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# Utility of Serum Inflammatory Markers in Predicting Microvascular Invasion and Survival in Patients with Hepatocellular Carcinoma

**Jian Zheng, MD**[1], **Ken Seier, MS**[2], **Mithat Gonen, PhD**[2], **Vinod P. Balachandran, MD**[1], **T. Peter Kingham, MD**[1], **Michael I. D'Angelica, MD**[1], **Peter J. Allen, MD**[1], **William R. Jarnagin, MD**[1], **Ronald P. DeMatteo, MD**[1]

[1]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

[2]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

## Abstract

**Background:** Preoperative serum inflammatory markers have been correlated to outcome following resection of hepatocellular carcinoma (HCC), but studies have had conflicting results. We aimed to evaluate the association of 6 inflammatory markers with recurrence-free survival (RFS), overall survival (OS), and microvascular invasion (MVI), a well-known prognostic factor.

**Methods:** In 370 patients who underwent resection of HCC from 1992 to 2016, we retrospectively evaluated their inflammatory indices and individual components, including neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), prognostic nutritional index (PNI), aspartate aminotransferase to platelet ratio index (APRI), and aspartate aminotransferase to neutrophil ratio index (ANRI). Univariate and multivariate analyses were performed to evaluate these markers for RFS, OS, and MVI.

**Results:** Median RFS was 23 months and median OS was 60 months. Factors independently associated with worse RFS were higher levels of PLR and alpha-fetoprotein, male gender, as well as presence of MVI and multiple nodules. Factors independently associated with worse OS were higher levels of PLR and international normalized ratio, male gender, older age, presence of MVI and multiple nodules, larger tumor, presence of cirrhosis, and absence of steatosis. MVI was identified in 47% of patients. Lower level of albumin, higher level of alpha-fetoprotein, and larger tumor on preoperative imaging were independently associated with MVI.

**Conclusions:** In this largest western series to evaluate the utility of preoperative inflammatory markers in patients with HCC, we found that only PLR was associated with RFS and OS, and albumin was associated with MVI.

**Correspondence:** Ronald P. DeMatteo, MD, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065. ronald.dematteo@uphs.upenn.edu.

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**Keywords**

Platelet to lymphocyte ratio; albumin; serum inflammatory indices; hepatocellular carcinoma; microvascular invasion; recurrence-free survival; overall survival

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide.[1] Multiple staging systems and nomograms have shown to be prognostic but they are cumbersome to use and have low concordance index on external validation.[2-5] Several serum inflammatory indices have also been proposed to improve survival prediction in patient following resection of HCC. They can be easily calculated in any patients with routine preoperative blood tests, including complete blood count and liver function tests. These serum inflammatory indices are reflective of the underlying immune health and systemic inflammation, which can affect cancer development and metastatic progression by promoting epigenetic changes, cell proliferation, angiogenesis, and cell invasion.[6]

Serum inflammatory indices that have been shown to be prognostic include neutrophil to lymphocyte ratio (NLR),[7-9] platelet to lymphocyte ratio (PLR),[10] lymphocyte to monocyte ratio (LMR),[11] prognostic nutritional index (PNI),[11,12] aspartate aminotransferase/platelet ratio index (APRI),[13-15] and aspartate aminotransferase/neutrophil ratio index (ANRI).[16] However, most of the prior studies only evaluated one or two serum inflammatory markers, most were limited to patients treated in Asia and Europe, and several had conflicting results.[12,17-19] Thus, a comprehensive evaluation and validation of all of these serum inflammatory indices would be valuable in patients with HCC treated in the U.S.

In addition to evaluating these preoperative serum inflammatory indices for prognostic purposes, we also aimed to evaluate them for their association with MVI. MVI is a significant risk factor for worse RFS and OS in patients following resection of HCC.[20-22] We hypothesized that preoperative serum inflammatory indices may also be utilized to predict MVI since both factors are prognostic. MVI is usually determined postoperatively on pathologic examination of the tumor since preoperative biopsy is not routinely performed.[23] Ability to predict MVI preoperatively may help guide treatment recommendations for patients considered for liver transplantation or resection.

In this study, we aimed to comprehensively evaluate the utility of preoperative serum inflammatory indices and their individual components for their correlation to RFS and OS as well as MVI in patients following resection of HCC.

