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ORIGINAL RESEARCH

Fibrinogen–Albumin Ratio Index Exhibits Predictive Value of Neoadjuvant Chemotherapy in Osteosarcoma

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Purpose: Inflammatory response and nutritional status are associated with cancer development and progression. The present study aimed to evaluate the predictive ability of the fibrinogen–albumin ratio index (FARI) to the efficacy of neoadjuvant chemotherapy (NAC) for osteosarcoma.

Patients and methods: A retrospective analysis involving 752 consecutive osteosarcoma patients between 2012 and 2020 was performed. Data on serum fibrinogen, albumin levels, white blood cell count, platelet count, and alkaline phosphatase (ALP) before and after NAC were collected. The predictive value of the NAC efficacy in osteosarcoma was assessed by constructing a receiver operating characteristic (ROC) curve and calculating the area under the curve (AUC). Prognosis and its predictive factors were analyzed by Kaplan–Meier method and COX regression analysis. Nomogram was established according to selected variables. The predictive performance of the nomogram model was assessed using C-statistics.

Results: A total of 203 patients were included. ROC analysis showed that both FARI before NAC (preFARI; AUC = 0.594, $p = 0.032$) and the change in FARI before and after NAC (dfFARI = preFARI-postFARI; AUC = 0.652, $p = 0.001$) exhibited more favorable predictive ability than ALP and other inflammation markers. The preFARI was divided into the high group (>6.1%) and the low group (≤6.1%) based on the optimal cut-off value of 6.1%. Patients with a high preFARI showed significantly decreased metastasis-free survival (MFS) and disease-free survival (DFS) (all $p<0.01$). In multivariable analysis, preFARI was an independent prognostic marker for patients with osteosarcoma. Predictive nomograms exhibited good ability to predict MFS (C-index = 0.748, se = 0.028) and DFS (C-index=0.727, se = 0.030).

Conclusion: Our findings indicated that FARI exhibits the favorable predictive ability for the efficacy of NAC for osteosarcoma, which could support clinicians and patients in clinical decision-making and treatment optimization.

Keywords: osteosarcoma, neoadjuvant chemotherapy, fibrinogen, albumin, fibrinogen–albumin ratio index, prognosis

Introduction

Osteosarcoma is the most common type of bone cancer in children and adolescents,[1] with an annual incidence of approximately 8–11 per million.[2,3] Although surgery combined with chemotherapy and other multidisciplinary therapies can significantly improve the prognosis of patients compared with that of the previous treatments alone, the 5-year survival rate for patients with osteosarcoma is still less than 70%.[4] It is reported that neoadjuvant chemotherapy (NAC) has shown great efficacy for osteosarcoma, and the 5-year overall survival (OS) has astonishingly increased to 60–70%.[5] NAC-induced tumor tissue necrosis rate based on pathological grading is the gold standard for assessing the effectiveness

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of NAC, which is also a prognostic factor for disease progression.[6–8] However, this crucial prognostic factor becomes relevant only after surgery. Accumulating evidence has shown that serum markers have prognostic value and are useful in monitoring responses to therapies; nevertheless, there are no guidelines recommended in clinical practice.[9,10]

Significant differences in inflammatory proteins such as fibrinogen (FIB) and albumin (ALB) have been widely researched in relation to cancer survival and repeatedly proven to be an independent prognostic factor.[11,12] ALB is an important acute-phase protein reflecting not only the inflammatory state but also the nutritional status.[13] FIB, as an essential acute-phase protein, plays a significant regulatory role in both the systemic inflammatory response and cancer progression, including proliferation, angiogenesis and metastasis of tumor cells.[14] The fibrinogen–albumin ratio index (FARI) has been proposed as a low-cost and widely used marker to predict cancer prognosis. Recent evidence showed that FARI has potential value in the early detection of cancer, and the significantly higher FARI was found in colorectal cancer patients compared with healthy controls.[15] Moreover, increasing research suggests that FARI is also a good prognostic factor for various tumors, such as gastric tumor,[16,17] non-small cell lung tumor,[18] gallbladder tumor,[19] prostate tumor,[20] breast tumor,[21] and hepatocellular tumor.[22] In colorectal and gallbladder cancer patients, higher FARI scores are observed in patients with unfavorable overall survival.[19,23,24] Thus, we speculate that FARI might be an effective prognostic indicator for cancer. Is there a certain correlation between FARI (fibrinogen and aluminum) and osteosarcoma? Although sarcoma and carcinoma are distinguishable in derivation, biological behavior, and microenvironment,[25] the study reported that FARI showed a similar association in sarcoma patients as it is in carcinoma patients.[26] Specifically, in operable sarcoma, patients with increased FARI had a shorter median survival than those with a low FARI.[26] However, sarcomas are a heterogeneous group that arises in soft tissue and bones,[27,28] resulting in remarkable differences in disease presentation, management, and survival. Therefore, FARI might have different roles in osteosarcoma patients in the context of NAC. Unfortunately, few studies have reported the role of FARI in prognosis and the prediction of response for NAC in osteosarcoma patients.

