Ann Surg Oncol (2019) 26:3682–3692
https://doi.org/10.1245/s10434-019-07586-3

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY



ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

# Fibrinogen–Albumin Ratio Index (FARI): A More Promising Inflammation-Based Prognostic Marker for Patients Undergoing Hepatectomy for Colorectal Liver Metastases

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## ABSTRACT

**Background.** Systemic inflammation response is involved in the development and progression of cancers. This study aimed to evaluate the prognostic value of a preoperative Fibrinogen–Albumin Ratio Index (FARI) in patients undergoing hepatectomy for colorectal liver metastases (CRLM) and compare it with established systemic inflammation markers, including the neutrophil–lymphocyte ratio, lymphocyte–monocyte ratio, platelet–lymphocyte ratio, and systemic immune–inflammation index.

**Methods.** Patients who underwent hepatectomy for CRLM between November 2002 and December 2016 were considered for inclusion. Time-dependent receiver operating characteristic (ROC) curve analysis was conducted to evaluate the ability of markers in predicting survival. Multivariable Cox regression analysis was used to identify independent predictors for overall survival (OS) or disease-free survival (DFS).

**Results.** A total of 452 consecutive patients were enrolled. The areas under the ROC curve of the FARI in predicting OS and DFS were superior to other inflammatory markers and carcinoembryonic antigen (CEA). The optimal cut-off value of the FARI was 7.6%. Patients with a high FARI (> 7.6%) showed significantly decreased OS and DFS (all $p < 0.001$). In multivariable analysis, the FARI was the only inflammatory marker that independently predicted OS and DFS. Additionally, regardless of patients having a high or low CEA, the FARI further stratified these patients into subgroups with significantly distinct OS and DFS (all $p < 0.05$). The FARI also showed good clinical utility in patients with different clinical characteristics.

**Conclusions.** A preoperative FARI is an independent predictor of OS and DFS for patients undergoing hepatectomy for CRLM, superior to the established systemic inflammation markers and CEA.

Colorectal cancer is the third most common malignant tumor and the second leading cause of cancer death worldwide.[1] In China, colorectal cancer is also a commonly diagnosed cancer and has a significant upward trend in both incidence and mortality over the last decade.[1,2] The liver is the most common metastatic site for colorectal cancer, and the majority of patients with colorectal cancer die as a result of colorectal liver metastases (CRLM).[3] Hepatectomy is considered a potentially curative treatment for CRLM, offering an approximately 40% 5-year survival rate in patients with resectable CRLM.[3–5] However, even after hepatectomy with curative intent, the postoperative recurrence rate of patients with CRLM remains high—over 70% within 5 years.[6] Hence, a reliable prognostic marker is desired to identify patients at high-risk of recurrence and to optimize their adjuvant therapies.

Inflammation is currently recognized as a hallmark of cancer that involves every step of tumor development.[7–9] An increasing body of evidence shows that systemic

**Electronic supplementary material** The online version of this article (https://doi.org/10.1245/s10434-019-07586-3) contains supplementary material, which is available to authorized users.



First Received: 9 April 2019;
Published Online: 1 July 2019

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inflammation response markers are associated with long-term survival in various tumors.[10–12] These systemic inflammation markers are usually derived from circulating blood leukocytes and acute-phase proteins. The neutrophil–lymphocyte ratio (NLR) is the most widely validated leukocyte-based inflammation marker and has shown prognostic value in a variety of cancers, including colorectal cancer.[10,13] In addition, the lymphocyte–monocyte ratio (LMR), platelet–lymphocyte ratio (PLR), and systemic immune–inflammation index (SII, derived from lymphocyte, neutrophil, and platelet counts) were also reported to be associated with survival in patients with various cancers.[10,11,13,14]

Among patients undergoing hepatectomy for CRLM, a considerable proportion require treatment with preoperative chemotherapy,[15–17] which could reduce the circulating neutrophil, lymphocyte, monocyte, and platelet counts. Failing to reflect the real inflammation response status in patients after chemotherapy, the ability of the above leukocyte-based inflammation markers may be limited in predicting the prognosis of CRLM patients after hepatectomy. Although Kishi et al.[18] reported that high preoperative NLR independently predicted poor survival in patients with CRLM treated with chemotherapy followed by hepatectomy, such predictive value was not confirmed in the study by Neal et al.[19]

C-reactive protein (CRP) and albumin are two critical acute-phase proteins in systemic inflammation response.[7] The modified Glasgow Prognostic Score (mGPS, a combination of elevated serum CRP and decreased serum albumin) and the CRP-albumin ratio (CAR) have also been reported to be associated with survival in cancer patients;[10,20] however, CRP is not routinely measured in the treatment of patients with CRLM, which limits its clinical utility.[14] As an important indicator of coagulation function, fibrinogen is routinely detected before hepatectomy. Similar to CRP, fibrinogen is also an acute-phase protein and its plasma level rises in systemic inflammation response.[21] Furthermore, elevated plasma fibrinogen levels were found to be associated with decreased survival in cancer patients.[22,23] Additionally, Ghanim et al.[21] reported that fibrinogen had equally high accuracy as CRP in predicting prognosis in malignant pleural mesothelioma. Accordingly, the Fibrinogen–Albumin Ratio Index (FARI), a combination of plasma fibrinogen and serum albumin, may have potential value in predicting the prognosis of patients with CRLM after hepatectomy.

This study aimed to evaluate the prognostic value of a preoperative FARI in patients undergoing hepatectomy for CRLM, and to compare it with established systemic inflammation markers, including NLR, LMR, PLR, and SII.

## PATIENTS AND METHODS

Ethical approval was obtained from the Peking University Cancer Hospital, and informed consent was obtained from all patients prior to participation in this study.

