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# Platelet-albumin (PAL) score as a predictor of perioperative outcomes and survival in patients with hepatocellular carcinoma undergoing liver resection in a Western center

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ABSTRACT

*Background and objectives:* Preoperative selection of patients with hepatocellular carcinoma (HCC) who will benefit from resection is highly advisable. The Platelet-Albumin (PAL) score was developed as a predictor of survival and morbidity following HCC resection. However, this has never been tested in western populations.
*Methods:* The impact of PAL score on perioperative outcomes and survival was evaluated and compared to Child-Pugh, Model for End-Stage Liver Disease (MELD), and albumin-bilirubin (ALBI) scores in patients who underwent HCC resection.
*Results:* A total of 182 patients were included. Postoperative morbidity was higher in patients with PAL grade II-III ($P = 0.039$), ALBI grade II-III ($P = 0.028$), and MELD >10 ($P = 0.042$). Post-hepatectomy liver failure (PHLF) occurred in 36 patients (19.8%) and was significantly higher in the PAL II-III and ALBI score II-III subgroup ($P = 0.001$). The PAL II-III group was the only one associated with higher perioperative mortality (OR 3.3, $P = 0.036$). The PAL score was an independent prognostic factor for overall survival in multivariate analysis ($P = 0.018$) and was the only one with the areas under the curve in ROC analysis significantly different for morbidity, PHLF, and mortality.
*Conclusions:* The PAL score predicts postoperative complications, mortality, PHLF, and survival following liver resection for HCC in western patients.

## 1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignant liver tumor and the third most frequent cause of cancer-associated mortality worldwide [1]. In western countries, 80–90% of HCCs develop in cirrhotic livers [2]. The treatment of HCC is complex and must be tailored to individual patients in a multidisciplinary context [3]. Therapeutic decisions should consider tumor-related factors, the presence and severity of chronic liver failure, and the patient's clinical condition [4]. Among curative therapeutic options, surgical resection, liver transplantation, and radiofrequency ablation stand out [5].

Resection plays a significant role in the treatment of patients with HCC and is the modality of choice for non-cirrhotic patients [6]. Compared to liver transplantation, liver resection is less expensive, has less restrictive criteria, and is immediately applicable with no waiting list [7]. In patients with chronic liver disease, resection is usually indicated for patients with preserved liver function and a liver remnant volume greater than 40% [8], but preoperative strategies to increase the future liver remnant can be employed to improve resectability [9]. The five-year overall survival (OS) and disease-free survival (DFS) rates for patients who underwent resection for HCC ranged from 50 to 75% and 30 to 55%, respectively [7,10].

Several oncologic prognostic factors for HCC resection have already been studied, including serum AFP levels, size and number of nodules, degree of cellular differentiation, presence of satellite nodules, and micro or macrovascular invasion [11]. However, new markers have been sought to refine the understanding of HCC prognosis, especially preoperatively, since the main known prognostic factors are accessible

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only after pathological evaluation of the specimen.

The risk following surgical resection is not only related to tumor characteristics, but also to liver function [12]. In this context, the assessment of liver disease severity is important to predict postoperative complications and can be established through different measures, including the traditional Child-Pugh and Model for End-Stage Liver Disease (MELD) classifications, indocyanine green clearance (ICG) [13,14], and more recently through new scores, such as albumin-bilirubin (ALBI) and albumin-indocyanine green evaluation (ALICE) [15,16].

Recently, Shindoh, et al. [16] proposed a new score based on serum albumin concentration and platelet count (platelet-albumin [PAL] score), showing that it was able to predict postoperative morbidity and long-term survival. More importantly, the authors emphasized that the PAL score could be a simple and available method to predict short- and long-term outcomes of patients undergoing curative resection for HCC independent of the oncological staging [16].

Despite the promising results in an eastern center, the PAL score has never been tested in western populations, where HCC presents unique clinical and epidemiological features [17–19].

The aim of this study was to evaluate the PAL score as a predictor of perioperative morbidity and mortality and long-term survival in patients with HCC who underwent resection in a referral western center. Additionally, we compared the PAL score with the ALBI, Child-Pugh, and MELD scores, which are routinely used in our institution.

## 2. Methods

This retrospective cohort study was based on a prospectively maintained database approved by our institution's ethics committee. Consecutive adult patients with pathologically proven HCC who underwent hepatectomy with curative intent between January 2008 and July 2019 were included.

The inclusion criteria were patients older than 18 years, uni-or oligonodular disease (up to three nodules), and absence of extrahepatic disease. Patients with chronic liver disease and compensated liver function were considered eligible as follows: Child-Pugh A (or B when minor peripheral resection was required) and MELD $\leq$10 (or higher when minor peripheral resection was required), without clinically significant portal hypertension (small caliber esophageal varices and platelets >100,000/mL), future liver remnant $\geq$40% [20], and serum bilirubin levels <2.0 mg/dL [21]. The exclusion criteria were positive margins, previous chemoembolization or ablation, and lack of patient data. All cases were discussed at a multidisciplinary meeting before the surgery.

The preoperative variables were sex, age, American Society of Anesthesiologists (ASA) classification, Charlson comorbidity index [22], presence and etiology of chronic liver disease, presence of portal hypertension, size and number of lesions, presence of vascular invasion, and laboratory tests (complete blood count, coagulation tests, urea, creatinine, bilirubin, albumin, and alpha-fetoprotein). Child-Pugh, MELD, ALBI, and PAL scores were calculated for each patient. The variables of interest were studied in three subgroups according to the stratification of the PAL score, as proposed by Shindoh et al. [16].

Surgeries were performed by one of three surgeons, experienced in either, open and laparoscopic liver surgery. The following data were retrieved for the intraoperative period: type of liver resection, operative time, estimated blood loss, and transfusion rate. Hepatectomies were defined as major extended when five or more contiguous hepatic segments were resected, major when three or four contiguous hepatic segments were resected, and as minor when the resection was restricted to two segments. In the postoperative period, the length of hospital stay, overall morbidity, specific complications, and perioperative mortality were recorded.

Perioperative morbidity was defined as any complication occurring in the first 30 days postoperatively and was stratified according to the Dindo-Clavien classification [23]. Perioperative mortality was defined as death during the hospital stay or within the first 90 days after liver resection. PHLF was defined as an increased international normalized ratio (INR) and hyperbilirubinemia on or after postoperative day 5, as proposed by the International Study Group of Liver Surgery [24].

The ALBI score was calculated as follows: (log10 bilirubin [μmol/L] $\times$ 0.66) + (albumin [g/L] $\times$ −0.085). The ALBI groups were defined as grade I if the score was $\leq$ −2.60, grade II between −2.60 and $\leq$ −1.39, and ALBI grade III if the score was > −1.39, as defined by Johnson et al. [14].

The PAL score was calculated using the following equation: − 0.777 $\times$ albumin [g/dL] − 0.575 $\times$ log10 (platelet count) [$10^4$/μL]. PAL score grade I was defined when $\leq$ −3.77, grade II when > −3.77 and $\leq$ −3.04, and grade III when > −3.04 [16].

## 3. Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median and range, and compared using the *t*-test or Mann-Whitney test. The normality of the quantitative data was assessed using the Kolmogorov-Smirnov test. Categorical variables were compared using the chi-square test or Fisher's exact test. For comparisons and statistical analysis, PAL and ALBI grades II and III were evaluated together. Statistical significance was set at $p < 0.05$.

Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. Associations with survival were evaluated using Cox proportional hazards regression and summarized with hazard ratios (HRs) and 95% confidence intervals (95% CIs). MELD, ALBI, and PAL scores were compared using receiver operating characteristic (ROC) analysis. As the Child-Pugh score is qualitative, it could not be directly compared to the other scores through ROC analysis. Comparison between the areas under the curves was done as proposed by DeLong et al. [25]. Statistical analysis was done using the Statistical Package for the Social Sciences version 25.

## 4. Results

During the study period, 182 patients with HCC who fulfilled the inclusion criteria underwent resection. All patients had a R0 resection, since positive margins were one of the exclusion criteria. Most patients had chronic liver disease (84.1%). Hepatitis C (50.5%), alcoholic disease (17.6%), and hepatitis B (14.3%) were the most common etiologies. Of 182 resections, 124 (68.1%) were anatomical liver resections, 49 (26.9%) major hepatectomies, and 6 (3.3%) major extended hepatectomies. Until December 2012, 76% of the surgeries were open; after January 2013, 35% of the surgeries were open and 65% were video-assisted or totally laparoscopic.

One hundred ten (60.4%) patients were classified as PAL score I, 56 (30.8%) as PAL score II, and 16 (8.8%) as PAL score III. One hundred nineteen (65.4%) patients were classified as ALBI score I, 55 (30.2%) as ALBI score II, and 8 (4.4%) as ALBI score III. One hundred and forty-eight patients (81.3%) were classified as Child-Pugh class A, and five (2.7%) patients were classified as Child-Pugh B. In 159 patients (87.4%), the MELD score was up to 10, and in 23 (12.6%) patients over 10.

