**Research Article**

Pamukkale Medical Journal
*doi:https://dx.doi.org/10.31362/patd.1471860*

# Use of albumin and CRP related immuno-nutritional markers for prediction of locoregional response to treatment in unresectable hepatocellular carcinoma

## *İnoperable Hepatosellüler karsinom'da lokorejyonel tedavi yanıtını öngörmek için albümin ve CRP ilişkili immüno-nutrisyon belirteçlerin kullanımı*

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Posted date:05.05.2024 Acceptance date:04.11.2024

**Abstract**

**Purpose:** We examined the relationship between albumin and C reactive protein (CRP)-related inflammation markers such as Controlling nutritional status (Conut) score, lymphocyte-albumin factor (LA), albumin-bilirubin score (ALBI), highly sensitive modified Glasgow prognostic score (Hs-mGPS), Glasgow prognostic score (GPS) and locoregional treatment response in HCC.

**Materials and methods:** One hundred and eighty HCC patients and 63 patients who underwent locoregional therapy were included in this study. Routine laboratory tests between the fourth and eighth week after treatment were recorded and albumin and CRP-related immuno-nutrition scores were calculated. Cut-off values from the literature were used. The predictive and prognostic value of these markers for overall survival (OS) and disease-free survival (DFS) after treatment were analyzed.

**Results:** The mean age was 63 years (min-max:26-87) and 59 (93.7%) of the patients were male. The mean follow-up period was 25 months and 53 patients were deceased (84.1%). Median overall survival (mOS):18.56 months (min-max:13.13-23.99); median disease-free survival (mDFS):7 months (min-max:3.63-10.37) after locoregional treatment. Age ($p$=0.019), Conut ($p$=0.001), GPS ($p$=0.028), Hs-mGPS ($p$=0.012), LA ($p$=0.017) and ALBI ($p$=0.002) were significantly correlated with mOS. Conut ($p$=0.002), GPS ($p$<0.001), Hs-mGPS ($p$=0.002), LA ($p$=0.002) and ALBI ($p$=0.001) were significantly correlated with mDFS. Multivariate analysis revealed that those aged ≥65 years (HR:2.10; 95% CI:1.02-4.30; $p$=0.042) and those who received no systemic therapy (HR:4.11; 95% CI:1.35-12.56; $p$=0.013) had an increased risk of death ($p$<0.001). Another significant result was that a GPS of '2' (HR:6.62; 95% CI:1.13-38.62; $p$=0.036) predicted a higher risk of progression ($p$<0.001).

**Conclusion:** In this study, we found that age, Conut score, GPS, HsmGPS, LA and ALBI score significantly predicted mOS and mDFS in locoregionally treated HCC patients. All these results suggest that our prognostic modelling may be useful in clinical practice.

**Keywords:** HCC, TACE, Conut score, GPS, HsmGPS.

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**Öz**

**Amaç:** Controlling nutritional status (Conut) skor, lenfosit-albümin faktörü (LA), Albümin-bilirubin skor (ALBİ), high sensitif modifiye Glasgow prognostik skor (Hs-mGPS), Glasgow prognostik skoru (GPS) gibi albümin ve C-reaktive protein (CRP) ilişkili inflamasyon belirteçleri ile HCC'de lokorejyonel tedavi yanıtı arasındaki ilişkiyi inceledik.

**Gereç ve yöntem:** Yüz seksen HCC hastasından lokorejyonel tedavi uygulanan 63 hasta bu çalışmaya dahil edildi. Tedavi sonrası dördüncü-sekizinci hafta aralığındaki rutin laboratuvar testleri kaydedilerek albümin ve CRP ilişkili immüno-nutrisyon skorları hesaplandı. Literatürde yer alan cut-off değerleri kullanıldı. Bu belirteçlerin genel sağkalım (OS) ve tedavi sonrası hastalıksız sağkalım (DFS) için prediktif ve prognostik değeri analiz edildi.