Herein, we conducted a retrospective study to assess the predictive value of FARI in terms of prognosis and NAC efficacy in osteosarcoma patients, and to compare it with alkaline phosphatase (ALP) and established systemic inflammation markers, including neutrophil–lymphocyte ratio (NLR), lymphocyte–monocyte ratio (LMR), platelet–lymphocyte ratio (PLR), and systemic immune–inflammation index (SII).

Methods

Study Population

In this retrospective study, patients with pathologically confirmed osteosarcoma and who have been treated NAC at the Shanghai Sixth People's Hospital from August 2011 to April 2020 were screened for inclusion in this study. Patients were required to have the complete data of the blood chemical analysis before NAC (pre-) and after NAC (post-), including serum fibrinogen, albumin levels, white blood cell (WBC) count, platelet (PLT) count, and ALP levels. Patients with infection, liver disease, abnormal coagulation function, direct surgical treatment, other malignant tumors, infused albumin or received blood transfusion before collecting blood sample, mental illness or cognitive impairment were not ineligible for our study. Additionally, we excluded the patients who had a history of oral anticoagulants or acetylsalicylic acid preparations within 3 months before admission. Patients who did not follow-up data and complete medical records were also excluded. The study was approved by the Institutional Review Board of Shanghai Jiao Tong University Affiliated Sixth People's Hospital (Approval no. 2021–080) and all participants signed a written informed consent in accordance with the Declaration of Helsinki.

Diagnosis and Grouping

The diagnosis of osteosarcoma was confirmed by a pathologic biopsy, and the disease was staged as per the Enneking stage.[29] The tumor necrosis rate was categorized as two grades: a high tumor necrosis rate (≥90%) was considered as a good response, and a low tumor necrosis rate (<90%) as a poor response.[30] Patients were classified as two subgroups (good response group and poor response) to evaluate the association between measurement indicators and response to NAC.

Measurement Indicators

The blood chemical analysis was performed using fully automatic biochemical analyzer (Hitachi 008AS) and hematology analyzer (Sysmex XN 9000) at the Department of Laboratory Science, Shanghai Sixth People's Hospital. All data from the blood chemical analysis before the first NAC dose and after the last NAC dose were collected, including the levels of serum fibrinogen, albumin, WBC, PLT, and ALP. The specific reference value range of each indicator was listed in the Appendix table Inflammatory indicators were calculated using the following formulas: FARI = (fibrinogen/albumin) × 100%; NLR = (neutrophil count/lymphocyte count); LMR = (lymphocyte count/monocyte count); PLR = (platelet count/lymphocyte count); SII = (PLT count × NLR). Differences in FARI (dfFARI) and ALP (dfALP) between pre-NAC and post-NAC were calculated as pre-levels minus post-levels. The optimal cut-off values for these measurement indicators were determined by the X-tile software.[31] Then, patients were stratified into several subgroups according to cut-off values of different measurement indicators.

Follow-Up

Follow-up appointments were made at Shanghai Sixth People's Hospital. Follow-up visits were conducted every 6 weeks to 3 months during the first 2 years, and every 3 weeks to 4 months during the second 2 years, every 2 to 6 months during the subsequent 5 years, and every 6 to 12 months thereafter. The follow-up visit includes medical history, physical examination, radiological assessments (X-ray of the primary site and chest X-ray), etc. Metastasis-free survival (MFS) was defined as the time from the date of osteosarcoma excision to the date of tumor metastasis or the date of last follow-up visit. Disease-free survival (DFS) was defined as the time from the date of osteosarcoma excision to the date of tumor recurrence/metastasis or the date of last follow-up visit.