The baseline characteristics of the patients are summarized in Table 1. There were no differences between the PAL I and PAL II-III groups regarding ASA classification, Charlson comorbidity index, the extent of liver resection, surgical approach (open or laparoscopic), type of resection (anatomical or non-anatomical), operative time and estimated blood loss. Only the MELD score and the transfusion rate were significantly higher in the PAL II-III group.

Perioperative morbidity was observed in 80 patients (43.9%), and 45 (56.2%) were classified as Dindo-Clavien I or II. PAL score grades II-III ($P = 0.032$), ALBI score grades II-III ($P = 0.028$), MELD >10 ($P = 0.042$), major liver resections ($P = 0.015$), open approach ($p = 0.000$), and transfusion $\geq$4 blood units ($p = 0.011$) were associated with a higher incidence of perioperative morbidity, as shown in Table 2. The

**Table 1**
Patients' baseline characteristics.

| Variable | PAL score IN = 110 (%) | PAL score II-IIIN = 72 (%) | p-value |
|---|---|---|---|
| Sex | | | 0.236[1] |
| Female | 32 (29.1) | 27 (37.5) | |
| Male | 78 (70.9) | 45 (62.5) | |
| Age | | | 0.684[3] |
| Mean | 60.83 | 61.76 | |
| Median | 63.50 | 60.50 | |
| Ethnicity | | | 0.11[1] |
| Non-White | 36 (32.7) | 32 (44.4) | |
| White | 74 (67.3) | 40 (55.6) | |
| Body Mass Index | | | 0.181[3] |
| Mean | 25.82 | 24.84 | |
| Median | 25.55 | 24.73 | |
| MELD | | | < 0.001[1] |
| ≤ 10 | 105 (95.5) | 54 (75.0) | |
| > 10 | 5 (4.5) | 18 (25.0) | |
| Mean | 7.94 | 9.08 | 0.013 [3] |
| ASA | | | 0.168 [2] |
| II | 65 (59.1) | 33 (45.8) | |
| III | 42 (38.2) | 35 (48.6) | |
| IV | 3 (2.7) | 4 (5.6) | |
| CCI | | | 0.139 [2] |
| 3 | 11 (10.0) | 2 (2.8) | |
| 4 | 15 (13.6) | 14 (19.4) | |
| 5 | 28 (25.5) | 9 (12.5) | |
| 6 | 25 (22.7) | 19 (26.4) | |
| 7 | 17 (15.5) | 14 (19.4) | |
| 8 | 9 (8.2) | 7 (9.7) | |
| 9 | 3 (2.7) | 4 (5.6) | |
| ≥ 10 | 2 (1.8) | 3 (4.2) | |
| Chronic Liver Disease | | | 0.306 [1] |
| No | 20 (18.2) | 9 (12.5) | |
| Yes | 90 (81.8) | 63 (87.5) | |
| Child-Pugh | | | 0.160 [2] |
| A | 89 (98.9) | 59 (93.7) | |
| B | 1 (1.1) | 4 (6.3) | |
| Alpha-fetoprotein | | | 0.503 [1] |
| < 1000 ng/mL | 94 (85.5) | 64 (88.9) | |
| ≥ 1000 ng/mL | 16 (14.5) | 8 (11.1) | |
| Number of nodules | | | 0.527 [1] |
| 1 | 94 (85.5) | 61 (84.7) | |
| 2-3 | 16 (14.5) | 11 (15.3) | |
| Size of largest nodule | | | 0.164 [2] |
| ≤ 50 mm | 61 (55,5) | 48 (66.7) | |
| > 50 mm | 49 (44.5) | 24 (33.3) | |
| Surgical approach | | | 0.167 [1] |
| Open | 52 (47.3) | 44 (61.1) | |
| Pure laparoscopic | 34 (30.9) | 18 (25.0) | |
| Hybrid | 24 (21.8) | 10 (13.9) | |
| Extent of Liver Resection | | | 0.698[1] |
| Minor | 74 (67.3) | 53 (73.6) | |
| Major | 32 (29.1) | 17 (23.6) | |
| Major extended | 4 (3.6) | 2 (2.8) | |
| Type of resection | | | 0.187[1] |
| Non-anatomic | 31 (28.2) | 27 (37.5) | |
| Anatomic | 79 (71.8) | 45 (62.5) | |
| Operative Time (min) [SD] | 338 [135] | 316 [129] | 0.284[3] |
| Estimated Blood Loss (mL) [SD] | 558 [696] | 577 [515] | 0.418[3] |
| Units of blood transfunded during surgery | | | 0.016[3] |
| 0–3 | 108 (98.2) | 65 (90.3) | |
| ≥ 4 | 2 (22.2) | 7 (9.7) | |

PAL: platelet-albumin score, MELD: Model for End-Stage Liver Disease, ALBI: albumin-bilirubin score, CCI: Charlson's comorbidity index; SD: Standard Deviation.
[1] Pearson's qui-square test.
[2] Fisher's exact test.
[3] Mann-Whitney's test.

**Table 2**
Risk factors for perioperative complications and post-hepatectomy liver failure.

| | Perioperative morbidity | | p-value | Post-hepatectomy Liver Failure | | p-value |
|---|---|---|---|---|---|---|
| | No N = 102 (%) | Yes N = 80 (%) | | No N = 146 (%) | Yes N = 36 (%) | |
| PAL score grade | | | 0.032 [1] | | | 0.001 [1] |
| I | 69 (67.6) | 41 (51.2) | | 97 (66.4) | 13 (36.1) | |
| II-III | 33 (32.4) | 39 (48.8) | | 49 (33.6) | 23 (63.9) | |
| Preoperative MELD | | | 0.042 [1] | | | 0.409 [2] |
| ≤ 10 | 94 (92.2) | 65 (81.2) | | 129 (88.4) | 30 (83.3) | |
| > 10 | 8 (7.8) | 15 (18.8) | | 17 (11.60 | 6 (16.7) | |
| Child-Pugh | | | 1.0 [2] | | | 0.257 [2] |
| A | 81 (96.4) | 67 (97.1) | | 114 (97.4) | 34 (94.4) | |
| B | 3 (3.6) | 2 (2.9) | | 3 (2.6) | 2 (5.6) | |
| ALBI score grade | | | 0.028 [1] | | | 0.001 [1] |
| I | 74 (72.5) | 45 (56.2) | | 104 (71.2) | 15 (41.7) | |
| II-III | 28 (27.5) | 35 (43.8) | | 42 (28.8) | 21 (58.3) | |
| Surgical approach | | | 0.000 [1] | | | 0.076 [1] |
| Open | 41 (40.2) | 55 (68.8) | | 71 (48.6) | 25 (69.4) | |
| Pure laparoscopic | 39 (38.2) | 13 (16.2) | | 46 (31.5) | 6 (16.7) | |
| Hybrid | 22 (21.6) | 12 (15.0) | | 29 (19.9) | 5 (13.9) | |
| Extent of Liver Resection | | | 0.005 [2] | | | 0.594 [2] |
| Minor hepatectomy | 80 (78.4) | 47 (58.8) | | 103 (70.5) | 24 (66.7) | |
| Major hepatectomy | 21 (20.6) | 28 (35.0) | | 39 (26.7) | 10 (27.8) | |
| Major extended hepatectomy | 1 (1.0) | 5 (6.2) | | 4 (2.7) | 2 (5.6) | |
| Units of blood transfused during surgery | | | 0.011 [2] | | | 0.08 [2] |
| 0 - 3 | 101 (99.0) | 72 (90.0) | | 141 (96.6) | 32 (88.9) | |
| ≥ 4 | 1 (1.0) | 8 (10.0) | | 5 (3.4) | 4 (11.1) | |

PAL: platelet-albumin score, MELD: Model for End-Stage Liver Disease, ALBI: albumin-bilirubin score.
[1] Pearson's qui-square test.
[2] Fisher's exact test.

Child-Pugh score was not associated with morbidity (p = 1.0). Bile leak occurred in 16 patients (8.8%), all with spontaneous resolution; no interventions were necessary. Perioperative complications are detailed in Table 3.