### *Patients*

From November 2002 to December 2016, all consecutive patients who underwent their first hepatectomy with curative intent for CRLM at the Hepatopancreatobiliary Surgery Department I of Peking University Cancer Hospital were considered for inclusion in this study. Patients who had preoperative extrahepatic metastases, who underwent re-hepatectomy for recurrent CRLM, or who had a palliative resection (R2 resection) were excluded.

### *Diagnosis and Definitions*

A diagnosis of CRLM was confirmed on the basis of histopathologic evidence. R1 resection was defined as the presence of tumor cells within 1 mm from the surgical margin, and the threshold of 50 ng/mL was used to define high and low carcinoembryonic antigen (CEA).[24] The Clinical Risk Score (CRS) developed by Fong et al.[25] was calculated in line with previous reports (details shown in electronic supplementary Table 1). A CRS of 0–2 was defined as low risk and a CRS of 3–5 was defined as high risk.

### *Systemic Inflammation Markers*

All blood test results, including serum fibrinogen and albumin levels, white blood cell count, and platelet count, were obtained within 2 weeks before surgery. Inflammatory indices were calculated using the following formulas: FARI = (fibrinogen: albumin) $\times$ 100%; NLR = (neutrophil count:lymphocyte count); LMR = (lymphocyte count:-monocyte count); PLR = (platelet count:lymphocyte count); SII = (platelet count) $\times$ NLR.

### *Treatment and Follow-Up*

Preoperative routine examinations for patients with CRLM included abdominal and pelvic contrast-enhanced magnetic resonance imaging (MRI), liver and kidney function tests, and serum CEA measurement. The decision to conduct hepatectomy was made by a multidisciplinary team meeting, attended by surgeons, medical oncologists, and radiologists. During the operation, intraoperative ultrasound was routinely conducted to detect new lesions.

Combined radiofrequency ablation (RFA) was selected when tumors were deeply located in the liver, or were difficult to resect. [26,27] Details of preoperative evaluation and operative techniques have been described previously.[28]

Patients were followed up 1 month post surgery and every 3 months thereafter. At each follow-up, abdominal contrast-enhanced computed tomography (CT) or MRI scan, liver function test, and serum CEA measurement were routinely conducted. Tumor recurrence was defined as the presence of intrahepatic or extrahepatic new lesions revealed by imaging. Patients with tumor recurrence were treated by repeat surgery, radiofrequency, systemic chemotherapy, targeted therapies, or radiotherapy, as appropriate. Overall survival (OS) was calculated from the date of hepatectomy to the date of death from disease, and disease-free survival (DFS) was calculated from the date of hepatectomy to the date of tumor recurrence.

### *Statistical Analysis*

Continuous variables were presented as median (interquartile range [IQR]) and were compared using the Mann–Whitney *U* test, while categorical variables were expressed as numbers (%) and were compared using the two-sided Chi square test or Fisher's exact test. Time-dependent receiver operating characteristic (ROC) curve analysis was conducted using the inverse probability of censoring weighting (IPCW) approach,[29] and the area under the ROC curve (AUC) was estimated to evaluate the ability of inflammation markers in predicting OS and DFS. X-tile analysis, in which the optimal cut-off value is determined at a point where the log-rank statistic is the largest, for 5-year OS was performed to find the optimal cut-off values of inflammatory markers.[30] OS and DFS rates were estimated using the Kaplan–Meier method and were compared between groups using the log-rank test. Multivariable Cox regression analysis was conducted to determine the independent predictors of OS or DFS. Time-dependent ROC curve analysis was performed using the 'timeROC' package in R version 3.4.4 (http://www.r-project.org/); X-tile analysis was conducted using X-tile software version 3.6.1 (Yale University); and other statistical analyses were carried out using SPSS® version 19.0 (IBM Corporation, Armonk, NY, USA). A $p$ value $< 0.050$ was considered statistically significant.

## RESULTS

From November 2002 to December 2016, a total of 603 consecutive patients underwent hepatectomy for CRLM; 151 patients were excluded due to repeated hepatectomy (71), preoperative extrahepatic metastases (66), or palliative surgery (14). The remaining 452 patients were included in our study.

### *Patient Characteristics*

Of the enrolled 452 patients, the majority were male and the median age was 57 years (IQR 50–64); 255 patients (56.4%) had primary tumors located within the colon, while the remaining 197 patients had primary tumors located within the rectum. The proportion of synchronous CRLM was 52.7%, and 32.2% were detected with RAS mutation. The median levels of FARI, NLR, LMR, PLR, and SII were 7.3% (IQR 6.2–8.8%), 2.2 (IQR 1.5–3.1), 3.6 (IQR 2.7–4.8), 123 (IQR 94–170), and 390 (IQR 265–628), respectively. The detailed baseline characteristics of the included patients are summarized in Table 1.

### *Comparison of the Ability of Systemic Inflammation Markers in Predicting Overall Survival (OS) and Disease-Free Survival (DFS)*

The AUC of the FARI in predicting OS was continuously superior to that of NLR, LMR, PLR, and SII after 2 years postoperatively (Fig. 1a). Similarly, the AUC of the FARI in predicting DFS was higher than that of NLR, LMR, PLR, and SII at any time point after hepatectomy (Fig. 1b). Additionally, the AUCs of the FARI for OS and DFS were also greater than those of CEA (Fig. 1a, b). The AUCs of the FARI in predicting 1-, 3-, 5-, and 7-year OS and DFS were 0.606, 0.605, 0.567, 0.596, and 0.589, 0.640, 0.620, 0.655, respectively. The data for NLR, LMR, PLR, SII, and CEA are shown in electronic supplementary Table 2.

### *X-Tile Analysis to Determine the Optimal Cut-Off Values of Systemic Inflammation Markers*

X-tile analysis for 5-year OS determined that the optimal cut-off value of the FARI was 7.6% (electronic supplementary Fig. 1a). According to this cut-off value, patients were dichotomized into low ($\leq$ 7.6%, $n$ = 260) and high ($>$ 7.6%, $n$ = 192) FARI groups. The optimal cut-off values for NLR, LMR, PLR, and SII were 2.6, 3.4, 186, and 517, respectively (electronic supplementary Fig. 1b–e). The NLR, LMR, PLR, and SII high and low groups were also created based on their respective optimal cut-off values.