**Bulgular:** Yaş ortalaması 63 (min-max:26-87) olan hastaların 59'u (%93,7) erkekti. Ortalama takip süresi 25 ay olup 53 hasta merhumdu (%84,1). Median genel sağkalım (mOS):18,56 ay (min-max:13,13-23,99); lokorejyonel tedavi sonrası mDFS:7ay (min-max:3,63-10,37) olarak belirlendi. Yaş ($p$=0,019), Conut ($p$=0,001), GPS ($p$=0,028), Hs-mGPS ($p$=0,012), LA ($p$=0,017) ve ALBI ($p$=0,002) ile mOS arasında istatistiksel anlamlı ilişki bulundu. Conut ($p$=0,002), GPS ($p$<0,001), Hs-mGPS ($p$=0,002), LA ($p$=0,002) ve ALBI ($p$=0,001) ile median hastalıksız sağkalım (mDFS) arasındaki ilişki istatistiksel olarak anlamlı bulundu. Multivariate analiz sonucunda; ≥65 yaş olanların (HR:2,10; %95 CI:1,02-4,30; $p$=0,042) ve hiç sistemik tedavi almayanların (HR:4,11; %95 CI:1,35-12,56; $p$=0,013) ölüm riskinin arttığı belirlendi ($p$<0,001). Bir diğer anlamlı sonuç ise GPS'nin '2' olmasının (HR:6,62; %95 CI:1,13-38,62; $p$=0,036) yüksek progresyon riskini öngördüğü idi ($p$<0,001).

**Sonuç:** Lokorejyonel tedavi uygulanan HCC'li hastalarda; yaş, Conut skor, GPS, HsmGPS, LA ve ALBI skorun, hastaların mOS ve mDFS için önemli prediktif faktörler olduğunu saptadık. Tüm bu sonuçlar oluşturduğumuz prognostik modellemenin klinik pratikte kullanımının yararlı olabileceğini düşündürmektedir.

**Anahtar kelimeler:** HCC, TACE, Conut skor, GPS, HsmGPS.

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## Introduction

Hepatocellular carcinoma (HCC) typically develops in the context of chronic liver disease and cirrhosis, making it the third leading cause of cancer-related mortality. Screening at-risk patients using alpha-feto protein (AFP) and abdominal ultrasonography (USG) allows for early diagnosis, which enables curative treatments such as surgery or local therapies. For patients ineligible for liver transplantation, systemic and/or local therapies are used based on the stage of the disease, tumour size, location, and liver reserve. Treatment options include surgery (resection or transplantation), radiofrequency ablation (RFA) for smaller tumours, transarterial chemoembolization (TACE) for patients with adequate liver reserve, and systemic therapy (atezolizumab +bevacizumab, sorafenib, lenvatinib, cabozantinib, regorafenib) for patients with good performance status. In cases of poor Eastern Cooperative Oncology Group performance score (ECOG performance), best supportive care is recommended [1-3].

The five-year survival rate for advanced HCC is around 18%, but early diagnosis can raise this to 70%. Delayed diagnosis leads to a significant loss in survival, but this can be mitigated through early detection and the use of prognostic markers during treatment [4-6]. Prognosis varies depending on symptoms and tumour burden, and the Child-Pugh classification may not fully capture disease progression in all patients. Some symptoms, such as ascites or portal hypertension, can elevate Child scores, yet patients may still respond to symptomatic treatment. Consequently, there is ongoing research into more precise prognostic markers for guiding treatment decisions. A review of the literature suggests that combining different parameters with a single marker could enhance the accuracy of the Child score [7-11].

Treatment response for HCC is often assessed using radiological tests, such as contrast-enhanced abdominal magnetic resonance (MRI), which is performed one month after treatment and then every three months. The MRI should be dynamic, covering

the late arterial, portal venous, and late venous phases post-contrast. Lack of contrast uptake in the tumour center after local treatment suggests necrosis, whereas contrast uptake indicates residual tumour [12, 13]. However, coagulative hemorrhagic necrosis following RFA or TACE may cause bright images that can complicate the interpretation of residual tumours, particularly in the first month. Specialized radiologists and technicians are needed to minimize these issues [14].

Due to the heterogeneity of advanced HCC patients, MRI alone may not provide a full evaluation of all cases, and clinician experience can affect the objectivity of radiological results. Additionally, two-dimensional tumour size measurements are insufficient for fully evaluating treatment response. The clinician must assess viable tumour tissue, vascularity, margins, and any residual or recurrent tumour using imaging, though this can be limited by access and expertise [12, 13].

Locoregional treatment response is typically assessed between four and eight weeks post-treatment. Several prognostic markers derived from routine blood and biochemical tests have been identified in solid tumours, which could allow for quicker treatment adjustments in patients with disease progression.