Thirty-six patients (19.8%) developed PHLF. The occurrence of PHLF was significantly higher in patients with PAL scores II-III (OR = 3.50, 95%CI 1.63–7.50, P = 0.001) and ALBI score II-III (OR 3.46, 95% CI, 1.63–7.36, P = 0.001). The Child-Pugh score (OR = 2.80, 95% CI, 0.45–17.4, P = 0.257), preoperative MELD (OR = 1.51, 95% CI, 0.55–4.17, P = 0.409) were not associated with PHLF. Postoperative ascites occurred in 27 (75%) of 36 patients with PHLF and six patients (16%) presented with encephalopathy. The extent of liver resection and the number of transfused blood units were also not associated with PHLF (Table 2). The correlation between PHLF, PAL, and ALBI scores was also

**Table 3**
Perioperative complications following liver resection for HCC.

| | PAL Score | | p-value |
|---|---|---|---|
| | I | II – III | |
| | N = 110 (%) | N = 72 (%) | |
| Total Complications | 41 (37.3) | 39 (54.1) | 0.032 [1] |
| Pneumonia | 3 (2.7) | 1 (1.4) | 1.0 [2] |
| Wound Infection/Dehiscence | 9 (8.2) | 5 (6.9) | 0.759 [1] |
| Thrombosis | 2 (1.8) | 3 (4.2) | 0.386 [2] |
| Bleeding | 0 (0.0) | 2 (2.8) | 0.155 [2] |
| Bile Leak | 13 (11.8) | 3 (4.2) | 0.075 [1] |
| PHLF | 13 (11.8) | 23 (31.9) | 0.001 [1] |
| Clavien-Dindo | | | 0.657 [1] |
| I - II | 21 (19.1) | 24 (33.3) | |
| ≥ IIIa | 21 (19.1) | 14 (19.4) | |

PAL: platelet-albumin score; PHLF: posthepatectomy liver failure.
[1] Pearson's qui-square test.
[2] Fisher's exact test.

confirmed when evaluating only Child-Pugh A patients (P = 0.002 and P = 0.003, respectively).

The perioperative mortality rate was 7.1% (n = 13). Most deaths were related to septic complications, such as pneumonia or secondary bacterial peritonitis. One patient died of acute myocardial infarction. PAL score grades II-III were significantly associated with a higher risk of perioperative mortality (OR 3.31, 95% CI, 1.03–10.60, P = 036). ALBI score grades II-III (P = 0.065), Child-Pugh score (P = 1.0), and MELD score >10 (P = 0.216) were not associated with perioperative mortality (Table 4).

The scores were compared using the ROC analysis. PAL score had the highest AUC for all the outcomes, although the difference between the areas was not significant using the DeLong's method [25]. PAL score was the only score that had an AUC significantly higher than 0.5 when evaluating postoperative mortality (Table 5) (see Fig. 1).

Multivariate Cox regression was applied with stepwise backward selection. Initially, all factors were included in the model for a univariate analysis. Then, factors that showed no or limited statistically significant association (P > 0.1) with each prognostic indicator adjusted for the remaining factors in the model, were deleted from the model in stepwise fashion. The factors tested were as follows: PAL score, ALBI score, AFP, nodule size, Milan criteria, preoperative Child, preoperative MELD, and chronic liver disease. PAL score grade II-III was an independent prognostic factor for OS (HR = 1.85, 95% CI, 1.11–3.08, P = 0.018) in the multivariate analysis (Table 6 and Fig. 2), but it was not associated with DFS. ALBI, MELD and Child-Pugh scores were not predictors of OS (HR = 1.31, 95% CI, 0.591–2.907, P = 0.506; HR = 1.163, 95% CI, 0.598–2.261, P = 0.656; and HR = 0.513, 95% CI, 0.119–2.207, P = 0.370; respectively). ALBI and Child-Pugh were not associated with DFS. Most patients with HCC relapse were either referred for transplantation or ablation; only 6 patients (with a single nodule, and preserved liver function) were submitted to repeated liver resection.

**Table 4**
Perioperative mortality and associated factors following liver resection for HCC.

| | Perioperative Mortality | | p-value |
|---|---|---|---|
| | No | Yes | |
| | N = 169 (%) | N = 13 (%) | |
| PAL score grades | | | 0.036 [1] |
| I | 106 (62.7) | 4 (30.8) | |
| II-III | 63 (37.3) | 9 (69.2) | |
| ALBI score grades | | | 0.065 [2] |
| I | 114 (67.5) | 5 (38.5) | |
| II-III | 55 (32.5) | 8 (61.5) | |
| Child-Pugh | | | 1.0 [2] |
| A | 137 (92.6) | 11 (100.0) | |
| B | 5 (3.5) | 0 (0.0) | |
| MELD | | | 0.216 [2] |
| ≤10 | 149 (88.2) | 10 (76.9) | |
| >10 | 20 (11.8) | 3 (32.1) | |
| Extent of liver resection | | | 1.0 [2] |
| Minor hepatectomy | 117 (69.2) | 10 (76.9) | |
| Major hepatectomy | 46 (27.2) | 3 (23.1) | |
| Major extended hepatectomy | 6 (3.6) | 0 (0.0) | |
| Units of blood transfused during surgery | | | 0.128 [2] |
| 0 - 3 | 162 (95.9) | 11 (84.6) | |
| ≥ 4 | 7 (4.1) | 2 (15.4) | |

PAL: platelet-albumin score, MELD: Model for End-Stage Liver Disease, ALBI: albumin-bilirubin score.
[1] Pearson's qui-square test.
[2] Fisher's exact test.

## 5. Discussion

Assessment of liver function is mandatory for therapeutic decisions in patients with chronic liver disease who develop HCC. Several scores and classifications were used to predict outcomes in these patients preoperatively [13–16].

The evaluation of both oncologic staging and liver function parameters in a single score is difficult, since liver function is strongly correlated with the choice of treatment [16], and in turn, with the prognosis. Thus, it is preferable to evaluate these parameters separately. Shindoh et al. [16] demonstrated that the PAL score, in addition to being a fine tool for liver function assessment, is also a reliable predictor of survival outcomes regardless of the oncological HCC stage. Platelets are key factors in HCC's progression [26,27], and are affected by the severity of liver disease. Both platelets and albumin are important markers of the liver functional reserve [28]. Therefore, a score that take both albumin and platelets into account could biologically predict surgical complications and survival in these patients.

The Child-Pugh score is a well-established scoring system based solely on clinical and laboratory data [29], and patients classified as Child-Pugh A are supposed to present good postoperative outcomes following liver resections. However, even Child-Pugh A patients can develop PHLF [30]. On the other hand, it is possible to perform minor resections in patients with Child-Pugh B with safety. Therefore, a score that allowed a refinement in the preoperative risk assessment of these patients (especially Child-Pugh A and B7) would be useful.

The MELD score is also useful for predicting the risk of postoperative complications. It has been shown that liver resection can be safely performed in patients with MELD score <10 [31]. Indeed, higher MELD scores were associated with an increased incidence of postoperative complications in our cohort. In our experience, for 23 patients with a MELD >10, only limited resections were performed, and yet it was associated with a higher incidence of complications. Considering that in our series, 87.3% of patients presented with a MELD score <10, we sought another assessment tool to predict postoperative morbidity.

Although MELD and Child-Pugh scores are useful and established scores, there is a need to refine preoperative risk assessment, especially in patients with close-to-normal preoperative liver function (MELD <10 and Child-Pugh A or B7).

The indocyanine green clearance test (ICG), used in many eastern centers as a method to evaluate liver function, is rarely available in western centers.

When compared with the Child-Pugh score, the ALBI score was a better predictor of both short- and long-term surgical outcomes [32,33]. However, in our treatment protocol, we avoided resection in patients with serum bilirubin levels greater than 2 mg/dL, which was the same criteria used by Shindoh and previously proposed by Makuuchi et al. [21]. Shindoh [16] demonstrated a stronger predictive power of the PAL score compared to the ALBI score for both short- and long-term surgical outcomes. In the present study, PAL score had the highest AUC in the ROC analysis regarding morbidity, PHLF and mortality, thus confirming Shindoh's findings. Since the PAL score does not depend on bilirubin concentration, it is a better tool to predict postoperative outcomes.

**Table 5**
AUC of liver function scores for short-term surgical outcomes.

| | PAL Score | | ALBI Score | | MELD | |
|---|---|---|---|---|---|---|
| | AUC (95%CI) | p | AUC (95%CI) | p | AUC (95%CI) | p |
| Postoperative Morbidity | 0.605 (0.528–0.675) | 0.016 | 0.603 (0.530–0.677) | 0.015 | 0.592 (0.517–0.674) | 0.028 |
| PHLF | 0.653 (0.549–0.757) | 0.004 | 0.648 (0.574–0.717) | 0.006 | 0.590 (0.514–0.662) | 0.096 |
| Perioperative Mortality | 0.666 (0.507–0.840) | 0.046 | 0.630 (0.453–0.807) | 0.118 | 0.599 (0.426–0.772) | 0.234 |

Values represent the area under the curve in receiver-operating characteristics curve analysis.
PAL: platelet-albumin score, MELD: Model for End-Stage Liver Disease, ALBI: albumin-bilirubin score, AUC: area under the curve.

**Table 6**
Multivariate analysis of global and disease free survival.

| Variable | | HR (IC95%) | P value |
|---|---|---|---|
| Global Survival | | | |
| Alpha-fetoprotein | <200 | 1 | |
| | ≥200 | 1,76 (1,00–3,09) | 0,049 |
| PAL | I | 1 | |
| | II-III | 1,85 (1,11–3,08) | 0,018 |
| Disease-free survival | | | |
| Alpha-fetoprotein | <200 | 1 | |
| | ≥200 | 1,73 (1,04–2,88) | 0,035 |
| PAL | I | 1 | |
| | II-III | 1,10 (0,66–1,84) | 0,715 |

HR: hazard ratio; IC95%: 95% confidence interval.