**TABLE 1** Baseline characteristics of the entire 452 patients, as well as patients in the high (> 7.6%) and low (≤ 7.6%) FARI groups

| Variables | Total [*n* = 452] | Low FARI [*n* = 260] | High FARI [*n* = 192] | *p* value |
|---|---|---|---|---|
| Sex | | | | 0.180[a] |
| Male | 289 (63.9) | 173 (66.5) | 116 (60.4) | |
| Female | 163 (36.1) | 87 (33.5) | 76 (39.6) | |
| Age, years [median (IQR)] | 57 (50–64) | 55 (48–63) | 59 (52–65) | 0.001[b] |
| Primary tumor | | | | |
| T category [*n* = 402][c] | | | | 0.603[a] |
| T1-2 | 44 (10.9) | 27 (11.6) | 17 (10.0) | |
| T3-4 | 358 (89.1) | 205 (88.4) | 153 (90.0) | |
| N category [*n* = 407][c] | | | | 0.855[a] |
| N0 | 136 (33.4) | 78 (33.1) | 58 (33.9) | |
| N1-2 | 271 (66.6) | 158 (66.9) | 113 (66.1) | |
| Site | | | | 0.800[a] |
| Colon | 255 (56.4) | 148 (56.9) | 107 (55.7) | |
| Rectum | 197 (43.6) | 112 (43.1) | 85 (44.3) | |
| Liver metastases | | | | |
| Presentation timing | | | | 0.005[a] |
| Synchronous | 238 (52.7) | 122 (46.9) | 116 (60.4) | |
| Metachronous | 214 (47.3) | 138 (53.1) | 76 (39.6) | |
| Tumor size, cm | | | | <0.001[a] |
| ≤ 5 | 382 (84.5) | 235 (90.4) | 147 (76.6) | |
| > 5 | 70 (15.5) | 25 (9.6) | 45 (23.4) | |
| Tumor number | | | | 0.021[a] |
| Single | 193 (42.7) | 123 (47.3) | 70 (36.5) | |
| Multiple | 259 (57.3) | 137 (52.7) | 122 (63.5) | |
| Distribution | | | | 0.827[a] |
| Unilobar | 261 (57.7) | 149 (57.3) | 112 (58.3) | |
| Bilobar | 191 (42.3) | 111 (42.7) | 80 (41.7) | |
| RAS status [*n* = 432][c] | | | | 0.759[a] |
| Mutated | 139 (32.2) | 78 (31.6) | 61 (33.0) | |
| Wild | 293 (67.8) | 169 (68.4) | 124 (67.0) | |
| CRS [*n* = 434][c] | | | | 0.006[a] |
| 0–2 | 263 (60.6) | 167 (66.0) | 96 (53.0) | |
| 3–5 | 171 (39.4) | 86 (34.0) | 85 (47.0) | |
| Preoperative chemotherapy | 285 (63.1) | 161 (61.9) | 124 (64.6) | 0.562[a] |
| Surgical margin | | | | 0.919[a] |
| R0 | 401 (88.7) | 231 (88.8) | 170 (88.5) | |
| R1 | 51 (11.3) | 29 (11.2) | 22 (11.5) | |
| Combining ablation | 36 (8.0) | 16 (6.2) | 20 (10.4) | 0.098[a] |
| Postoperative chemotherapy | 284 (74.3) | 157 (72.4) | 127 (77.0) | 0.306[a] |
| CEA, ng/mL | | | | 0.359[a] |
| ≤ 50 | 378 (83.6) | 221 (85) | 157 (81.8) | |
| > 50 | 74 (16.4) | 39 (15.0) | 35 (18.2) | |
| CA19-9, U/mL | | | | 0.138[a] |
| ≤ 37 | 309 (68.4) | 185 (71.2) | 124 (64.6) | |
| > 37 | 143 (31.6) | 75 (28.8) | 68 (35.4) | |
| FARI, % [median (IQR)] | 7.3 (6.2–8.8) | 6.4 (5.7–7.0) | 9.1 (8.3–10.3) | <0.001[b] |
| NLR [median (IQR)] | 2.2 (1.5–3.1) | 2.1 (1.5–2.9) | 2.3 (1.6–3.3) | 0.055[b] |
| LMR [median (IQR)] | 3.6 (2.7–4.8) | 3.9 (2.8–4.9) | 3.4 (2.5–4.7) | 0.017[b] |

**TABLE 1** continued

| Variables | Total [$n$ = 452] | Low FARI [$n$ = 260] | High FARI [$n$ = 192] | $p$ value |
|---|---|---|---|---|
| PLR [median (IQR)] | 123 (94–170) | 117 (92–158) | 140 (95–191) | 0.008[b] |
| SII [median (IQR)] | 390 (265–628) | 370 (250–561) | 456 (299–706) | 0.001[b] |

Data are expressed as $n$ (%) unless otherwise specified

*CA19-9* carbohydrate antigen 19-9, *CEA* carcinoembryonic antigen, *CRS* Clinical Risk Score, *FARI* Fibrinogen–Albumin Ratio Index, *LMR* lymphocyte–monocyte ratio, *NLR* neutrophil–lymphocyte ratio, *PLR* platelet–lymphocyte ratio, *SII* systemic immune–inflammation index, *IQR* interquartile range

[a]Comparison of data between the high and low FARI groups using the two-sided Chi square test

[b]Comparison of data between the high and low FARI groups using the Mann–Whitney $U$ test