In this study, we retrospectively evaluated inoperable HCC patients who underwent locoregional therapy. Haemogram and biochemistry values were recorded between the fourth and eighth week post-treatment. While albumin and CRP alone are markers of inflammation, we analyzed the relationship between albumin and CRP-related inflammation markers such as Controlling nutritional status (Conut) score, Glasgow prognostic score (GPS), highly sensitive modified Glasgow prognostic score (Hs-mGPS), Albumin-bilirubin score (ALBI) and lymphocyte-albumin factor (LA) and treatment response in HCC. To the best of our knowledge, no previous study has systematically modeled these markers in HCC patients receiving locoregional therapy, and we believe our findings will contribute to the literature.

## Materials and methods

### Patient characteristics and data collection

Locoregional therapies are powerful treatments frequently used in the treatment of patients who are not suitable for operation in HCC treatment. Different local treatment options are offered according to the size, number and location of the tumour. Radiofrequency ablation and transarterial treatments were applied in our patients. Between January 2011 and December 2023, 180 HCC patients who were followed up in the Medical Oncology Clinic of Pamukkale University were reviewed. Among all patients, 63 patients who underwent locoregional treatment during follow-up were included in the study. Clinical and demographic characteristics of the patients such as complaints at presentation, diagnostic features, exposure to etiological risk factors, performance status, tumour size, stage at presentation were evaluated. In studies evaluating locoregional treatments, the timing of treatment response has been suggested as the fourth to eighth week interval on average, and in this study, routine laboratory tests and clinical data requested in the fourth to eighth week interval were evaluated. Haemogram, biochemistry and hepatic viral serology results were recorded. Albumin, CRP, haemoglobin, lymphocyte, platelet, bilirubin, cholesterol, lactate dehydrogenase (LDH) and body mass index (BMI) values were taken from these routine blood values and albumin and CRP-related inflammation scores were calculated. These scores are Conut score, LA factor, ALBI score, Hs-mGPS, GPS.

Inflammatory response and nutrition are important in cancer pathology [10, 15-17]. There is no prognostic scoring that can predict DFS and OS after locoregional treatment in patients with HCC. Child score which is frequently used in the follow-up of HCC, does not adequately cover all of these patients with a heterogeneous group. Of the two parameters included in the Child score, the degree of encephalopathy and ascites are left to the clinician's interpretation, which limits objective scoring and is insufficient to sensitively predict response after local treatment in HCC [15]. Therefore, a prognostic marker is needed.

To the best of our knowledge, there is no clinical study in the literature evaluating whether the albumin and CRP-related inflammatory scores investigated in this study predict treatment response, early recurrence due to residual tumour, DFS and OS in locoregionally treated HCC cases. This study was planned considering that prognostic markers that are easily accessible to clinicians and can be easily repeated at each visit will be guiding.

**Purposes of use and calculationof albumin and CRP related prognostic markers**

**Conut score:** Is an immunonutrition score calculated on the basis of albumin, cholesterol and lymphocyte count in peripheral blood. The score obtained by adding the scores obtained from these three parameters constitutes the Conut score. '0-1' indicates normal malnutrition, '2-4' indicates light malnutrition and '5-8' indicates moderate malnutrition (Table 1) [10].

**Table 1.** Conut score calculation undernutrition status

| | Albumin (g/dL) | Albumin Score | Total lymphocytes (/mm$^3$) | Total lymphocytes score | Total cholesterol (mg/dL) | Total cholesterol score | Conut Score |
|---|---|---|---|---|---|---|---|
| **Normal** | ≥3.5 | 0 | >1600 | 0 | >180 | 0 | 0-1 |
| **Light** | 3.0-3.49 | 2 | 1200-1599 | 1 | 140-180 | 1 | 2-4 |
| **Moderate** | 2.5-2.9 | 4 | 800-1199 | 2 | 100-139 | 2 | 5-8 |

**ALBI score:** A simple and objective liver function test using only serum albumin and bilirubin levels. Unlike Child scoring, which is limited to use in patients with cirrhosis, this score can be used in all stages of liver disease. It was calculated with the formula "($_{log10}$ bilirubin (micromol/L)x0.66)+(albumin (g/L)x-0.085)" obtained from data analysis of more than 6000 HCC patients in the literature. ALBI score was grouped as I (score ≤-2.60), II (score >-2.60 with ≤-1.39) and III (>-1.39) [15].