Although the difference between the AUCs for PAL, ALBI, and MELD scores was not significant according to DeLong's method [25], it is noteworthy that PAL score was the only score with the three AUCs significantly higher than 0.5, and the only score which AUC for mortality was significantly higher than 0.5.

The PAL score is a widely available test that requires only basic and routine biochemical data and is significantly associated with postoperative morbidity, PHLF, and perioperative mortality in this cohort. The groups (PAL I and II–III) were similar, and the only difference was the MELD score, higher in the II-III group, which was expected considering that the PAL score also evaluates liver function, as demonstrated by Shindoh [16]. Although MELD was not developed as a tool to evaluate liver function, it can be seen as an indirect measure of function, as it comprises bilirubin and INR, thus explaining why MELD was higher in PAL II-III subgroup. Another possible interpretation would be that the higher MELD in PAL II-III subgroup was an eventual bias to the postoperative complication analysis, as MELD is a well-known predictor of postoperative complications. When evaluating only Child A patients, who were supposed to present an uneventful postoperative course, the PAL score predicted PHLF, regardless of the extent of liver resection. Therefore, our study confirms the data supporting the PAL score as a good alternative to stratify the risk of postoperative complications. Moreover, PAL score was also good in predicting perioperative mortality and PHLF following liver resection for HCC, without any possible bias related to the higher MELD in PAL II-III subgroup, as MELD was not associated to PHLF or mortality in our cohort.

In Shindoh's [16] study, the $\log_{10}$ (platelet count) and the albumin level were independent predictors of survival. In this study, PAL score was an independent prognostic factor for OS, but not for DFS. The impact on OS was probably due to PAL's relation with liver function; the absence of impact on DFS was probably due to a small sample size, or because recurrence is mostly related to tumor biology rather than liver function.

The overall complication rate, incidence of PHLF, and perioperative mortality rate observed in our series are in accordance with western cohorts [23,34–37]. The higher operative morbidity associated with open surgeries is probably related to the preoperative selection of more complex cases and larger tumors for the open approach. The higher operative mortality when compared with colorectal liver metastasis resection is explained by the fact that over 80% of our patients presented with chronic liver disease, and that 30.2% of patients underwent major liver resections. These data reinforce the need for a precise preoperative

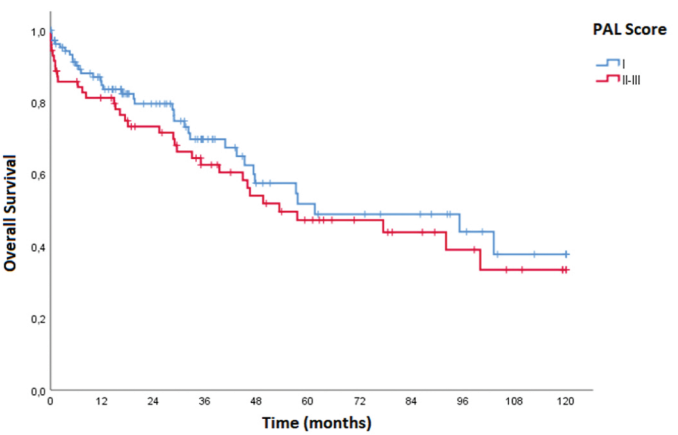


**Fig. 2.** Overall survival and PAL score (p = 0.018).

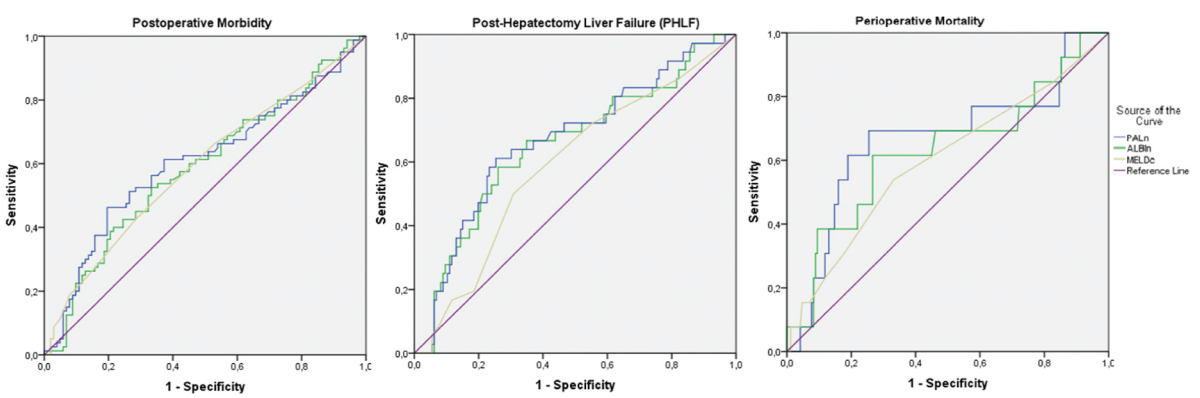


**Fig. 1.** AUCs for postoperative morbidity, PHLF and Mortality.

evaluation and the use of a reliable scoring system to predict morbidity, PHLF, and mortality in such patients.

The limitations of this study include its retrospective nature and the relatively small sample size. However, we would like to emphasize that this is the first study to employ the PAL score in a western population with HCC who underwent liver resection. Larger and multicentric studies in Western populations are needed to confirm our data. Based on the results of this study, our group started to routinely employ the PAL score in the preoperative evaluation of patients with HCC.

## 6. Conclusions

The PAL score is a simple and useful tool that predicts postoperative complications, PHLF, and perioperative mortality in patients with HCC who underwent liver resection with curative intent. The PAL score also had an independent impact on OS, but not on DFS. It adds information to help the multidisciplinary team decide the best therapeutic strategy for each patient and should be incorporated into the routine of liver surgery units.

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This study was approved by the Institution's Ethics Committee (nº 4.228.790).

## Author statement

Platelet-albumin (PAL) score as a predictor of perioperative outcomes and survival in patients with hepatocellular carcinoma undergoing liver resection in a Western center.

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This study was approved by the Institution's Ethics Committee (nº 4.228.790).

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RESEARCH

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# Preoperative inflammatory markers as prognostic predictors after hepatocellular carcinoma resection: data from a western referral center

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## Abstract

**Background:** Recent studies from eastern centers have demonstrate an association between inflammatory response and long-term outcomes after hepatocellular carcinoma (HCC) resection. However, the prognostic impact of inflammatory markers in western patients, with distinct tumor and epidemiologic features, is still unknown.

**Aim:** To evaluate the prognostic impact of preoperative neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR), as well as their impact according to tumor size (< 5 cm, 5–10 cm, > 10 cm) in patients undergoing HCC resection with curative intent.

**Methods:** Optimal cut-off values for NLR, PLR, and MLR were determined by plotting the receiver operator curves. Overall survival (OS) and disease-free survival (DFS) curves were calculated using the Kaplan–Meier method and compared using the log-rank test. The Cox method was used to identify independent predictors of OS and DFS.

**Results:** In total, 161 consecutive adult patients were included. A high NLR (> 1.715) was associated with worse OS (P = 0.018). High NLR (> 2.475; P = 0.047) and PLR (> 100.25; P = 0.028) were predictors of short DFS. In HCC < 5 cm, MLR (> 1.715) was associated with worse OS (P = 0.047). In the multivariate analysis, high PLR was an independent predictor of worse DFS [hazard ratio (HR) 3.029; 95%CI 1.499–6.121; P = 0.002].

**Conclusion:** Inflammatory markers are useful tools to predict long-term outcomes after liver resection in western patients, high NLR was able to stratify subgroups of patients with short OS and DFS, an increased PLR was an independent predictor of short DFS, while high MLR was associated with short OS in patients with early HCC.

**Keywords:** Hepatectomy, Hepatocellular carcinoma, Inflammation, Prognosis, Survival analysis

## Introduction

Hepatocellular carcinoma (HCC) is the third most frequent cause of cancer-associated mortality worldwide, with more than 900,000 deaths per year [1, 2]. Among the curative modalities, resection is one of the mainstays of HCC treatment; however, the recurrence rate remains high, reaching 50–80% in 5 years [3].

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The main prognostic factors for patients with HCC who underwent resection are serum alpha-fetoprotein levels, the number of lesions, tumor size, and presence of vascular invasion and satellite nodules [4]. However, most of these factors can only be assessed after surgical specimen evaluation and cannot be used for preoperative patient selection. For this reason, the search for preoperative prognostic markers that may help understand the tumors' biology is advisable.

Recent studies have shown an association between inflammatory response and long-term outcomes in several solid gastrointestinal tumors [5, 6]. However, the prognostic impact of inflammatory markers in patients who underwent surgical resection for HCC is still under debate.

The neutrophil-to-lymphocyte ratio (NLR) is the most studied preoperative biomarker for patients with HCC [7]. Moreover, recent studies have suggested that the NLR is also a prognostic factor in specific subgroups, such as patients with small tumors (< 5 cm) [8] or large HCCs (> 10 cm) [9]. However, other authors have failed to detect an association between NLR and HCC prognosis [10]. In recent years, a few eastern studies also suggested the impact of other inflammatory markers, such as the platelet-to-lymphocyte ratio (PLR) and monocyte-to-lymphocyte ratio (MLR), on long-term outcomes of HCC patients [11].