## METHODS

### Patients

With the approval of the Institutional Review Board at Memorial Sloan Kettering Cancer Center, we retrospectively reviewed 391 consecutive patients with complete macroscopic resection of HCC from 1992 to 2016. Of 391 patients, 21 (5%) who died or lost to follow up within 3 months of operation were excluded from the study in order to evaluate RFS

and OS. We did not include patients with R2 resection, prior liver resection for HCC, or pathologically confirmed fibrolamellar HCC or combined HCC and cholangiocarcinoma. Patients were selected for resection given sufficient future liver remnant, absence of distant metastasis, and adequate general health. Patients were evaluated for resection and followed postoperatively for recurrence as previously described.[24]

## Clinicopathologic variables

We reviewed demographic information and medical history, including age at resection, gender, Child Pugh classification, primary liver diseases, and history of metabolic syndrome. Metabolic syndrome was defined as meeting any 3 of the following risk factors: body mass index ≥25, type 2 diabetes, hypertension, and hyperlipidemia.[25] We also obtained preoperative levels of AFP, serum inflammatory indices, and their individual components.

For the inflammatory markers, all test results were obtained within 1 month preoperatively and had concomitant white blood cell counts that were within the normal range of 4-11 K/uL. Inflammatory indices in patients with leukopenia and leukocytosis were excluded in the analysis given the likelihood of alteration from an acute infectious or inflammatory process instead of chronic cancer-related effects. NLR was calculated by the absolute count of neutrophils to lymphocytes, PLR was calculated by platelets to lymphocytes, and LMR was calculated by absolute lymphocytes to monocytes.[9-11] PNI was measured by albumin (g/L) + 5 x absolute lymphocyte count.[12] APRI was measured by [AST (units/L)/upper limit of normal range]/platelets ($10^9$/L) x 100 as previously described, and the upper limit of normal for AST was 37 units/L.[15] ANRI was measured by AST/absolute neutrophils.[16]

In addition to evaluating preoperative laboratory tests, we also examined preoperative abdominal imaging, details of the operation, pathology from the resected tumor, as well as RFS and OS.

## Statistics

Categorical variables were expressed as frequency and percentage and were compared using Fisher's exact test. Continuous variables were expressed as mean and standard deviation and were compared using the Wilcoxon rank sum test. Univariate analyses of categorical and continuous variables were performed using univariate logistic regression and Cox proportional hazard models, respectively. All significant preoperative and postoperative variables from univariate analysis were evaluated in the multivariate analysis of RFS and OS, whereas only significant preoperative variables from univariate analysis were evaluated in the multivariate analysis for prediction of MVI. Tumor size and number from histology were used in the multivariate model for RFS and OS, whereas tumor details from preoperative imaging were used in the multivariate analysis for prediction of MVI.

Multivariate analysis was performed using a two-step process. The first step selected the prognostic clinical factors using Cox proportional hazard models and separately selected serum inflammatory markers using Lasso penalized regression[26]. Lasso penalized regression was utilized in this study in order to examine all 6 serum inflammatory indices despite of moderate to high correlation of several serum inflammatory indices with each other. The second step combined the selected variables from the first step and refit using Cox

proportional hazard model. Serum inflammatory markers were presented as a standard deviation from the mean, and their prognostic utility was evaluated by incremental increases in standard deviations. Kaplan-Meier curves were generated for RFS and OS using the MVI status or using the optimal cutoff for inflammatory marker as determined by the method of maximally selected rank statistics. P-values < 0.05 from 2-sided tests were considered significant. Statistical analyses were performed using R version 3.3.2 (cran.r-project.org) and SAS 9.4.

## RESULTS

With a median follow-up of 56 months for all survivors, median RFS and OS were 23 and 60 months, respectively. Patients with high levels of AFP, platelets, NLR, and PLR, as well as low levels of albumin, LMR and PNI had worse RFS and OS on univariate analysis (Table 1). In addition, patients with worse prognosis included male gender, Child Pugh class B, high operative blood loss, local extrahepatic invasion, R1 margin, large tumors, multiple nodules, MVI, cirrhosis, and absence of steatosis.