**GPS:** This prognostic marker including albumin and CRP predicts inflammation and nutrition. The scoring system is shown in Table 2 [16].

**Hs-mGPS:** A more sensitive prognostic immuno-nutrition score was obtained by changing the cut-off values of CRP and albumin used in GPS. The scoring system is given in Table 2 [16].

**Table 2.** The Glasgow Prognostic Score and High sensitivity modified Glasgow prognostic score systems

| **The Glasgow Prognostic Score (GPS)** | |
|---|---|
| **Scoring systems** | **Score** |
| CRP (≤10 mg/L) and albumin (≥35 g/L) | 0 |
| CRP (≤10 mg/L) and albumin (<35 g/L) | 1 |
| CRP (>10 mg/L) and albumin (≥35 g/L) | 1 |
| CRP (>10 mg/L) and albumin (<35 g/L) | 2 |
| **High sensitive modified Glasgow prognostic score (Hs-mGPS)** | |
| **Scoring systems** | **Score** |
| CRP (≤0.3 mg/L) and albumin (≥3.5 mg/L) | 0 |
| CRP (>0.3 mg/L) and albumin (≥3.5 mg/L) | 1 |
| CRP (>0.3 mg/L) and albumin (<3.5 mg/L) | 2 |

CRP: C-reaktive protein

**LA factor:** This marker, which predicts inflammation, is calculated as "lymphocyte × albumin" by multiplying lymphocyte count and albumin concentration. It has been defined as a prognostic marker in different solid tumours in the literature [17].

**Statistics analysis**

Statistical analyses were performed using "IBM SPSS Statistics for Windows. Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)". Descriptive statistics are presented as Median±SD for continuous variables, n and % for categorical variables. Kaplan Meier method was used for survival (OS, DFS) analyses. Univariate analysis was performed. Finally, Multivariate Cox Regression results were given for the evaluation of statistically significant parameters in survival analysis. Statistically significant results ($p$<0.05) are indicated with a (*) sign next to the $p$ value.

We evaluated which of these markers were predictive and prognostic for DFS and OS. DFS was defined as the time from the date of locoregional treatment to the first progression of disease. OS was defined as the time from the date of diagnosis to the time of death or last follow-up. Cut-off values of prognostic markers in the literature were used.

Pamukkale University Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee approval was obtained (number: E-60116787-020-507040, board meeting dated 20.03.2024 and numbered E.507040).

**Results**

Clinical and demographic characteristics of HCC patients who underwent locoregional therapy are shown in Table 3. The mean age was 63 years (min-max: 26-87) and 59 (93.7%) of the patients were male. The etiology of HCC was hepatitis B virus (HBV) in 25 (39.7%), hepatitis C virus (HCV) in 5 (7.9%), non-alcoholic steatohepatitis (NASH) on the background of diabetes mellitus (DM) in 12 (19%) and alcohol use in 11 (17.5%). The most common presenting complaint was abdominal pain (27 patients (42.9%). The mean follow up period was 25 months and 53 patients were deceased (84.1%) (Table 3). Cut-off values of prognostic markers in the literature were used. The power of LA factor ($p$=0.045) and ALBI score ($p$=0.014) to predict mortality was statistically significant. Clinical and demographic data of the patients who underwent locoregional treatment are presented in Table 3.

In this study, age, Conut score, GPS, HsGPS, HsGPS, LA factor and ALBI score were included in the model created from prognostic markers. The power of these markers to predict two and five year OS and DFS after locoregional therapy in inoperable HCC was evaluated. In the whole patient group, mOS:18.56 months (min-max:13.13-23.99); mDFS:7 months (min-max:3.63-10.37) after locoregional therapy. Age ($p$=0.019), Conut score ($p$=0.001), GPS ($p$=0.028), Hs-mGPS ($p$=0.012), LA ($p$=0.017) and ALBI score ($p$=0.002) were significantly correlated with mOS. The relationship between Conut ($p$=0.002), GPS ($p$<0.001), Hs-mGPS ($p$=0.002), LA ($p$=0.002) and ALBI ($p$=0.001) and mDFS was statistically significant (Table 4).