Despite promising outcomes, few studies conducted in western centers, where HCC presents distinct tumor and epidemiologic characteristics, have assessed the ability of NLR, PLR and MLR to predict long-term survival in patients with HCC undergoing liver resection [12]. Additionally, to our knowledge, no western studies have evaluated the impact of inflammatory markers on subsets of patients according to tumor size.

The primary endpoint of this study was to evaluate the prognostic impact of the NLR, PLR, and MLR on the long-term outcomes of patients who underwent curative hepatic resection for HCC. The secondary endpoint was to evaluate the prognostic impact of these markers on subgroups of patients according to tumor size: < 5 cm, 5–10 cm, and > 10 cm.

## Methods

This study was approved by the Institutional Ethics Committee of the Hospital das Clinicas, University of Sao Paulo School of Medicine (number: 3.004.022) and conducted according to the Standards for Reporting Studies of Diagnostic Accuracy (STARD) [13].

All methods were performed in accordance with the World Medical Association Declaration of Helsinki.

From a prospective database, consecutive adult patients with pathologically proven HCC who underwent liver resection with curative intent between January 2007 and December 2018 were evaluated. The inclusion criteria were as follows: patients older than 18 years, uni or oligonodular disease (up to three nodules), and absence of extrahepatic disease. Patients with chronic liver disease and compensated liver function were considered eligible as follows: Child–Pugh A (or B7 when minor peripheral resection was required), Model of End Stage Liver Disease (MELD) scores ≤ 10, and future liver remnant ≥ 40%. Portal hypertension was not an absolute contraindication for surgery, patients with small caliber esophageal varices and platelets > 100.000/mL were eligible when minor resection was required [14]. The exclusion criteria were presence of extrahepatic disease, R1/R2 resection, previous systemic or locoregional treatment addressed to HCC, presence of infection, and use of preoperative therapeutic antibiotics or corticosteroids.

All patients underwent clinical evaluation and laboratory tests for liver function. Preoperative workup included abdominal helicoidal computed tomography (CT) or magnetic resonance imaging (MRI), and thoracic CT. Preoperative diagnosis was based on image characteristics; biopsy was only indicated if diagnostic doubt persisted after radiologic evaluation. When CT or MRI showed signs of portal hypertension, upper digestive endoscopy was performed. Surgery was performed after a multidisciplinary meeting discussion.

The following preoperative characteristics were studied: age, sex, body mass index (BMI), preoperative laboratory tests, etiology of chronic liver disease, size and location of the lesions, presence of cirrhosis, and portal hypertension. Inflammatory markers were evaluated within 7 days of surgery. The NLR was calculated by dividing the absolute neutrophil count (number of neutrophils/mL) by the absolute lymphocyte count (number of lymphocytes/mL); the PLR was calculated by dividing the absolute platelet count (number of platelets/mL) by the absolute lymphocyte count (number of lymphocytes/mL); and the MLR was calculated by dividing the absolute monocyte count (number of monocytes/mL) by the absolute lymphocyte count (number of lymphocytes/mL).

For the intra- and postoperative periods, the following data were retrieved: blood transfusion requirement, length of stay in the intensive care unit (ICU), length of hospital stay, perioperative complications, overall survival (OS), and disease-free survival (DFS). The specimens obtained were assessed for the number of nodules, size of the larger nodule [in millimeters (mm)], degree of tumor differentiation (histological grade), presence of satellite lesions, and presence of vascular invasion.

Perioperative morbidity was defined as any event occurring during the first 90 postoperative days. OS was

defined as the time interval between liver resection and the date of death or the most recent follow-up date if the patient was alive. DFS was defined as the time interval between liver resection and recurrence at any site (diagnosed on imaging or biopsy), the most recent follow-up date or death. Postoperative follow-up was performed using imaging and laboratory tests every 4 months for the first 2 years, and then annually.

### Statistical analysis

Continuous data were expressed as median and interquartile range [or 95% confidence interval (CI)] or mean ± standard deviation (SD). Categorical variables were expressed as percentages. Quantitative data were compared using the t-test or Mann–Whitney U-test, as appropriate. For categorical variables, Fisher's exact test or the $\chi^2$ test was used. Statistical significance was set at 5%.

The optimal cut-off values for the NLR, PLR, and MLR were calculated using receiver operator curves (ROC) and Youden's index. Thereafter, the patients were divided into two groups: below and above the calculated cut-offs. OS and DFS were estimated using the Kaplan–Meier method and compared using the log-rank test. Univariate and multivariate Cox proportional hazards models were used to identify predictors associated with OS and DFS. Variables with statistical significance ($P < 0.05$) on univariate analysis were included in the multivariate analysis.

## Results

### Baseline characteristics

During the study period, 207 patients with histologically confirmed diagnosis of HCC underwent liver resection; one patient (0.5%) was younger than 18 years, 12 (4.8%) patients underwent preoperative transarterial chemoembolization (TACE) or radiofrequency ablation, nine patients (4.3%) had a preoperative MELD > 10, 18 (8.7%) patients underwent R1 resections, and six (2.9%) presented signs of infection or the use of antibiotics immediately before the surgery. After applying the exclusion criteria, 161 patients were enrolled in the study. The baseline characteristics of the patients are summarized in Table 1. The main causes of chronic liver disease were hepatitis C (60%), hepatitis B (20%), nonalcoholic steatohepatitis (NASH, 11%), alcoholic liver disease (5%), and other etiologies (4%) and the median number of nodules was 1 ± 1.

The median follow-up was 62 months. During the follow-up period 72 patients (44,7%) died and 75 recurred (47.2%). The median OS was 57 months (95%CI 35–78). The OS of the entire cohort was 65.2% at 3 years, 47.6% at 5 years and 28.4% at 10 years, while DFS was 61.1% at 3

**Table 1** Baseline characteristics of the included patients (N = 161)

| | |
|---|---|
| Age (years) | |
| Mean ± SD | 62 ± 11 |
| Median (min–max) | 63 (18–86) |
| Sex (%) | |
| Male | 108 (67.1%) |
| Female | 53 (32.9%) |
| BMI (kg/m$^2$) | |
| Mean ± SD | 25.4 ± 4.5 |
| Median (quartile 25–75) | 24.9 (22.6–27.7) |
| Cirrhosis (%) | |
| Yes | 135 (83.9%) |
| No | 26 (16.1%) |
| Child–Pugh (%)† | |
| A5 | 111 (82.2%) |
| A6 | 17 (12.6%) |
| B7 | 7 (5.2%) |
| Preoperative MELD | |
| Mean ± SD | 8 ± 3 |
| Median (quartile 25–75) | 8 (7–9) |
| Portal hypertension (%) | |
| Yes | 43 (26.7%) |
| No | 92 (73.3%) |
| Esophageal varices (%) | |
| Yes | 22 (13.7%) |
| No | 21 (86.3%) |
| Hemoglobin (g/dL) | |
| Mean ± SD | 13.7 ± 3.8 |
| Median (quartile 25–75) | 13.7 (12.6–14.9) |
| Platelet count (/mm$^3$) | |
| Mean ± SD | 186,410 ± 97,208 |
| Median (quartile 25–75) | 170,000 (118,000–230,000) |
| Bilirubin (g/dL) | |
| Mean ± SD | 0.72 ± 0.22 |
| Median (quartile 25–75) | 0.65 (0.47–0.89) |
| Aspartate aminotransferase (AST, U/L) | |
| Mean ± SD | 62.0 ± 61.0 |
| Median (quartile 25–75) | 42.0 (28.0–68.0) |
| Alanine aminotransferase (ALT, U/L) | |
| Mean ± SD | 54.7 ± 51.0 |
| Median (quartile 25–75) | 38.0 (25.0–69.0) |
| INR | |
| Mean ± SD | 1.1 ± 0.1 |
| Median (quartile 25–75) | 1.1 (1.0–1.2) |
| Creatinine (mg/dL) | |
| Mean ± SD | 1.0 ± 1.0 |
| Median (quartile 25–75) | 0.9 (0.7–1.1) |
| Alpha-fetoprotein (ng/mL) | |
| Mean ± SD | 2483.1 ± 9906.5 |
| Median (quartile 25–75) | 19.0 (4.7–172.7) |