[c]Number of patients for whom data were available

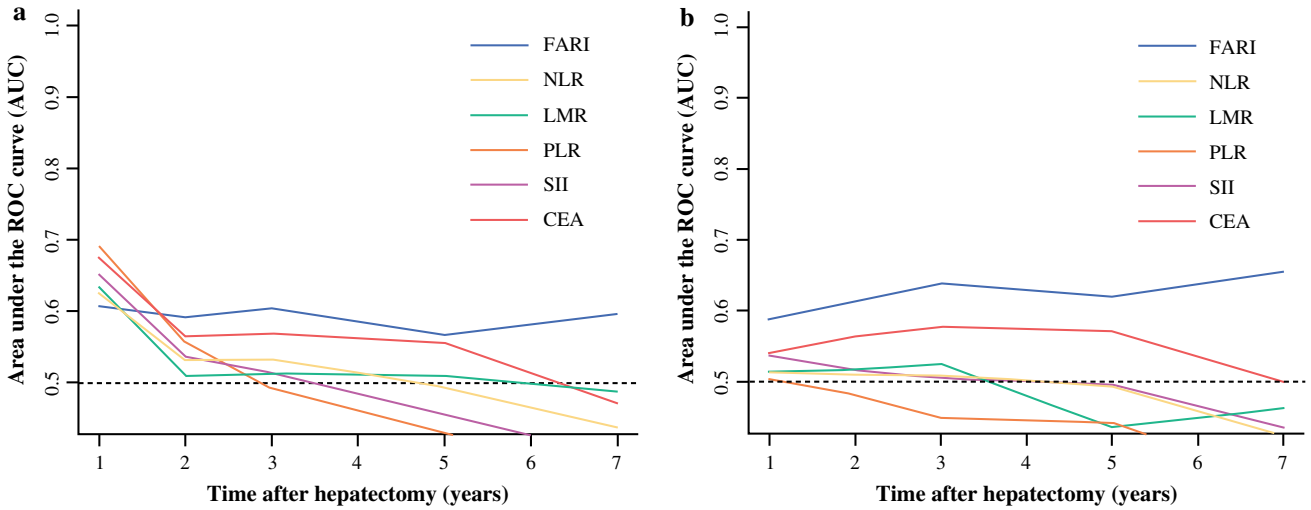


**FIG. 1** Time-dependent ROC curve analysis to compare the ability of FARI, NLR, LMR, PLR, SII, and CEA in predicting **a** overall survival and **b** disease-free survival. The horizontal axis represents the time after hepatectomy, and the vertical axis represents the corresponding area under the ROC curve for survival at different time points. *ROC* receiver operating characteristic, *FARI* Fibrinogen–Albumin Ratio Index, *NLR* neutrophil–lymphocyte ratio, *LMR* lymphocyte–monocyte ratio, *PLR* platelet–lymphocyte ratio, *SII* systemic immune–inflammation index, *CEA* carcinoembryonic antigen

### *Relationship of the Fibrinogen–Albumin Ratio Index and Clinicopathologic Parameters*

Compared with patients in the low FARI group, those in the high FARI group were more likely to have advanced age ($p$ = 0.001), synchronous CRLM ($p$ = 0.005), large tumor size ($p < 0.001$), multiple liver metastases ($p$ = 0.021), and high CRS ($p$ = 0.006). The high FARI group also had significantly lower LMR ($p$ = 0.017), higher PLR ($p$ = 0.008), and higher SII ($p$ = 0.001). Although NLR was higher in the high FARI group, the significance was marginal ($p$ = 0.055). The detailed clinicopathologic parameters between the two groups of patients are compared in Table 1.

### *OS and DFS in the High and Low FARI Groups*

With a median follow-up of 28 months (IQR 19–46), 102 patients (53.1%) in the high (> 7.6%) FARI group died compared with 104 (40.0%) in the low (≤ 7.6%) FARI group. The 1-, 3-, and 5-year OS in the high FARI group (89.9%, 46.0%, and 31.3%, respectively) was significantly lower than in the low FARI group (92.6%, 64.2%, and 52.3%, respectively; $p < 0.001$) (Fig. 2a). A total of 321 patients (71.0%) experienced tumor recurrence during the follow-up period, including 151 patients (78.6%) in the high FARI group and 170 patients (65.4%) in the low FARI group. Of these patients with recurrence, intrahepatic recurrence developed in 246 patients (76.6%), whereas the remaining 75 patients (23.4%) only had extrahepatic recurrence. The 1-, 3-, and 5-year DFS was 36.3%, 18.6%,