In patients under 65 years of age, the two and five year OS rates were 70.4% and 48.6%, respectively; in patients over 65 years of age, the two and five year OS rates were 46.3% and 8.6%, respectively ($p$=0.019). In patients with normal Conut score, two and five year OS rates were 80% and 40%, respectively; in patients with mild and moderate malnutrition according to Conut score, two year OS rates were 49.7% and 26.1% and five year OS rates were 26.1% and 8.7%, respectively ($p$=0.001). In patients with GPS '0', two and five year OS rates were respectively 63.2% and 29.2%; in patients with GPS '1' and '2', two year OS rates were 32% and 8%, respectively; five year OS rates were 13.7% and 8%, respectively ($p$=0.028). In patients with Hs-mGPS '0', the two and five year OS rates were 68.8% and 31.3%, respectively, while in patients with Hs-mGPS '1' and '2', the two year OS rates were 45% and 20.6%, respectively ($p$=0.012).

**Table 3.** Clinical and demographic characteristics of HCC patients who underwent locoregional therapy

| Variables | Total n=63 (%) |
|---|---|
| **Age, Median (min-max)** | 63 (26-87) |
| ≤65 | 34 (54%) |
| >65 | 29 (46%) |
| **Gender, n (%)** | |
| Male | 59 (93.7%) |
| Female | 4 (6.3%) |
| **Etiology, n (%)** | |
| HBV (Hepatitis B virüs) | 25 (39.7%) |
| HCV (Hepatitis C virüs) | 5 (7.9%) |
| Diabetes Mellitus | 12 (19%) |
| **Alcohol, n (%)** | |
| - | 52 (82.5%) |
| + | 11 (17.5%) |
| **Ecog, n (%)** | |
| 0-1 | 59 (93.6%) |
| ≥2 | 4 (6.3%) |
| **Location, n (%)** | |
| Right | 40 (63.5%) |
| Left | 6 (9.5%) |
| Multifocal | 17 (27.0%) |
| **Diagnostic sympton, n (%)** | |
| Asymptomatic | 20 (31.7%) |
| Abdominal swelling | 4 (6.3%) |
| Abdominal pain | 27 (42.9%) |
| Fatigue | 10 (15.9%) |
| Jaundice and Nause | 2 (3.2%) |
| **TM size, n (%)** | |
| <50 mm | 27 (42.9%) |
| ≥50 mm | 36 (57.1%) |
| **Number of TMs, n (%)** | |
| Multiple | 28 (44.4%) |
| 1 | 28 (44.4%) |
| 2 | 7 (11.1%) |
| **Stage, n (%)** | |
| 1 | 22 (34.9%) |
| 2 | 7 (11.1%) |
| 3 | 15 (23.8%) |
| 4 | 19 (30.2%) |
| **1. line treatment, n (%)** | |
| - | 9 (14.3%) |
| Sorafenib | 51 (81.0%) |
| Other treatments (atezolizumab+bevacizumab/nivolumab) | 3 (4.8%) |
| **Mortality, n (%)** | |
| Live | 10 (15.9%) |
| Deceased | 53 (84.1%) |
| **Follow up period, Mean±SD** | 24.96±27.37 |

Descriptive statistics are presented as Median±SD for continuous variables, n and % for categorical variables

**Table 4.** Predictive effect of prognostic markers on two year and five year os and dfs data in locoregionally treated HCC Patients