Statistical Analysis

Statistical analyses were carried out by using SPSS 26.0 software, GraphPad Prism 8.0.2, X-tile Software version 3.6.1 and R4.2 software. Continuous variables were expressed as median (interquartile range [IQR]) and compared using the Mann–Whitney *U*-test (age, preALP, preNLR, preLMR, prePLR, and preSII) or Students't-tests according to the normality of data. Categorical variables were expressed as numbers (%) and compared using two-sided Chi-square (χ^2) or Fisher's exact tests. The predictive value of the NAC efficacy in osteosarcoma was assessed by constructing a receiver operating characteristic (ROC) curve and calculating the area under the curve (AUC). MFS and DFS rates were estimated using Kaplan–Meier method, and the between-group comparison was conducted using the Log rank test. The independent prognosis factors for the MFS and DFS of osteosarcoma were analyzed using COX regression analysis and presented by plotting forest diagrams. The independent influencing factors were used for creating a prediction model of prognosis in osteosarcoma patients; the nomogram was then constructed based on the selected variables visually, and the prediction model's performance was further evaluated through Harrell's C-statistic (C-index). P-values <0.05 were considered to be of statistical significance.

Results

Patient Characteristics

Between August 2011 and April 2020, 752 consecutive patients with osteosarcoma were screened, and a total of 203 patients meeting the inclusion criteria were included. Of the 203 patients included, the majority were male (62.1%) with a median age of 17 years (IQR 14–22 years). One hundred and thirty-three patients (65.5%) had primary tumors located in the femur, while the remaining 70 patients (34.5%) had primary tumors located in the tibia. The median baseline preFARI, preNLR, preLMR, prePLR, preSII, and preALP values were 6.2% (IQR, 5.3–7.5%), 1.9 (IQR, 1.5–2.4), 4.6 (IQR, 3.6–6.0), 133.5 (IQR, 104.7–170.0), 514.3 (IQR, 375.0–706.9), and 163 U/L (IQR, 104 U/L-279 U/L), respectively. At the last follow-up, 13 (13.5%) had recurrence, and 45 (46.9%) had tumor metastasis. The majority of patients (68.5%) had a necrosis rate of <90% and was determined as poor response. Additionally, 31.5% of patients had a necrosis rate of ≥90% and was determined to have a good response. The detailed baseline characteristics of the included patients are shown in Table 1.

Table 1 Baseline Characteristics of Included Patients

Characteristics	Total (n = 203)	Low preFARI (n = 96)	High preFARI (n = 107)	*p* value
Sex-n (%)				0.360[a]
Male	126 (62.1%)	62 (64.6%)	60 (59.8%)	
Female	77 (37.9%)	34 (35.4%)	43 (40.2%)	
Age, years-median (IQR)	17 (14–22)	18 (14–23)	16 (13–22)	0.136[b]
Tumor size-n (%)				0.017[a]
<10 cm	133 (65.5%)	71 (74.0%)	62 (58.0%)	
≥10 cm	70 (34.5%)	25 (26.0%)	45 (42.0%)	
Site-n (%)				0.460[a]
femur	133 (65.5%)	60 (62.5%)	73 (68.2%)	
tibia	70 (34.5%)	36 (37.5%)	34 (31.8%)	
Necrosis-n (%)				0.032[b]
≥90%	64 (31.5%)	24 (25.0%)	40 (37.4%)	
<90%	139 (68.5%)	72 (75.0)	67 (62.6%)	
Stage-n (%)				0.181[a]
IIA	16 (7.9%)	5 (5.2%)	11 (10.3%)	
IIB	187 (92.1%)	91 (94.8%)	96 (89.7%)	
preALP, U/L-median (IQR)	163 (104–279)	158 (101–283)	184 (114–265)	0.575[b]
Normal (≤112)	55 (27.1)	30 (31.3)	25 (23.4)	
Elevation (>112)	148 (72.9)	66 (68.7)	82 (76.6)	
preFARI, %-median (IQR)	6.2 (5.3–7.5)	4.8 (5.2–5.6)	7.2 (6.5–8.5)	<0.001[b]
preNLR-median (IQR)	1.9 (1.5–2.4)	1.9 (1.4–2.2)	1.9 (1.5–2.5)	0.265[b]
preLMR-median (IQR)	4.6 (3.6–6.0)	5 (4–7)	3.2 (4.4–5.75)	>0.999[b]
prePLR-median (IQR)	133.5 (104.7–170.0)	126.2 (100.8–166.0)	136.7 (107.6–174.8)	0.073[b]
preSII-median (IQR)	514.3 (375.0–706.9)	451.5 (314.0–652.6)	566.2 (413.6–777.1)	0.011[b]
Recurrence-n (%)				
Yes/No	23(11.3)/180(88.7)	13 (13.5)/83 (77.6)	10 (9.3)/97 (90.7)	0.346[a]
Metastasis-n (%)				
Yes/No	74(36.4)/129(63.5)	45 (46.9)/51 (53.1)	29 (27.1)/78 (72.9)	0.004[a]