**Table 1** (continued)

| | |
|---|---|
| Albumin (g/dL) | |
| Mean ± SD | 4.0 ± 0.3 |
| Median (quartile 25–75) | 4.1 (3.7–4.5) |
| Neutrophil count (/mm$^3$) | |
| Mean ± SD | 3601 ± 3465 |
| Median (quartile 25–75) | 3300 (2300–4410) |
| Lymphocyte count (/mm$^3$) | |
| Mean ± SD | 1869 ± 773 |
| Median (quartile 25–75) | 1700 (1300–2300) |
| Monocyte count (/mm$^3$) | |
| Mean ± SD | 575 ± 308 |
| Median (quartile 25–75) | 510 (400–700) |
| NLR | |
| Mean ± SD | 2.3 ± 2.2 |
| Median (quartile 25–75) | 1.9 (1.4–2.6) |
| PLR | |
| Mean ± SD | 115.4 ± 89.4 |
| Median (quartile 25–75) | 96.2 (67.0–144.4) |
| MLR | |
| Mean ± SD | 3.8 ± 2.0 |
| Median (quartile 25–75) | 3.5 (2.4–4.6) |
| Tumor size (mm) | |
| Mean ± SD | 62.0 ± 50.7 |
| Median (quartile 25–75) | 42 (29.0–80.0) |
| Number of nodules | |
| Mean ± SD | 1.23 ± 0.7 |
| Median (quartile 25–75) | 1.0 (1.0–1.0) |
| Tumor grade (%) | |
| Well differentiated | 9 (5.6%) |
| Moderately differentiated | 104 (64.6%) |
| Poor differentiated | 28 (17.4%) |
| Unavailable | 20 (12.4%) |
| Satellite nodules (%) | |
| Yes | 40 (24.8%) |
| No | 121 (75.2%) |
| Vascular invasion (%)[††] | |
| Yes | 82 (50.9%) |
| No | 75 (43.8%) |
| Unavailable | 4 (2.5%) |

*SD* standard deviation; *BMI* body mass index; *MELD* Model for End-Stage Liver Disease; *INR* international normalized ratio; *NLR* neutrophil-to-lymphocyte ratio; *PLR* platelet-to-lymphocyte ratio; *MLR* monocyte-to-lymphocyte ratio

[†] % of patients with cirrhosis

[††] Micro and macrovascular invasion histologically documented in the specimen

years, 44.4% at 5 years and 20.1% at 10 years (Additional file 1: Fig. S1).

### Optimal cut-offs for NLR, PLR and MLR

The cut-off values of the inflammatory markers were determined by plotting the ROC curves for mortality and recurrence after resection. The best cut-offs calculated using the Youden index are listed in Table 2.

### Prognostic value of inflammatory markers for OS and DFS

A high NLR (> 1.715) was associated with short OS in patients who underwent HCC resection. The median OS in the subgroup of patients with high and low NLR were 40 months (95%CI 25–54) and 92 months (95%CI 49–120), respectively. The 5-year OS was 56% in the low NLR group and 40% in the high NLR group (P = 0.018, Fig. 1).

Clinicopathological characteristics of patients with low (≤ 1.715) and high NLR (> 1.715) are summarized in Additional file 1: Table S1. Patients with high NLR had lower serum albumin levels [4.1 g/dL (3.7–4.5) vs. 4.3 g/dL (4.1–4.6); P = 0.028] and larger tumors [77 mm (35–100) vs. 39 mm (21–45); P < 0.001] and were associated with higher values of PLR [134 (91.2–160) vs. 72.4 (53.7–93.2); P < 0.001] and MLR [4.4 (3.4–5.5) vs. 3.1 (2–3.8); P < 0.001].

High NLR (> 2.475) and PLR (> 100.25) were associated with short DFS in HCC patients treated with hepatectomy (Fig. 2).

Patients with high NLR (> 2.475) presented higher total bilirubin levels [0.7 g/dL (0.5–0.9) vs. 0.6 g/dL (0.5–0.7); P = 0.020] and larger tumors [67 mm (40–100) vs. 40 mm (25–65); P = 0.003] when compared to patients with low NLR. There was also an association with high PLR [147.2 (104.5–176) vs. 82.3 (60–108); P < 0.001] and high MLR [3.8 (3–5.2) vs. 2.1 (1.6–3.3); P < 0.001] (Additional file 1: Table S2).

Patients with high PLR (> 100.25) presented higher serum levels of total bilirubin [0.7 g/dL (0.5–0.9) vs. 0.6 g/dL (0.4–0.8); P = 0.004], larger tumors [75 mm (40–125) vs. 34 mm (22–45); P < 0.001], and a higher frequency of vascular invasion (62.1% vs. 42%; P = 0.020). Additionally, an association with higher values of NLR [2.5 (1.9–3.5) vs. 2.5 (1.9–3.6); P < 0.001] and MLR [4 (3–5.2) vs. 3.1 (1.8–3.8); P < 0.001] were observed (Additional file 1: Table S3).

### Risk factors for OS and DFS after hepatectomy

All clinicopathological and surgical characteristics were included in the univariate analysis. Variables associated with OS and DFS after HCC resection on univariate and multivariate analysis are shown in Table 3.

### Subgroup analysis

Survival analysis was also performed in patients with HCC according to tumor size: < 5 cm (group 1, N = 98), 5–10 cm (group 2, N = 35), and > 10 cm (group 3, N = 28).

A high MLR (> 1.750) was associated with short OS in group 1 (P = 0.047) (Additional file 1: Fig. S2). None

**Table 2** Diagnostic accuracy of the calculated cut-offs for mortality and recurrence

| | Cut-off | Sensibility | Specificity | 1—Specificity | LR+ | LR− |
|---|---|---|---|---|---|---|
| Mortality | | | | | | |
| NLR | > 1.715 | 0.639 | 0.483 | 0.517 | 1.236 | 0.747 |
| PLR | > 115.050 | 0.375 | 0.697 | 0.303 | 1.236 | 0.897 |
| MLR | > 1.750 | 0.917 | 0.112 | 0.888 | 1.033 | 0.742 |
| Recurrence | | | | | | |
| NLR | > 2.475 | 0.307 | 0.732 | 0.268 | 1.146 | 0.947 |
| PLR | > 100.250 | 0.520 | 0.620 | 0.380 | 1.367 | 0.775 |
| MLR | > 2.680 | 0.747 | 0.310 | 0.690 | 1.082 | 0.818 |

The NLR, PLR, and MLR areas under the curve (AUC) for mortality were 0.541 (95%CI 0.451–0.631), 0.479 (95%CI 0.388–0.571), and 0.454 (95%CI 0.365–0.543), respectively. Regarding recurrence, the calculated AUC were 0.479 (95%CI 0.385–0.573), 0.519 (95%CI 0.424–0.614), and 0.469 (95%CI 0.372–0.565), respectively

*NLR* neutrophil-to-lymphocyte ratio; *PLR* platelet-to-lymphocyte ratio; MLR monocyte-to-lymphocyte ratio; *LR+* positive likelihood ratio; *LR−* negative likelihood ratio

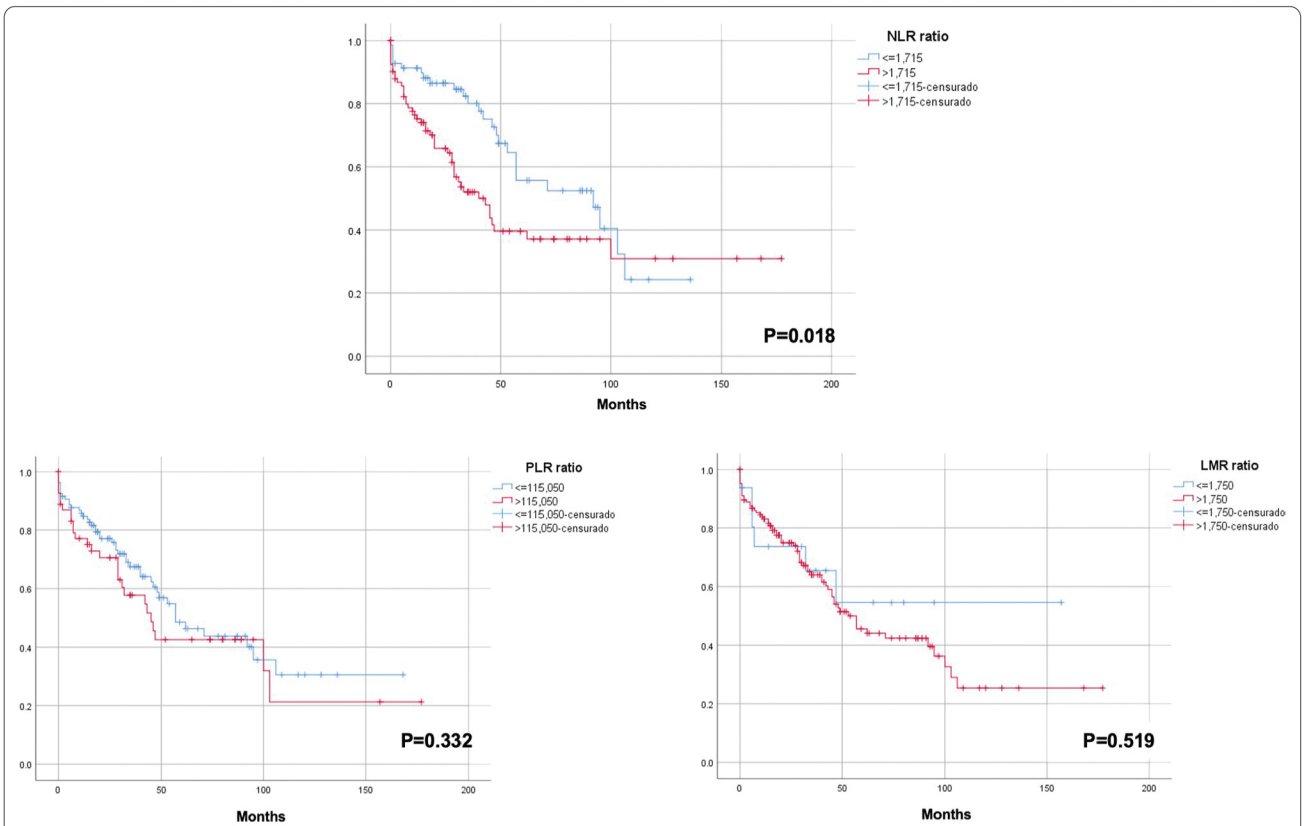


**Fig. 1** Overall survival of hepatocellular carcinoma patients with low (blue) and high (red) neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR)

of the inflammatory markers were associated with DFS in this subset of patients (Additional file 1: Fig. S3). In groups 2 and 3, the NLR, PLR, and MLR were not associated with OS or DFS (Additional file 1: Figs. S4–S7).