In this study, 173 (47%) had tumor MVI. Similar to patients with worse RFS and OS, those with MVI had high AFP, AST, platelets, NLR, and PLR, and lower levels of albumin, LMR, and PNI compared to those without MVI on univariate analysis (Table 2). Median RFS was 14 months for patients with MVI compared to 36 months for those without MVI ($p < 0.001$, Fig. 1A). Median OS was 39 months for patients with MVI compared to 82 months for patients without MVI ($p < 0.001$, Fig. 1B). On multivariate analysis with evaluation of all serum inflammatory indices and their individual components and with incorporation of all other preoperative clinical variables, higher level of AFP, lower level of albumin, and larger tumor size on preoperative imaging were independently associated with MVI (Table 3A).

In multivariate evaluation of preoperative and postoperative factors, those independently associated with worse RFS were male gender, higher level of AFP and PLR, as well as presence of MVI and multiple nodules (Table 3B). Factors independently associated with worse OS were older age, male gender, higher level of INR and PLR, MVI, and multiple nodules, larger tumor, and presence of cirrhosis but absence of steatosis (Table 3C).

For the preoperative level of PLR, the optimal cutoff associated with prognosis was determined to be 275 for RFS and 298 for OS. Patients with a preoperative level of PLR above 275 had significantly worse RFS compared to those with lower PLR (median RFS of 30 months vs. 6.5 months, $p = 0.007$, Fig. 2A). Similarly, patients with a preoperative level of PLR above 298 had significantly worse RFS compared to those with lower PLR (median OS of 66 months vs. 31 months, $p = 0.018$, Fig. 2B). Notably, although patients with MVI had higher level of PLR as a continuous variable or as dichotomized by the optimal cutoff of above 275 ($p= 0.012$) on univariate analysis, PLR was not independently associated with the presence of MVI on multivariate analysis.

## DISCUSSION

To our knowledge, this is the largest western series to comprehensively evaluate the utility of preoperative serum inflammatory indices and their individual components to predict MVI,

RFS and OS in patients following resection of HCC. While multiple inflammatory markers were associated with MVI, RFS, and OS on univariate analysis, only albumin and PLR were independently associated with MVI and survival on multivariate analysis.

Interestingly, hypoalbuminemia was associated with MVI in this study. Low serum level of albumin alone and as part of PNI have been associated with worse survival in patients following resection of HCC in prior studies, but not independently associated with MVI.[3,11,12] Albumin is a negative acute-phase protein and therefore it decreases in inflammatory states.[27] Hypoalbuminemia may also be due to impaired liver synthesis because of underlying liver disease.[28] Although 98% of patients had Child Pugh class A, liver function as stratified by albumin-bilirubin (ALBI) calculation revealed that 74% of our patients were ALBI grade 1, 23% were grade 2, and 1% were grade 3[29]. Thus, low albumin in association with MVI and aggressive tumor biology likely reflects an underlying inflammatory and hypermetabolic state from cancer-induced cachexia as well as some degree of hepatic dysfunction.[29,30]

A high level of PLR was independently associated with worse RFS and OS in this study, consistent with several prior studies in HCC patients considered for resection and liver transplantation.[10,31,32] An elevated PLR results from an increased level of platelets and/or decreased level of lymphocytes. Platelets can promote angiogenesis by releasing vascular endothelial growth factor and they can protect tumor cells from cytolysis by natural killer cells and promote metastasis.[33,34] On the other hand, lymphocytes comprise the adaptive, anti-tumoral immune response, and thus their reduction has been shown to promote hepatocarcinogenesis and to be associated with worse prognosis[35-37].

Although both platelets and lymphocytes are integral parts of the interaction between cancer cells and immune cells, several studies also showed conflicting results in the prognostic utility of PLR[12,38]. It is important to note that most of these studies were evaluated in patients treated in Asia. One explanation could be that a majority of HCC patients in Asia has chronic hepatitis B leading to liver cirrhosis and concomitant thrombocytopenia, and thus, perhaps inflammation-mediated thrombocytosis may play a smaller role in Asian patients with HCC[39,40]. In contrast, many patients treated at Western centers have metabolic syndrome and liver steatosis, which may cause chronic inflammation in addition to cancer-related inflammation[41-43].

