA	NA

Abbreviations: total bilirubin (TBil), albumin, alanine aminotransferase (ALT), glutamate aspartate aminotransferase (AST), Child-Pugh score, a-fetoprotein (AFP), recurrence-free survival (RFS).

^ Post-operative parameter.

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