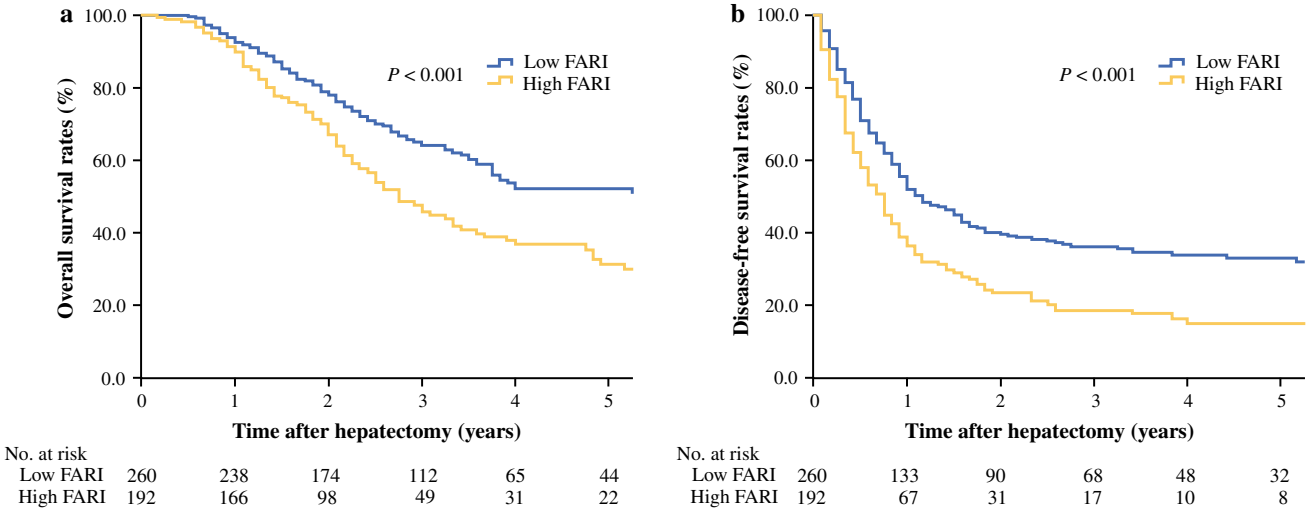


**FIG. 2** Comparison of **a** overall survival ($p < 0.001$) and **b** disease-free survival ($p < 0.001$) between patients with high (> 7.6%) and low (≤ 7.6%) FARI in the entire patient cohort. *FARI* Fibrinogen–Albumin Ratio Index

and 14.9%, respectively, in the high FARI group, and was also significantly lower than in the low FARI group (52.0%, 36.3%, and 33.1%, respectively; $p < 0.001$) (Fig. 2b).

*Univariable and Multivariable Analyses for OS*

Univariable analyses showed that the FARI, NLR, LMR, and PLR were significantly associated with OS, as well as primary tumor N category, synchronous CRLM, tumor size, tumor number, distribution of CRLM, RAS status, postoperative chemotherapy, and serum CEA and CA19-9 levels (Table 2). Multivariable analysis determined that the FARI (> 7.6% vs. ≤ 7.6%: hazard ratio [HR] 1.631, 95% confidence interval [CI] 1.155–2.303; $p = 0.005$) was an independent predictor of OS in patients undergoing hepatectomy for CRLM, followed by tumor size, distribution of CRLM, RAS status, and serum CEA level (Table 2).

*Univariable and Multivariable Analyses for DFS*

In univariable analyses, the FARI and PLR were significantly associated with DFS, as well as primary tumor T and N categories, synchronous CRLM, tumor size, tumor number, distribution of CRLM, RAS status, postoperative chemotherapy, and serum CEA and CA19-9 levels (Table 2). In multivariable analysis, the FARI (> 7.6% vs. ≤ 7.6%: HR 1.448, 95% CI 1.114–1.884; $p = 0.006$) was identified as an independent predictor of DFS in CRLM patients after hepatectomy, followed by primary tumor N category, tumor number, RAS status, postoperative chemotherapy, and serum CEA level (Table 2).

*Subgroup Analyses of OS and DFS Based on Carcinoembryonic Antigen Levels*

Using the cut-off value of 7.6%, the FARI stratified patients with a low CEA into two subgroups with significantly distinct OS and DFS (OS: $p = 0.002$; DFS: $p = 0.001$) (Fig. 3a, b). Likewise, for patients with a high CEA, those in the high FARI subgroup also had significantly lower OS and DFS compared with those in the low FARI subgroup (OS: $p = 0.034$; DFS: $p = 0.003$) (Fig. 3c, d).

*Subgroup Analyses to Assess the Clinical Utility of the FARI in Predicting OS and DFS*

To further assess the clinical utility of the FARI in predicting OS and DFS, subgroup analyses using univariable Cox regression were conducted on the basis of sex (female or male), age (≤ 60 or > 60 years), primary tumor site (colon or rectum), synchronous or metachronous CRLM, RAS status (mutated or wild), with or without preoperative chemotherapy, and low (0–2) or high (3–5) CRS. Consequently, a high FARI (> 7.6%) showed an association with poor OS and DFS in all subgroup analyses (Fig. 4a, b). Although it failed to obtain statistical significance in subgroup analyses of OS and DFS in RAS-mutated patients, and subgroup analyses of DFS in patients with synchronous CRLM and those with primary tumor located within the rectum, the trend of poor prognosis in patients with a high FARI was consistent (Fig. 4a, b).

**TABLE 2** Univariable and multivariable analyses to determine independent predictors of overall survival and disease-free survival