Although steatosis-related inflammation can be tumorigenic, the presence of any steatosis was associated with improved overall survival in our study. This is likely because the presence of any liver steatosis did not result in steatohepatitis and we included not only patients with severe steatosis (4%), but also any mild (71%) or moderate (26%) steatosis as per the Kleiner-Brunt histologic scoring system. In addition, we operated on more patients with steatosis (38%) than with cirrhosis (25%), and the majority of patients with any steatosis (76%) lacked cirrhosis in our cohort. Many of our patients were also overweight and obese, with 60% having BMI ≥ 25% and 22% having BMI ≥ 30%.

In addition to PLR as a prognostic factor for both RFS and OS in patients following resection of HCC, other prognostic factors included MVI, multiple nodules, and male

gender, consistent with previous reports[2,3,5]. In addition, higher level of AFP was also independently associated with worse RFS, whereas older age, higher INR, larger tumor size, and cirrhosis were independently associated with worse OS[2,3,5].

A limitation of this study is that it is retrospective and from a single institution with its associated biases. Preoperative serum inflammatory markers were either not performed in 8 to 12% of patients within 1 month preoperatively or were excluded given an acute inflammatory or infectious state. All patients included had a normal WBC within 1 month of surgery in order to eliminate effects of acute inflammatory changes and to capture cancer-related inflammatory changes. Although our findings may be applicable to those in the Western centers, its applicability to patients treated in other parts of world may be limited. However, we are working on external validation with our international collaborators.

In conclusion, of a plethora of preoperative serum inflammatory markers evaluated, only albumin was independently associated with MVI, and PLR was independently associated with RFS and OS. Further evaluation of these readily applicable serum markers should be performed on a larger sample size and compared between diverse patient populations.

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**Synopsis:**

This study presents a comprehensive evaluation of six preoperative serum inflammatory markers in predicting outcomes after resection of hepatocellular carcinoma. Lower serum albumin was associated with microvascular invasion whereas higher platelet to lymphocyte ratio was associated with recurrence-free and overall survival.