Abbreviations: High preFARI, FARI-value >6.1%; Low preFARI, FARI-value ≤6.1%. a, two-sided chi-square test or Fisher exact probability test for comparison; b, Mann–Whitney *U*-test was chosen. ALP, alkaline phosphatase; FARI, the fibrinogen–albumin ratio index; NLR, neutrophil–lymphocyte ratio; LMR, lymphocyte–monocyte ratio; PLR, platelet–lymphocyte ratio; SII, systemic immune–inflammation index.

The FARI is Associated with Better Response

Prior to NAC, the mean FARI (p=0.038, Figure 1A) was significantly higher in the good response group than that in the poor response group. There were no significant differences between the two groups regarding NLR (p=0.653, Figure 1B), LMR (p=0.430, Figure 1C), PLR (p=0.059, Figure 1D), SII (p=0.480, Figure 1E), and ALP (p=0.072, Figure 1F).

With regard to the change of FARI and ALP levels before and after NAC, we found that both the mean FARI (p=0.002, Figure 1G) and ALP (p<0.001, Figure 1H) levels significantly decreased after NAC. Similarly, the mean FARI (p=0.001, Figure 1I) was significantly higher in the good response group compared with the poor response group, while no significant differences in the mean ALP (p=0.265, Figure 1J) were found between the two groups. The results above indicate that preFARI and dfFARI are associated with better response, having the potential to be effective predictive indicators of NAC.

Cut-off Value

Through the X-tile software, cutoff values of preFARI, preALP, preNLR, preLMR, prePLR, and preSII were confirmed to be 6.1%, 393 U/L, 3.1, 3.1, 94, and 544, respectively. Meanwhile, the cutoff values of dfFARI and dfALP was −0.3