| OS (months) | 2 years (%) | 5 years (%) | Median (95% CI) | *p* |
|---|---|---|---|---|
| **Overall** | 59.5 | 36.6 | 18.56 (13.13-23.99) | |
| **Age** | | | | |
| <65 | 70.4 | 48.6 | 22.20 (6.93-37.47) | 0.019* |
| ≥65 | 46.3 | 8.6 | 10.76 (2.60-18.93) | |
| **CONUT score** | | | | |
| Normal | 80.0 | 40.0 | 47.33 (26.65-68.01) | |
| Mild | 49.7 | 28.4 | 20.80 (2.88-38.72) | 0.001* |
| Moderate | 26.1 | 8.7 | 10.76 (0.00-22.61) | |
| **GPS** | | | | |
| 0 | 63.2 | 29.6 | 37.70 (18.90-58.49) | |
| 1 | 32.0 | 13.7 | 15.56 (6.14-24.98) | 0.028* |
| 2 | 8.0 | 8.0 | 4.60 (0.39-8.80) | |
| **Hs-mGPS** | | | | |
| 0 | 68.8 | 31.3 | 37.70 (14.70-60.69) | |
| 1 | 45.5 | - | 15.56 (-) | 0.012* |
| 2 | 20.6 | 8.8 | 7.10 (0.00-15.85) | |
| **LA** | | | | |
| >4.08 | 57.7 | 32.4 | 34.73 (9.21-60.25) | 0.017* |
| ≤4.08 | 23.6 | 8.8 | 11.76 (4.82-18.70) | |
| **ALBI** | | | | |
| ≥-2.6 (score-2) | 38.9 | 9.0 | 7.10 (0.00-16.11) | 0.002* |
| <-2.6 (score-1) | 60.6 | 31.1 | 37.70 (15.86-59.53) | |
| **DFS (months)** | **2 years (%)** | **5 years (%)** | **Median (95% CI)** | ***p*** |
| **Genel** | 19.0 | 4.8 | 7.00 (3.63-10.37) | |
| **Age** | | | | |
| <65 | 26.5 | 2.9 | 9.00 (4.42-13.57) | 0.191 |
| ≥65 | 10.3 | 6.9 | 3.00 (1.02-4.97) | |
| **CONUT** | | | | |
| Normal | 60.0 | 20.0 | 27.00 (0.00-54.91) | |
| Mild | 29.6 | 7.4 | 10.00 (4.91-15.08) | 0.002* |
| Moderate | 4.3 | - | 3.00 (2.54-3.45) | |
| **GPS** | | | | |
| 0 | 52.6 | 10.5 | 27.00 (12.84-41.15) | |
| 1 | 6.9 | 3.4 | 6.00 (2.17-9.82) | <0.001* |
| 2 | - | - | 1.00 (0.01-1.99) | |
| **Hs-mGPS** | | | | |
| 0 | 56.3 | 12.5 | 27.00 (11.44-42.55) | |
| 1 | 9.0 | - | 7.00 (4.84-9.15) | 0.002* |
| 2 | 5.6 | 2.8 | 3.00 (2.67-3.23) | |
| **LA** | | | | |
| >4.08 | 40.0 | 8.0 | 14.00 (2.31-25.68) | 0.002* |
| ≤4.08 | 5.3 | 2.6 | 3.00 (2.66-3.34) | |
| **ALBI** | | | | |
| ≥-2.6 (score-2) | 5.3 | 2.6 | 3.00 (2.66-3.33) | 0.001* |
| <-2.6 (score-1) | 40.0 | 8.0 | 16.93 (8.77-25.09) | |

95% CI: Confidence interval, Conut: nutritional score, GPS: Glasgow score, HsmGPS: high sensitive modified Glasgow score LA: lymphocyte-albumin factor, ALBI: albumin-bilirubin score, $p<0.05$ was considered statistically significant, Kaplan Meier curve, Long rank test, Statistically significant results ($p<0.05$) are indicated with a (*) sign next to the *p* value

In patients with LA >4.08, two and five year OS rates were 57.7% and 32.4%, respectively; in patients with LA ≤4.08, two and five year OS rates were 23.6% and 8.8%, respectively ($p$=0.017). In patients with ALBI score-1, two and five year OS rates were 60.6% and 31.1%, respectively; in patients with ALBI score-2, two and five year OS rates were 38.9% and 9%, respectively ($p$=0.002). In this study, Conut, GPS, HsmGPS, HsmGPS, LA, ALBI were found to statistically significantly predict mOS and mDFS after local treatment in HCC patients treated locoregionally. All these results suggest that the use of our prognostic modelling in clinical practice is useful (Table 4).

As a result of univariate analysis, age, CONUT, Glasgow, Hs-mGPS, LA and ALBI variables were found statistically significant in terms of predicting the risk of death and DFS after locoregional treatment ($p$<0.05). These variables found to be significant in the univariate analysis were included in the multivariate Cox regression model. According to the results of multivariate analysis, it was determined that being over 65 years of age (HR:2.10; 95% CI:1.02-4.30; $p$=0.042) and not receiving systemic treatment before or after locoregional treatment (HR:4.11; 95% CI:1.35-12.56; $p$=0.013) increased the risk of death ($p$<0.001). Another significant result obtained in the multivariate analysis showed that GPS of '2' (HR:6.62; 95% CI:1.13-38.62; $p$=0.036) and no systemic treatment before or after locoregional treatment (HR:7.00; 95% CI:2.22-22.09; $p$=0.001) predicted a higher risk of progression ($p$<0.001) (Table 5). There were no statistically significant results in the multivariate analysis of other markers in the prognostic model (age, Conut score, HsGPS, LA factor and ALBI score) ($p$>0.05).