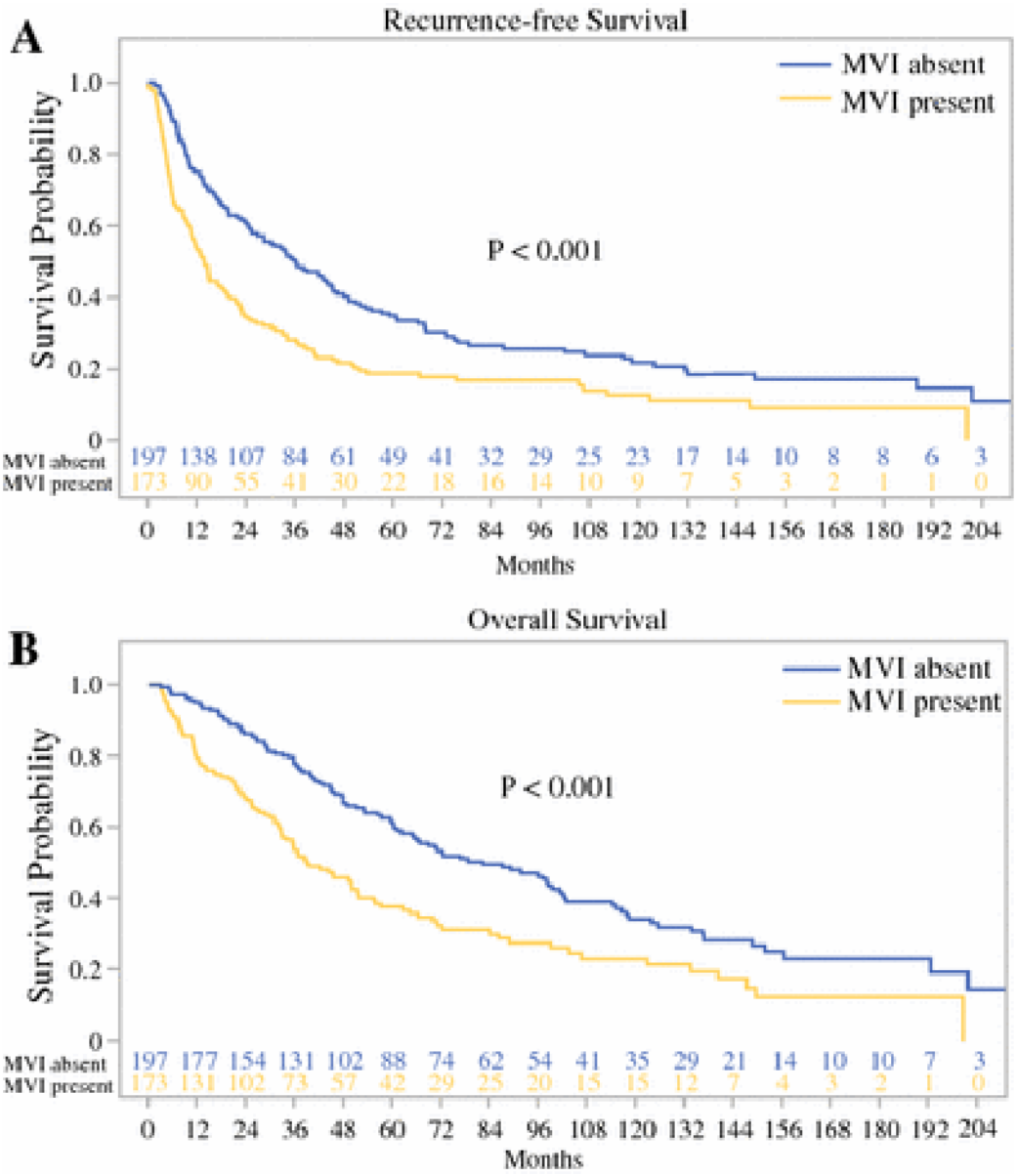


**Fig. 1.**
Relation of microvascular invasion (MVI) to (A) RFS and (B) OS.

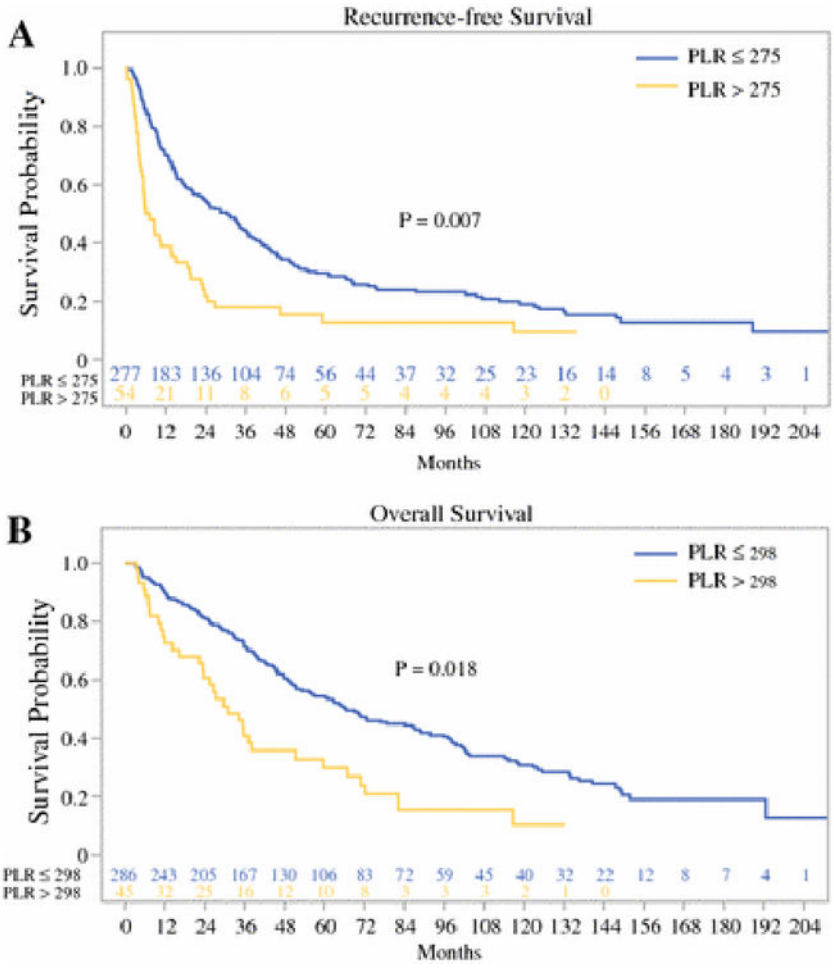


**Fig. 2.**

Relation of platelet to lymphocyte ratio (PLR) to (A) RFS and (B) OS.