| Variables | Overall survival | | | | | | Disease-free survival | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Univariable | | | Multivariable | | | Univariable | | | Multivariable | | |
| | HR | 95% CI | *p* value | HR | 95% CI | *p* value | HR | 95% CI | *p* value | HR | 95% CI | *p* value |
| Sex (male vs. female) | 0.804 | 0.608–1.062 | 0.124 | – | – | – | 0.873 | 0.697–1.093 | 0.236 | – | – | – |
| Age (years) | 1.003 | 0.990–1.016 | 0.629 | – | – | – | 0.993 | 0.983–1.003 | 0.184 | – | – | – |
| Primary tumor | | | | | | | | | | | | |
| T category (T3-4 vs. T1-2) | 1.399 | 0.837–2.338 | 0.200 | – | – | – | 1.561 | 1.027–2.371 | 0.037 | 1.518 | 0.951–2.423 | 0.081 |
| N category (N1-2 vs. N0) | 1.571 | 1.133–2.179 | 0.007 | 1.413 | 0.982–2.034 | 0.063 | 1.459 | 1.135–1.877 | 0.003 | 1.355 | 1.018–1.803 | 0.037 |
| Site (rectum vs. colon) | 1.223 | 0.930–1.608 | 0.150 | – | – | – | 1.120 | 0.899–1.396 | 0.313 | – | – | – |
| Liver metastases | | | | | | | | | | | | |
| Synchronous vs. metachronous | 1.381 | 1.047–1.821 | 0.022 | 0.984 | 0.682–1.420 | 0.931 | 1.561 | 1.251–1.948 | < 0.001 | 1.250 | 0.938–1.664 | 0.127 |
| Tumor size, cm (> 5 vs. ≤ 5) | 1.630 | 1.167–2.278 | 0.004 | 1.562 | 1.038–2.352 | 0.033 | 1.354 | 1.018–1.801 | 0.037 | 1.174 | 0.811–1.699 | 0.396 |
| Tumor number (multiple vs. single) | 1.483 | 1.118–1.968 | 0.006 | 1.321 | 0.883–1.978 | 0.176 | 1.733 | 1.380–2.175 | < 0.001 | 1.914 | 1.455–2.516 | < 0.001 |
| Distribution (bilobar vs. unilobar) | 1.410 | 1.072–1.853 | 0.014 | 1.603 | 1.151–2.232 | 0.005 | 1.411 | 1.133–1.759 | 0.002 | 1.032 | 0.763–1.395 | 0.839 |
| RAS status (mutated vs. wild) | 1.952 | 1.465–2.601 | < 0.001 | 1.731 | 1.235–2.426 | 0.001 | 1.449 | 1.147–1.830 | 0.002 | 1.329 | 1.010–1.748 | 0.042 |
| Preoperative chemotherapy (yes vs. no) | 1.073 | 0.811–1.421 | 0.621 | – | – | – | 1.157 | 0.923–1.451 | 0.206 | – | – | – |
| Surgical margin (R1 vs. R0) | 1.347 | 0.843–2.150 | 0.212 | – | – | – | 1.378 | 0.981–1.936 | 0.065 | – | – | – |
| Combining ablation (yes vs. no) | 0.890 | 0.470–1.685 | 0.720 | – | – | – | 1.413 | 0.952–2.099 | 0.086 | – | – | – |
| Postoperative chemotherapy (yes vs. no) | 0.691 | 0.497–0.961 | 0.028 | 0.727 | 0.504–1.048 | 0.087 | 0.655 | 0.504–0.851 | 0.002 | 0.597 | 0.447–0.799 | 0.001 |
| CEA, ng/mL (> 50 vs. ≤ 50) | 1.732 | 1.244–2.412 | 0.001 | 1.552 | 1.045–2.305 | 0.030 | 1.582 | 1.200–2.085 | 0.001 | 1.603 | 1.157–2.222 | 0.005 |
| CA19-9, U/mL (> 37 vs. ≤ 37) | 1.520 | 1.146–2.014 | 0.004 | 1.034 | 0.710–1.507 | 0.861 | 1.344 | 1.068–1.692 | 0.012 | 1.250 | 0.926–1.688 | 0.145 |
| FARI (> 7.6% vs. ≤ 7.6%) | 1.707 | 1.298–2.246 | < 0.001 | 1.631 | 1.155–2.303 | 0.005 | 1.594 | 1.278–1.988 | < 0.001 | 1.448 | 1.114–1.884 | 0.006 |
| NLR (> 2.6 vs. ≤ 2.6) | 1.329 | 1.005–1.756 | 0.046 | 0.996 | 0.684–1.452 | 0.985 | 1.174 | 0.937–1.472 | 0.163 | – | – | – |
| LMR (≤ 3.4 vs. > 3.4) | 1.412 | 1.074–1.856 | 0.013 | 1.125 | 0.795–1.593 | 0.506 | 1.116 | 0.896–1.390 | 0.328 | – | – | – |
| PLR (> 186 vs. ≤ 186) | 1.546 | 1.124–2.127 | 0.007 | 1.278 | 0.856–1.907 | 0.230 | 1.352 | 1.034–1.767 | 0.028 | 1.321 | 0.936–1.863 | 0.114 |
| SII (> 517 vs. ≤ 517) | 1.272 | 0.963–1.679 | 0.090 | – | – | – | 1.233 | 0.985–1.543 | 0.068 | – | – | – |

*CA19-9* carbohydrate antigen 19-9, *CEA* carcinoembryonic antigen, *CI* confidence interval, *FARI* Fibrinogen–Albumin Ratio Index, *HR* hazard ratio, *LMR* lymphocyte–monocyte ratio, *NLR* neutrophil–lymphocyte ratio, *PLR* platelet–lymphocyte ratio, *SII* systemic immune–inflammation index