**Table 5.** OS and DFS after locoregional therapy in HCC with prognostic markers multivariate cox regression results of their power to predict data

| Variables | OS Multivariate HR (95% CI) | *p* | DFS Multivariate HR (95% CI) | *p* |
|---|---|---|---|---|
| **Age (Ref:≤65)** | 2.10 (1.02-4.30) | 0.042 | - | |
| **Conut (Ref:normal)** | | 0.057 | | 0.821 |
| Mild | 1.23 (0.36-4.17) | 0.737 | 1.07 (0.35-3.24) | 0.892 |
| Moderate | 1.96 (0.23-16.20) | 0.532 | 1.84 (0.31-10.64) | 0.494 |
| Severe | 7.23 (0.71-73.74) | 0.095 | 1.52 (0.21-10.86) | 0.673 |
| **GPS (Ref:0)** | | 0.141 | | 0.024* |
| 1 | 0.58 (0.82-4.18) | 0.595 | 2.47 (0.48-12.57) | 0.276 |
| 2 | 1.31 (0.16-10.57) | 0.797 | 6.62 (1.13-38.62) | 0.036* |
| **Hs-mGPS (Ref:0)** | | 0.875 | | 0.422 |
| 1 | 0.76 (0.11-5.02) | 0.777 | 0.64 (0.12-3.33) | 0.596 |
| 2 | 0.45 (0.01-11.55) | 0.633 | 0.23 (0.02-2.83) | 0.257 |
| **LA (Ref:>4.08)** | 0.61 (0.21-1.75) | 0.365 | 1.14 (0.50-2.62) | 0.742 |
| **ALBI (Ref:<-2.6)** | 0.22 (0.04-1.02) | 0.054 | 0.36 (0.11-1.17) | 0.092 |
| | $p$<0.001; -2 Log Likelihood=313.10 | | $p$<0.001; -2 Log Likelihood=367.37 | |

Nutritional score, GPS: Glasgow score, Hs-mGPS: high sensitive modified Glasgow score, LA: lymphocyte-albumin factor
ALBI: albumin-bilirubin score, $p$<0.05 was considered statistically significant, Multivariate Cox Regression analysis
Statistically significant results ($p$<0.05) are indicated with a (*) sign next to the $p$ value

## Discussion

The prognostic model created in this clinical study included patient age, Conut score, GPS, Hs-mGPS, LA, and ALBI score. These markers' ability to predict two- and five-year OS and DFS after locoregional therapy in inoperable HCC patients was evaluated. In the entire patient group, the mOS was 18.56 months (min-max:13.13-23.99) and the mDFS was 7 months (min-max:3.63-10.37) after locoregional therapy. Age ($p$=0.019), Conut ($p$=0.001), GPS ($p$=0.028), Hs-mGPS ($p$=0.012), LA ($p$=0.017), and ALBI ($p$=0.002) were significantly correlated with mOS. Similarly, Conut ($p$=0.002), GPS ($p$<0.001), Hs-mGPS ($p$=0.002), LA ($p$=0.002), and ALBI ($p$=0.001) were significantly correlated with mDFS. In patients under 65 years, the two- and five-year OS rates were 70.4% and 48.6%, respectively, while for those over 65 years, the rates were 46.3% and 8.6% ($p$=0.019). Age over 65 was identified as an independent parameter for increased risk of recurrence and death after treatment (HR:2.10; 95% CI:1.02-4.30; $p$=0.042).

In univariate analysis, age, Conut, GPS, Hs-mGPS, LA, and ALBI were significant predictors of death and DFS after locoregional therapy ($p$<0.05). Multivariate analysis showed that increased age (HR:2.10; 95% CI:1.02-4.30; $p$=0.042) and absence of systemic therapy before locoregional therapy (HR:4.11; 95% CI:1.35-12.56; $p$=0.013) were independent predictors of increased mortality. GPS score of '2' was also significantly associated with increased risk of progression (HR:6.62; 95% CI:1.13-38.62; $p$=0.036). However, other markers in the prognostic model (age, Conut score, Hs-mGPS, LA ratio, and ALBI score) did not yield statistically significant results for OS and DFS ($p$>0.05).