**Table 1.**

Prognostic characteristics of the study patients.

| | Characteristics | RFS p-value HR (95% CI) | OS p-value HR (95% CI) |
|---|---|---|---|
| **Demographic and history** | | | |
| Age * | 65 (12) | 0.144 1.1 (1.0-1.2) | **0.005** 1.2 (1.1-1.4) |
| Male | 271 (73%) | **0.002** 1.6 (1.2-2.1) | < **0.001** 1.8 (1.3-2.5) |
| Child Pugh class B | 7 (2%) | **0.028** 2.3 (1.1-4.9) | < **0.001** 4.0 (1.9-8.5) |
| Primary liver disease | | 0.846 # 1.0 (0.8-1.2) | 0.168 # 0.8 (0.6-1.1) |
| Hepatitis B | 93 (25%) | | |
| Hepatitis C | 68 (18%) | | |
| Hepatitis B + C | 6 (2%) | | |
| Alcoholic | 40 (11%) | | |
| Hemochromatosis | 6 (2%) | | |
| None | 157 (42%) | | |
| Metabolic syndrome | 101 (27%) | 0.741 1.0 (0.8-1.4) | 0.364 1.1 (0.9-1.5) |
| **Preoperative tests** | | | |
| AFP, ng/mL * | 7799 (33988) | <**0.001** 1.4 (1.2-1.6) | **0.045** 1.2 (1.0-1.4) |
| Neutrophil, K/mcL * | 4.3 (1.4) | 0.229 1.1 (1.0-1.2) | 0.101 1.1 (1.0-1.3) |
| Lymphocyte, K/mcL * | 1.5 (0.6) | 0.110 0.9 (0.8-1.0) | 0.298 0.9 (0.8-1.1) |
| Monocyte, K/mcL * | 0.4(0.2) | 0.098 1.1 (1.0-1.3) | **0.037** 1.1 (1.0-1.3) |
| Total bilirubin, mg/dL * | 0.7 (0.4) | 0.239 1.1 (1.0-1.2) | 0.163 1.1 (0.9-1.3) |
| INR * | 1.1 (0.2) | 0.208 1.1 (1.0-1.1) | **0.010** 1.1 (1.0-1.2) |
| Creatinine, mg/dL * | 1.1 (0.4) | 0.340 1.1 (0.9-1.2) | 0.102 1.1 (1.0-1.3) |
| AST, units/L * | 59 (50) | **0.032** 1.1 (1.0-1.2) | 0.117 1.1 (1.0-1.3) |
| Platelet, K/mcL * | 236 (106) | **0.016** 1.2 (1.0-1.3) | **0.024** 1.2 (1.0-1.3) |
| Albumin, g/dL * | 4.1 (0.4) | **0.007** 0.8 (0.8-1.0) | < **0.001** 0.8 (0.7-0.9) |
| NLR * | 3.3 (2.1) | **0.007** 1.2 (1.0-1.3) | **0.015** 1.2 (1.0-1.4) |
| PLR * | 186 (135) | < **0.001** 1.3 (1.2-1.5) | **0.001** 1.3 (1.1-1.4) |
| LMR * | 4.3 (2.1) | **0.019** 0.8 (0.7-1.0) | **0.012** 0.8 (0.7-1.0) |
| PNI * | 48.9 (5.9) | **0.002** 0.8 (0.7-0.9) | < **0.001** 0.8 (0.7-0.9) |