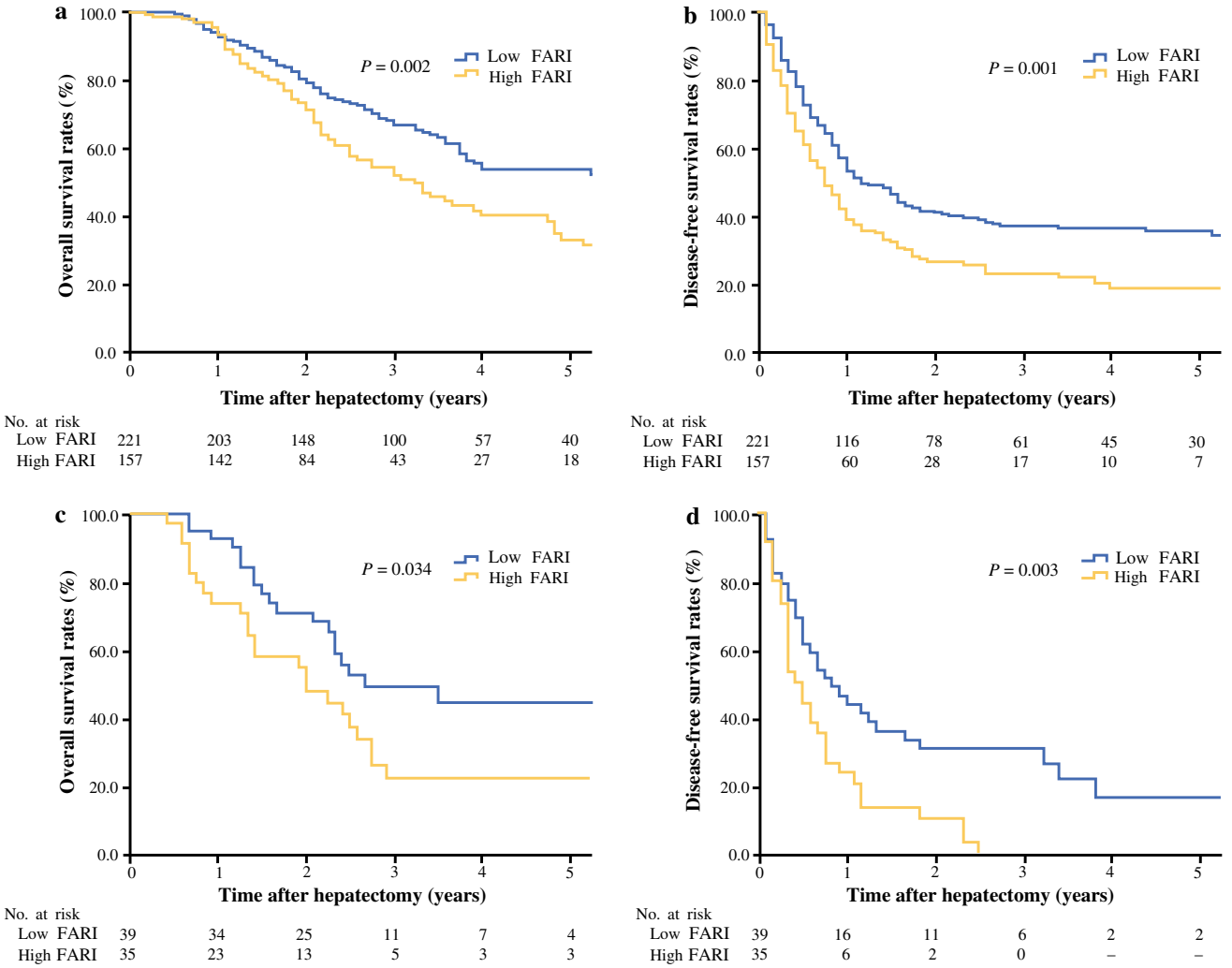


**FIG. 3** Subgroup analyses of OS and DFS in patients with high (> 7.6%) and low (≤ 7.6%) FARI according to CEA levels. **a** OS in patients with a low CEA (≤ 50 ng/mL; $p = 0.002$); **b** DFS in patients with a low CEA ($p = 0.001$); **c** OS in patients with a high CEA (> 50 ng/mL; $p = 0.034$); and **d** DFS in patients with a high CEA ($p = 0.003$). *OS* overall survival, *DFS* disease-free survival, *FARI* Fibrinogen–Albumin Ratio Index, *CEA* carcinoembryonic antigen

## DISCUSSION

The present study first evaluated the prognostic significance of a preoperative FARI in patients undergoing hepatectomy for CRLM, and compared it with established inflammatory markers. The results of this study suggest that the predictive ability of a preoperative FARI in OS and DFS is greater than the established NLR, LMR, PLR, and SII. Moreover, a preoperative FARI is an independent predictor for OS and DFS. Furthermore, with a greater prognostic predictive ability than CEA, and a consistent prognostic value in patients with different clinical characteristics, the FARI is a promising inflammation-based prognostic marker for patients undergoing hepatectomy for CRLM.

There is growing evidence that systemic inflammation response plays a critical role in the development and progression of malignancies.[7–9] The traditional leukocyte-based inflammation markers, including NLR, LMR, PLR, and SII, have been proposed as potential prognostic markers for patients with colorectal cancer after curative resection.[14,31–33] Nevertheless, the prognostic value of these markers in patients with CRLM is still controversial.[18,19] Fibrinogen and albumin are key components in systemic inflammation. Several studies have recently reported that the fibrinogen and albumin score or ratio showed prognostic value in esophageal cancer and hepatocellular carcinoma;[34,35] however, whether the FARI could predict the prognosis of CRLM patients is unknown.