## Discussion

Systemic inflammatory status has impact on carcinogenesis [15]. Recent studies have shown that the molecular environment created by humoral response favors

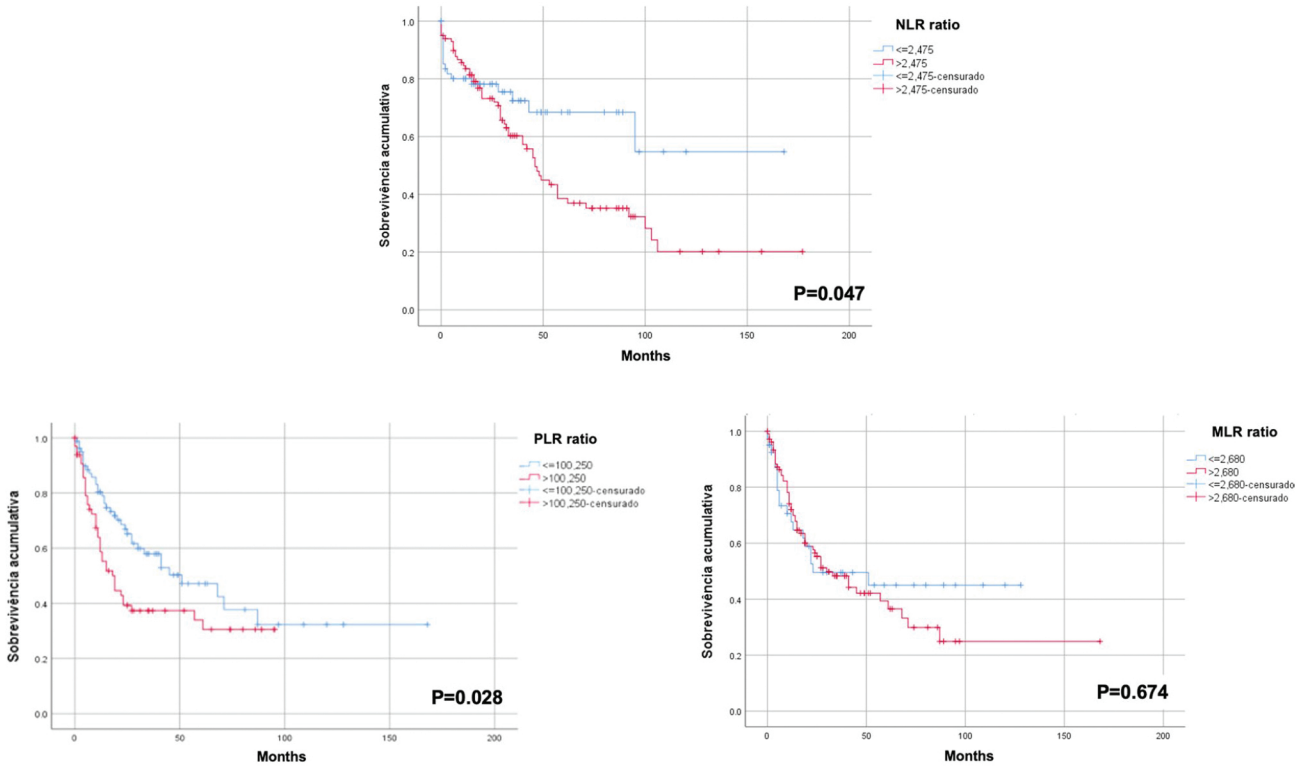


**Fig. 2** Disease-free survival of hepatocellular carcinoma patients with low (blue) and high (red) neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR)

**Table 3** Univariate and multivariate analyses of prognostic factors associated with overall and disease-free survival

| Overall survival | | | Disease-free survival | | |
|---|---|---|---|---|---|
| **Variable** | **P** | **HR IC95%** | **Variable** | **P** | **HR IC95%** |
| Univariate analysis | | | | | |
| Hepatitis C | 0.016 | 1.98 (1.13–3.40) | Satellites nodules | 0.023 | 1.77 (1.08–2.92) |
| Portal hypertension | 0.005 | 2.16 (1.25–3.74) | Vascular invasion | 0.005 | 1.97 (1.22–3.19) |
| Esophageal varices | 0.047 | 1.90 (1.10–3.60) | Age > 50 years | 0.050 | 0.54 (0.95–1.00) |
| Transfusion | 0.002 | 2.38 (1.38–4.10) | Bilirubin > 1.2 mg/dL | 0.034 | 2.41 (1.15–5.07) |
| Perioperative complications | 0.006 | 2.00 (1.21–3.34) | AST > 50 U/dL | 0.020 | 1.63 (1.10–2.59) |
| Vascular invasion | 0.007 | 2.02 (1.20–3.40) | Alpha-fetoprotein > 20 ng/mL | < 0.001 | 3.64 (2.23–5.91) |
| Bilirubin > 1.2 mg/dL | 0.048 | 1.90 (1.05–3.60) | NLR > 2.475 | 0.047 | 1.28 (1.01–1.96) |
| AST > 50 U/dL | 0.021 | 1.85 (1.09–3.14) | PLR > 100.25 | 0.028 | 1.60 (1.02–2.52) |
| ICU stay > 3 days | < 0.001 | 3.06 (1.80–5.23) | | | |
| Alpha-fetoprotein > 20 ng/mL | < 0.001 | 3.42 (1.96–5.91) | | | |
| NLR > 1.715 | 0.018 | 1.61 (1.01–2.67) | | | |
| Multivariate analysis | | | | | |
| Portal hypertension | < 0.001 | 7.04 (2.40-20.66) | Vascular invasion | 0.022 | 2.36 (1.13–4.93) |
| Vascular invasion | | | AST > 50 ng/mL | 0.001 | 3.32 (1.60–6.91) |
| AST > 50 U/dL | 0.032 | 3.06 (1.10–8.47) | PLR > 100.25 | 0.002 | 3.03 (1.50–6.12) |
| ICU stay > 3 days | 0.003 | 5.04 (1.75–14.49) | | | |

Multivariate analysis showed that the presence of portal hypertension, preoperative aspartate aminotransferase, and ICU stay > 3 days were independent predictors of short OS. Regarding DFS, AST level > 50 U/dL presence of vascular invasion and high PLR were predictors of a high recurrence rate

*AST* aspartate aminotransferase; *ICU* intensive care unit; *NLR* neutrophil-to-lymphocyte ratio; *PLR* platelet-to-lymphocyte ratio

conjunctive matrix degradation, neoangiogenesis, and activation of cell profiles favoring tissue invasion and metastatic dissemination. Therefore, an increase in humoral inflammatory response can lead to worse oncological outcomes [15]. Conversely, lymphocytic cellular response (mediated by T lymphocytes CD4+, CD8+, and NK cells) inhibits carcinogenesis, leading to better oncological prognosis [16]. Recent studies have also shown the interaction between platelets and tumoral microenvironment [17]. The main platelet-associated mechanisms are based on signaling pathways that orchestrate tumor growth, activation of angiogenesis, and metastatic dissemination [18].

The prognostic impact of systemic inflammatory response has been studied in several gastrointestinal tumors, such as pancreatic, colorectal, and gastric cancers [19, 20]. The main advantages of inflammatory markers include calculation using routine laboratory tests, low cost, and access to results before therapeutic intervention [21].

The NLR is the most studied inflammatory index. A large metanalysis, comprising more than 40,000 patients showed an association of high NLR with lower survival rate in patients with several solid tumors [22].