| | Characteristics | RFS p-value HR (95% CI) | OS p-value HR (95% CI) |
|---|---|---|---|
| APRI * | 0.8 (0.8) | 0.087 1.1 (1.0-1.2) | 0.483 1.1 (0.9-1.2) |
| ANRI * | 14.9 (13.6) | 0.268 1.1 (1.0-1.2) | 0.233 1.1 (0.9-1.2) |
| **Operative data** | | | |
| Major hepatectomy | 177 (48%) | **0.013** 1.3 (1.1-1.7) | 0.064 1.3 (1.0-1.7) |
| Operative blood loss, mL * | 645 (776) | < **0.001** 1.2 (1.1-1.4) | < **0.001** 1.3 (1.2-1.4) |
| Pringle time, minutes * | 34 (17) | 0.388 1.1 (0.9-1.2) | 0.522 1.0 (0.9-1.2) |
| Tumor rupture | 15 (4%) | 0.868 0.9 (0.5-1.7) | 0.605 1.2 (0.6-2.2) |
| Local extrahepatic invasion | 18 (5%) | < **0.001** 2.5 (1.5-4.2) | **0.014** 2.0 (1.2-3.4) |
| R1 margin | 18 (5%) | < **0.001** 2.8 (1.7-4.6) | < **0.001** 3.4 (2.0-5.6) |
| **Pathological data** | | | |
| Largest tumor, cm * | 7.6 (4.7) | < **0.001** 1.3 (1.1-1.4) | < **0.001** 1.3 (1.1-1.5) |
| <5 | 117 (32%) | | |
| 5-10 | 160 (43%) | | |
| > 10 | 93 (25%) | | |
| Multiple nodules | 101 (27%) | < **0.001** 2.2 (1.7-2.8) | < **0.001** 1.9 (1.4-2.5) |
| Differentiation | | | |
| Well | 54 (15%) | | |
| Moderate (vs. well) | 220 (60%) | 0.533 1.1 (0.8-1.6) | 0.502 (0.8-1.7) |
| Poor (vs. well) | 91 (25%) | 0.190 1.3 (0.9-1.9) | 0.361 (0.8-1.9) |
| Vascular invasion | 173 (47%) | < **0.001** 1.7 (1.4-2.2) | < **0.001** 1.8 (1.4-2.4) |
| Cirrhosis | 94 (25%) | **0.007** 1.4 (1.1-1.9) | **0.003** 1.5 (1.2-2.1) |
| Steatosis | 141 (38%) | **0.004** 0.7 (0.5-0.9) | **0.004** 0.6 (0.5-0.9) |

*HR* hazard ratio, *CI* confidence interval, *RFS* recurrence-free survival, *OS* overall survival, *AFP* α-fetoprotein, *INR* international normalized ratio, *AST* asparate aminotransferase, *NLR* neutrophil to lymphocyte ratio, *PLR* platelet to lymphocyte ratio, *LMR* lymphocyte to monocyte ratio, *PNI* prognostic nutritional index, *APRI* AST to platelet ratio index, *ANRI* AST to neutrophil ratio index. Categorical variables are expressed as frequency (percentage). Continuous variables are expressed as mean (standard deviation).

*per 1 standard deviation increase.

#p-value compares hepatitis B or C or both vs. no history of viral hepatitis. Bolded p-values indicate statistical significance.

**Table 2.**

Comparison of characteristics in patients based on tumor microvascular invasion (MVI).

| | All patients (n=370) | MVI present (n=173) | MVI absent (n=197) | P-value |
|---|---|---|---|---|
| **Demographic and history** | | | | |
| Age | 65 (12) | 65 (13) | 66 (11) | 0.712 |
| Male | 271 (73%) | 130 (75%) | 141 (72%) | 0.481 |
| Child Pugh class B | 7 (2%) | 5 (3%) | 2 (1%) | 0.259 |
| Primary liver disease | | | | |
| Hepatitis B | 93 (25%) | 50 (29%) | 43 (22%) | 0.346# |
| Hepatitis C | 68 (18%) | 30 (17%) | 38 (19%) | |
| Hepatitis B + C | 6 (2%) | 3 (2%) | 3 (2%) | |
| Alcoholic | 40 (11%) | 16 (9%) | 24 (12%) | |
| Hemochromatosis | 6 (2%) | 0 (0%) | 6 (3%) | |
| None | 157 (42%) | 74 (43%) | 83 (42%) | |
| Metabolic syndrome | 101 (27%) | 45 (26%) | 56 (28%) | 0.641 |
| **Preoperative blood tests** * | | | | |
| AFP, ng/mL | 7799 (33988) | 15776 (48872) | 1087 (5056) | < **0.001** |
| Neutrophil, K/mcL | 4.3 (1.4) | 4.4 (1.4) | 4.2 (1.4) | 0.075 |
| Lymphocyte, K/mcL | 1.5 (0.6) | 1.5 (0.6) | 1.6 (0.7) | 0.139 |
| Monocyte, K/mcL | 0.4 (0.2) | 0.4 (0.2) | 0.4 (0.1) | 0.523 |
| Total bilirubin, mg/dL | 0.7 (0.4) | 0.7 (0.3) | 0.8 (0.4) | 0.319 |
| INR | 1.1 (0.2) | 1.1 (0.1) | 1.1 (0.2) | 0.151 |
| Creatinine, mg/dL | 1.1 (0.4) | 1.1 (0.5) | 1.1 (0.3) | 0.457 |
| AST, units/L | 59 (50) | 66 (55) | 53 (44) | **0.001** |
| Platelet, K/mcL | 236 (106) | 249 (112) | 225 (100) | **0.026** |
| Albumin, g/dL | 4.1 (0.4) | 4.1 (0.5) | 4.2 (0.4) | **0.018** |
| NLR | 3.3 (2.1) | 3.5 (1.9) | 3.2 (2.3) | **0.014** |
| PLR | 186 (135) | 199 (133) | 173 (136) | **0.016** |
| LMR | 4.3 (2.1) | 4.1 (2.2) | 4.5 (2.0) | **0.039** |
| PNI | 48.9 (5.9) | 48.0 (6.2) | 49.7 (5.5) | **0.009** |
| APRI | 0.8 (0.8) | 0.8 (0.9) | 0.8 (0.8) | 0.119 |
| ANRI | 14.9 (13.6) | 16.0 (14.5) | 13.9 (12.7) | 0.057 |
| **Preoperative imaging** | | | | |
| Largest tumor, cm | 7.6 (4.7) | 8.9 (5.0) | 6.6 (4.1) | < **0.001** |
| Multiple nodules | 44 (12%) | 23 (13%) | 21 (11%) | 0.520 |