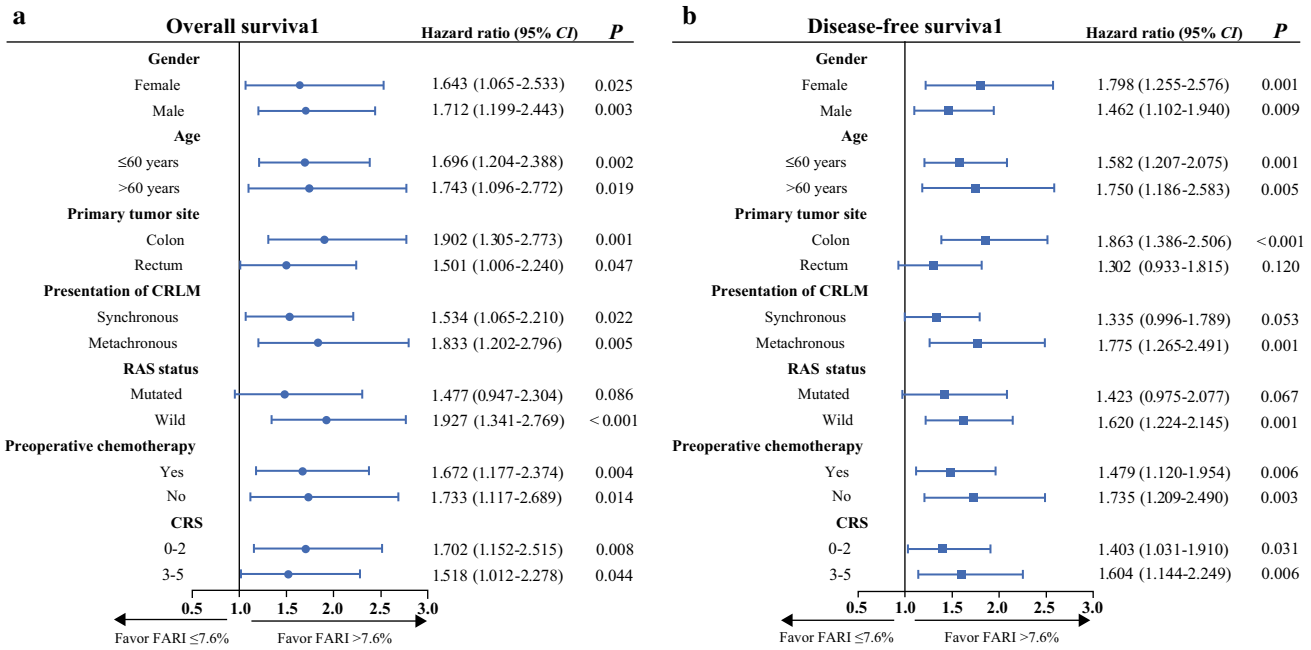


**FIG. 4** Subgroup analyses using univariable Cox regression to assess the discrimination ability of FARI for **a** overall survival and **b** disease-free survival in patients with different clinical characteristics. *CI* confidence interval, *CRLM* colorectal liver metastases, *CRS* Clinical Risk Score, *FARI* Fibrinogen–Albumin Ratio Index

In the current study, time-dependent ROC analysis revealed that the FARI was good for predicting OS and DFS in patients with CRLM after hepatectomy. Its predictive ability was stable and was greater than the established NLR, LMR, PLR, and SII. X-tile analysis determined a FARI of 7.6% was the optimized cut-off value. A high FARI (> 7.6%) was more likely to present in patients with synchronous CRLM, large tumor size, or multiple liver metastases, suggesting that the FARI could reflect tumor progression and metastasis in patients with CRLM. Our survival analyses revealed that both OS and DFS of patients with a high FARI were significantly lower than those with a low FARI. Multivariable analyses also identified the FARI as an independent predictor of OS and DFS. These findings demonstrate that a preoperative FARI is an independent prognostic marker for patients with CRLM after hepatectomy.

In comparison with the FARI, the established inflammation markers assessed in this study, including NLR, LMR, PLR, and SII, failed to show an independent prognostic value. Previous studies reported that a high preoperative NLR could independently predict OS in CRLM patients after hepatectomy.[18,36] In this study, NLR showed an association with OS, but was not an independent predictor. The result was in concordance with a study from the UK.[19] Neofytou et al.[37] found elevated preoperative PLR significantly decreased OS and DFS in their CRLM patients. Although elevated preoperative PLR also showed an association with decreased OS and DFS in our patients, it failed to remain significant in multivariable analysis. Likewise, LMR and SII also demonstrated no independent predictive value in both OS and DFS in this study. The poor performance of these markers in multivariable analysis may be because of their correlation to the FARI and their weaker prognostic impact compared with the FARI. In this study, a high FARI was associated with a high NLR, low LMR, high PLR, and high SII. However, ROC analysis showed the discriminatory power of NLR, LMR, PLR, and SII for OS and DFS was obviously inferior to that of the FARI. Hence, we conclude that in comparison with the established inflammation markers, the FARI could more accurately predict the prognosis of patients undergoing hepatectomy for CRLM.

Of note, these established inflammation markers are developed from circulating blood leukocytes. To improve prognosis, preoperative chemotherapy is commonly used in patients with CRLM, especially for those with initially unresectable lesions.[15–17] In the present study, > 60% patients undertook preoperative chemotherapy. Due to the bone marrow suppression caused by chemotherapy, these leukocyte-based inflammation markers could not reflect the real systemic inflammatory response of patients, lowering the accuracy of these markers in predicting prognosis.

CEA is the most widely used marker to predict the prognosis of CRLM patients.[24,25,38] In the current study, CEA was also identified as an independent predictor of OS

and DFS in CRLM patients after hepatectomy. Interestingly, ROC analysis showed that the FARI had a greater predictive ability than CEA in both OS and DFS. Moreover, in patients with both high and low levels of CEA, the FARI further stratified these patients into subgroups with significantly distinct OS and DFS. These indicate that the FARI may be a superior marker, compared with CEA, in predicting the prognosis of patients undergoing hepatectomy for CRLM.

Additionally, the FARI in this study also showed good clinical utility in patients with different clinical characteristics. The association between a high FARI and decreased OS and DFS was still maintained when considering subgroups by sex, age, primary tumor site, presentation timing of liver metastases, RAS status, with or without preoperative chemotherapy, and CRS grade. Given that patients with a high FARI have a high risk of recurrence, perioperative chemotherapy may be helpful for these patients to reduce recurrence and prolong survival. In addition, for early detection of recurrence in these patients, more frequent follow-up could be considered.

There are several limitations in this study. First, albumin and fibrinogen concentrations are influenced by several factors, such as coagulopathy and liver insufficiency, which may affect the accuracy of the FARI in predicting prognosis. Second, since CRP was not examined in preoperative work-up routines in our center, inflammatory markers related to CRP were not analyzed in the present study. Third, some patients received treatments in other centers when they had relapse. As a result, this study failed to analyze treatment measures for patients with recurrence, which may affect their OS. This may also be the reason why the predictive ability of the FARI for OS was less than that for DFS shown in this study. Additionally, this was a single-center study. Finally, the FARI optimal cut-off value may fluctuate if a different study population was evaluated. Hence, further studies are required to confirm the results of this current study.

## CONCLUSIONS

A preoperative FARI is an independent predictor of OS and DFS for patients undergoing hepatectomy for CRLM, superior to the established inflammation markers and CEA. Its simplicity, low cost, and powerful predictive ability make the FARI a promising inflammation-based prognostic marker for patients undergoing hepatectomy for CRLM.

**FUNDING** This study was supported by grants from the Chinese State Key Project for Basic Research (973) [2014CBA02001].

**DISCLOSURE** Yan-Yan Wang, Zhen-Zhen Liu, Da Xu, Ming Liu, Kun Wang, and Bao-Cai Xing declare no conflicts of interest.

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