Despite improvements in survival following locoregional therapy for HCC, the five-year recurrence rate remains high, at 70-80%, even in patients who undergo curative surgical resection or locoregional treatment. Due to the lack of strong post-treatment prognostic markers, tumour number, size, and pathological differentiation are currently used as indicators [18]. Necrosis and fibrosis, common in tumours treated with RFA, microwave ablation, TACE, and transarterial radioembolisation (TARE), also pose challenges in follow-up. While imaging modalities can distinguish treatment responders from non-responders, the correlation between necrosis extent and treatment outcomes is unclear, as imaging may overestimate necrosis [19, 20].

Inflammation plays a key role in the carcinogenesis of fatty liver, steatohepatitis, and HCC. Chronic inflammation creates an immunosuppressive microenvironment, promoting tumour formation and metastasis, and accelerating recurrence and metastasis [21]. This process informs the selection of prognostic markers. Previous clinical studies have aimed to predict locoregional treatment response in HCC patients based on various markers. For instance, Schobert et al. [22] included 46 HCC patients undergoing TACE and found that high pre-treatment neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were associated with poor tumour response and shorter PFS. The LA ratio, derived from lymphocytes and albumin, was also evaluated, with higher LA values predicting better outcomes, though these findings were not statistically significant in multivariate analysis.

Young et al. [23] used NLR, PLR, and aspartate aminotransferase to lymphocyte ratio index (ALRI) scores in a study of 167 HCC patients treated with TARE. The ALRI score, which combines AST and lymphocytes, was significantly associated with local recurrence and PFS. These markers, along with the Conut score, have been shown to predict malnutrition and have been validated as prognostic in studies involving liver resection or transplantation for HCC [24, 25].

Harimoto et al. [25] found that a higher Conut score was an independent risk factor for HCC recurrence and poor OS in 2461 HCC patients. However, in another study of 280 patients undergoing liver transplantation, while NLR and PLR were independent variables for predicting death and tumour recurrence, the Conut score was not predictive [26].

In this study, patients with low Conut scores had two- and five-year OS rates of 80% and 40%, respectively, compared to 49.7% and 26.1% for patients with mild malnutrition, and 26.1% and 8.7% for those with moderate malnutrition ($p$=0.001). Although the Conut score did not predict death and recurrence risk

after treatment, it remains a useful guide for the early detection and treatment of malnutrition. Other studies have demonstrated the prognostic value of markers such as GPS, tumour size, and PLR for PFS [27].

A retrospective study of 1625 HCC patients reported median OS of 15.7 months and a significant predictive value for GPS and Hs-mGPS, though multivariate analysis yielded no significant results [16]. Zhao et al. [28] found that the ALBI score was an independent predictor of progression after hepatic arterial infusion chemotherapy. Although ALBI scores were statistically significant as indicators of relapse and death, multivariate analysis did not find them to be independent variables for OS and DFS.

This study has limitations, including its single-centre design, small sample size, and retrospective data collection. Prospective studies with larger patient cohorts are necessary to confirm these findings. Similar limitations exist in studies evaluating inflammatory markers in cancer survival. However, inflammation and nutritional markers have shown significant associations with survival and recurrence risk, supporting their use in clinical practice.

In conclusion, this study hypothesizes that a prognostic marker could predict post-treatment outcomes in locoregionally treated HCC patients. We evaluated the predictive value of albumin and CRP-related inflammation and nutritional scores on survival and DFS. Our findings suggest that age, Conut score, GPS, Hs-mGPS, ALBI scores, and decreased LA ratio may help predict recurrence and death after locoregional therapy, providing valuable insight for clinical practice.

**Acknowledgement:** Co-researchers.

**Funding:** None.

**Authors contributions:** M.O. and G.G.D. constructed the main idea and hypothesis of the study. M.O. and G.G.D. developed the theory and arranged/edited the material and method section. M.O. and G.G.D. has done the evaluation of the data in the results section. The discussion section of the article was written by M.O. and G.G.D. and reviewed, corrected, and approved by S.D., B.Y.T., A.G.D., and A.Y. In addition, all authors discussed the entire study and approved the final version.

**Conflict of interest:** No conflict of interest was declared by the authors.

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