*MVI* microvascular invasion, *AFP* α-fetoprotein, *INR* international normalized ratio, *AST* aspartate aminotransferase. *NLR* neutrophil to lymphocyte ratio, *PLR* platelet to lymphocyte ratio, *LMR* lymphocyte to monocyte ratio, *PNI* prognostic nutritional index, *APRI* AST to platelet ratio index, *ANRI* AST to neutrophil ratio index. Categorical variables are expressed as frequency (percentage). Continuous variables are expressed as mean (standard deviation).

* per 1 standard deviation increase.

[#]p-value compares hepatitis B or C or both vs. no history of viral hepatitis. Bolded p-values indicate statistical significance.

**Table 3.**

Factors independently associated with microvascular invasion (MVI), RFS, and OS.

| **A. MVI** | | |
|---|---|---|
| | **OR (95% CI)** | **p-value** |
| AFP* | 5.471 (1.660-18.034) | 0.005 |
| Albumin* | 0.780 (0.609-0.999) | 0.049 |
| Radiologic tumor size* | 1.455 (1.133-1.869) | 0.003 |

*OR* hazard ratio, *CI* confidence interval, *AFP* α-fetoprotein. *per 1 standard deviation increase.

| **B. RFS** | | |
|---|---|---|
| | **HR (95% CI)** | **p-value** |
| Male | 1.502 (1.090-2.068) | 0.013 |
| AFP* | 1.303 (1.145-1.483) | < 0.001 |
| PLR* | 1.292 (1.129-1.479) | < 0.001 |
| Microvascular invasion | 1.539 (1.174-2.017) | 0.002 |
| Multiple nodules or satellites | 1.826 (1.357-2.458) | < 0.001 |

*HR* hazard ratio, *CI* confidence interval, *AFP* α-fetoprotein, *PLR* platelet to lymphocyte ratio. *per 1 standard deviation increase.

| **C. OS.** | | |
|---|---|---|
| | **HR (95% CI)** | **p-value** |
| Age* | 1.375 (1.171-1.614) | < 0.001 |
| Male | 1.764 (1.241-2.508) | 0.002 |
| INR* | 1.143(1.030-1.269) | 0.012 |
| PLR* | 1.235 (1.057-1.444) | 0.008 |
| Microvascular invasion | 1.763 (1.293-2.406) | < 0.001 |
| Multiple nodules or satellites | 1.474 (1.067-2.037) | 0.019 |
| Tumor size* | 1.297 (1.100-1.529) | 0.002 |
| Cirrhosis | 2.458 (1.702-3.551) | < 0.001 |
| Steatosis | 0.688 (0.497-0.952) | 0.024 |

*HR* hazard ratio, *CI* confidence interval, *INR* international normalized ratio, *PLR* platelet to lymphocyte ratio. *per 1 standard deviation increase.