However, the prognostic impact of inflammatory markers in patients with HCC who undergo resection remains controversial. Most studies that assessed these prognostic markers came from eastern centers, where HCC presents distinct clinical and epidemiological features [23]. The present study is one of the first from a western center to evaluate the association between the main inflammatory markers (NLR, PLR, and MLR) and long-term outcomes after liver resection for HCC. In our study, the mean age was 62 ± 11 years, similar to those in other western centers but higher than those in eastern centers (52 ± 9 years) [24]. Regarding chronic liver disease etiology, hepatitis C (60%) was the most frequent, followed by hepatitis B (20%) and NASH (11%). In contrast, in eastern centers, the prevalence of hepatitis B infection is higher than 50% [25]. Our data showed that 84% of patients had chronic liver disease and 94.8% were classified as Child–Pugh A. Beard et al. [26] compared surgical outcomes after HCC resection in cirrhotic and non-cirrhotic North American patients and found a cirrhosis prevalence of 73%. In the eastern centers, the prevalence of cirrhosis/chronic liver disease is lower than 54% [8].

The preoperative NLR is the most studied biomarker in patients with HCC. Although several studies have suggested that high NLR may correlate with a poor prognosis [7, 8], others failed to detect this association [10]. Furthermore, it is important to point out the wide heterogeneity regarding the cut-off values across the studies. Wang et al. [23] in a recent meta-analysis, included 17 studies (13 for OS and 7 for DFS) finding cut-off values for NLR ranging from 1.51 to 5.0. Moreover, most of the studies are from eastern centers, and use the same cut-off for OS and DFS [23, 27].

The present study showed that NLR > 1.715 and > 2.745 were associated with short OS and DFS in univariate analysis, respectively. A recent meta-analysis conducted by Xingshun et al. [28] including 20,475 patients with HCC (90 studies) who underwent different treatments (liver transplant, liver resection, ablation, and sorafenib) found that low baseline NLR was significantly associated with better OS (HR 1.80, 95%CI 1.59–2.04, P < 0.00001) and DFS (HR 2.23, 95% CI 1.80–2.76, P < 0.00001). In the subgroup of patients who underwent liver resection (12 studies, 3097 patients) low baseline NLR was also associated with better OS (HR 1.95, 95%CI 1.61–2.37, P < 0.00001) and DFS (HR 1.87, 95%CI 1.47–2.37, P < 0.00001).

However, in the multivariate analysis, the NLR was not an independent factor associated with OS or DFS in our study, which was also observed in other studies, especially from western centers. Sullivan et al. [10] evaluating patients with HCC found that the NLR was not a predictor for OS after surgical or locoregional treatment (HR 1.09; 95%CI 0.95–1.24; P = 0.23). Another study from the United Kingdom showed that the NLR was a predictor of DFS (HR 4.67; 95%CI 1.88–11.64; P = 0.001) but not a predictor of OS in cirrhotic patients undergoing HCC resection. Interestingly, no relationship was found between NLR and prognosis in non-cirrhotic patients [29]. Thus, the presence of cirrhosis may impact the predictive value of NLR, justifying the heterogeneous results between the available studies.

Few studies have addressed the prognostic impact of other inflammatory markers in HCC patients [30]. In our study, we observed that high PLR (> 100.25) was an independent factor of shorter DFS, which is consistent with recent studies [31]. Kaida et al. [32] evaluated patients with early-stage HCC who underwent resection and compared five inflammatory marker scores, showing that preoperative PLR was an independent predictor of recurrence. Similarly, Qing et al. [31] showed that increased preoperative platelet levels were associated with a higher recurrence rate following HCC resection. To date, few studies have evaluated the prognostic impact of MLR in HCC patients [33].

Recent studies have suggested that the inflammatory markers are also prognostic factors in specific subgroups, such as patients with small tumors (< 5 cm) [8] or large HCCs (> 10 cm) [9]. Historically, size is a main prognostic factor for HCC patients. Well-established staging systems such as TNM, Milan criteria and Barcelona Clinic Liver Cancer (BCLC) included tumor size in therapeutic

algorithm and prognostic stratification. In fact, 5 cm is a landmark in TNM staging (T2 vs. T3), Milan criteria and BLCL (early HCC). Additionally, some authors showed worse prognosis in patients with HCC > 10 cm (called large or huge HCCs). Based on these data, we stratified our patients according to tumor size (< 5 cm, 5–10 cm, and > 10 cm). An interesting finding of our study was the association of low MLR with better OS in patients with early-stage HCC (< 5 cm). This finding can be justified by the fact that activation of monocytes and macrophages usually occurs at earlier stages of tumor growth. Otherwise, in patients with larger lesions, other cells such as neutrophils and platelets play a predominant role in local invasion and metastatic dissemination [34].

Another independent factor associated with short OS in the present study was the presence of portal hypertension, which is in accordance with other studies [35]. In a meta-analysis comprising 2285 patients with HCC who underwent resection, the group of patients with portal hypertension presented short OS than the group without portal hypertension (HR 1.48; 95%CI 1.11–1.98; P = 0.007) [36]. An AST level > 50 U/dL was an independent factor related to both OS and DFS. The exact mechanism underlying this finding is poorly understood; however, it might be explained by the fact that AST is exclusively present in hepatocytes and released into the circulation during liver inflammatory insults. Additionally, the reduced clearance in progressive chronic hepatic disease can lead to an increase in AST levels [37]. In our study, microvascular invasion was also an independent prognostic factor for recurrence. In fact, vascular invasion is frequently associated with higher recurrence rates due to aggressive biological behavior, represented by a greater volume of micrometastatic disease and a higher frequency of mural invasion [38].

Based on our findings, all the studied inflammatory markers are useful tools to predict long-term outcomes after liver resection in western patients. High NLR was able to stratify subgroups of patients with short OS and DFS, and increased PLR was a marker of short DFS, while high MLR was associated with short OS in patients with early HCC. In fact, these markers were able to identify subgroups of patients with poor clinical features, such as higher bilirubin levels, larger tumors, and a higher frequency of vascular invasion. Therefore, inflammatory indexes are promising tools for preoperative selection of patients who require strict postoperative follow-up or even potential candidates for new adjuvant strategy protocols.

However, our findings should be viewed with caution due to some limitations. The first was the retrospective nature of this study, which increases the risk of selection, confusion, and measurement biases. Another limitation was the small number of patients enrolled, which may impair statistical power, especially in the subgroup analysis. Thus, the insights provided herein should be confirmed by larger prospective studies.

In conclusion, our study suggested that a high preoperative NLR is associated with short OS and DFS, whereas a high PLR is an independent factor associated with short DFS. In the subset of patients with HCC < 5 cm, a high MLR is associated with short OS.

#### Abbreviations

HCC: Hepatocellular carcinoma; NK: Natural killer cells; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; STARD: Standards for Reporting Studies of Diagnostic Accuracy; MELD: Model for End-Stage Liver Disease; CT: Computed tomography scan; MRI: Magnetic resonance imaging; BMI: Body mass index; ICU: Intensive care unit; OS: Overall survival; DFS: Disease-free survival; ROC: Receiver operator curves; TACE: Transarterial chemoembolization; NASH: Non-alcoholic steatohepatitis; SD: Standard deviation; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; INR: Interna; : tional normalized ratio; LR+: Positive likelihood ratio; LR−: Negative likelihood ratio; AUC: Area under the curve.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12893-022-01779-6.

**Additional file 1: Figure S1.** Overall and disease-free survival of patients with hepatocellular carcinoma included in the study (N=161). **Figure S2.** Overall survival of patients with hepatocellular carcinoma < 5 cm (Group 1) with low (blue) and high (red) neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR). **Figure S3.** Disease-free survival of patients with hepatocellular carcinoma < 5 cm (Group 1) with low (blue) and high (red) neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR). **Figure S4.** Overall survival of patients with hepatocellular carcinoma between 5 and 10 cm (Group 2) with low (blue) and high (red) neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR). **Figure S5.** Disease-free survival of patients with hepatocellular carcinoma between 5 and 10 cm (Group 2) with low (blue) and high (red) neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR). **Figure S6.** Overall survival of patients with hepatocellular carcinoma > 10 cm (Group 3) with low (blue) and high (red) neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR). **Figure S7.** Disease-free survival of patients with hepatocellular carcinoma > 10 cm (Group 3) with low (blue) and high (red) neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR). **Table S1.** Baseline characteristics of patients with low (≤ 1.715) and high (> 1.715) neutrophil-to-lymphocyte ratio (NLR). **Table S2.** Baseline characteristics of patients with low (≤ 2.475) and high (> 2.475) neutrophil-to-lymphocyte ratio (NLR). **Table S3.** Baseline characteristics of patients with low (≤ 100.25) and high (> 100.25) platelet-to-lymphocyte ratio (PLR)

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#### Author contributions

JPMS, FFC, AJFC and PH designed the study and wrote the main manuscript text. GMF, VBJ, JDMJ and SCN revise the manuscript. All authors read and approved the final manuscript.

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**Availability of data and materials**
The data that support the findings of this study are available from the corresponding author (J.P.M.S), upon reasonable request.

## Declarations

**Ethics approval and consent to participate**
This study was approved by the Ethics Committee of the Hospital das Clinicas, University of Sao Paulo School of Medicine (number: 3.004.022). Patient informed consent form was waived by the Ethics Committee of the Hospital das Clínicas, University of Sao Paulo School of Medicine (number: 3.004.022).

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

**Permission to reproduce material from other sources**
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