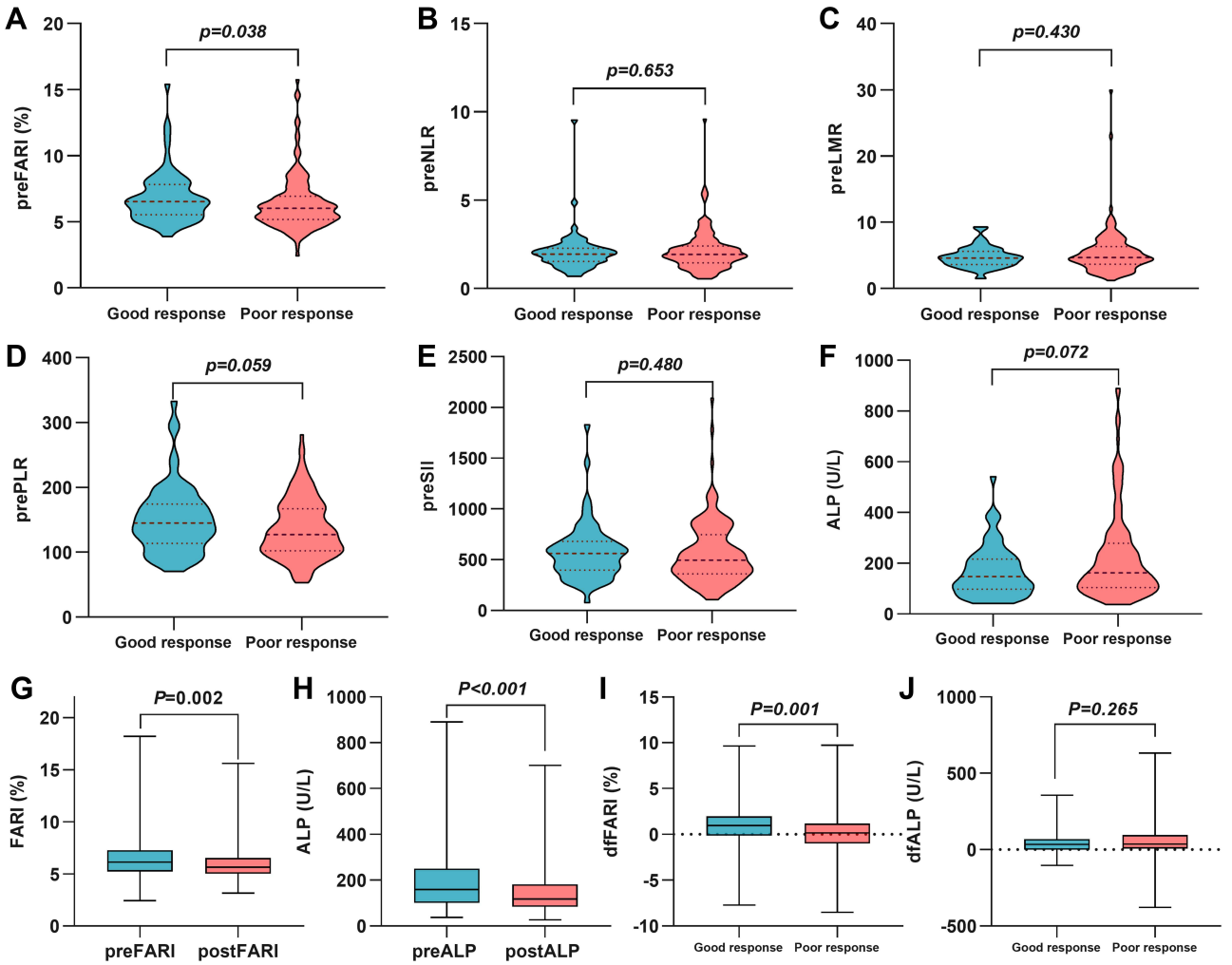

Figure 1 The distribution of FARI (**A**), NLR (**B**), LMR (**C**), PLR (**D**), SII (**E**), and ALP (**F**) before NAC, FARI (**I**) and ALP (**J**) after NAC in the good and poor response groups. The change of distribution of FARI (**G**) and ALP (**H**) between before NAC and after NAC.

Abbreviations: ALP, alkaline phosphatase; FARI, the fibrinogen–albumin ratio index; NLR, neutrophil–lymphocyte ratio; LMR, lymphocyte–monocyte ratio; PLR, platelet–lymphocyte ratio; SII, systemic immune-inflammation index.

and 121 U/L, respectively. According to the cut-off value, patients were divided into two subgroups: high-preFARI group with an FARI of >6.1% (n = 107, 52.7%) and low-preFARI group with an FARI of ≤6.1% (n = 96, 47.3%).

With regard to tumor size and disease stage, both large-tumor (≥10; 42.0% vs 26.0%; p=0.017) and high-tumor necrosis rate (≥90%; 37.4% vs 25.0%; p=0.032) patients in the high-preFARI group were more than the low-preFARI group. Meanwhile, we also found that the high-preFARI group has more patients with no metastasis compared with the low-preFARI group (72.9% vs 53.1%; p=0.004) (Table 1).

Predictive Value of Markers to NAC Response

To verify the predictive potential of these markers to NAC response, the ROC analysis was performed and AUC was calculated. As shown in Figure 2, the AUC values of preFARI and dfFARI were 0.594 (95% CI: 0.511–0.676; p = 0.032) and 0.652 (95% CI: 0.571–0.733; p = 0.001), respectively, which were greater than that of preALP (AUC = 0.452; 95% CI: 0.366–0.537; p = 0.269), preNLR (AUC = 0.480; 95% CI: 0.397–0.563; p = 0.652), preLMR (AUC = 0.465; 95% CI: 0.385–0.546; p = 0.429), prePLR (AUC = 0.583; 95% CI: 0.499–0.666; p=0.059), or preSII (AUC = 0.531; 95% CI: 0.449–0.614; p=0.476). These results indicated that FARI had a better ability in preoperative prediction for the NAC response in osteosarcoma patients.

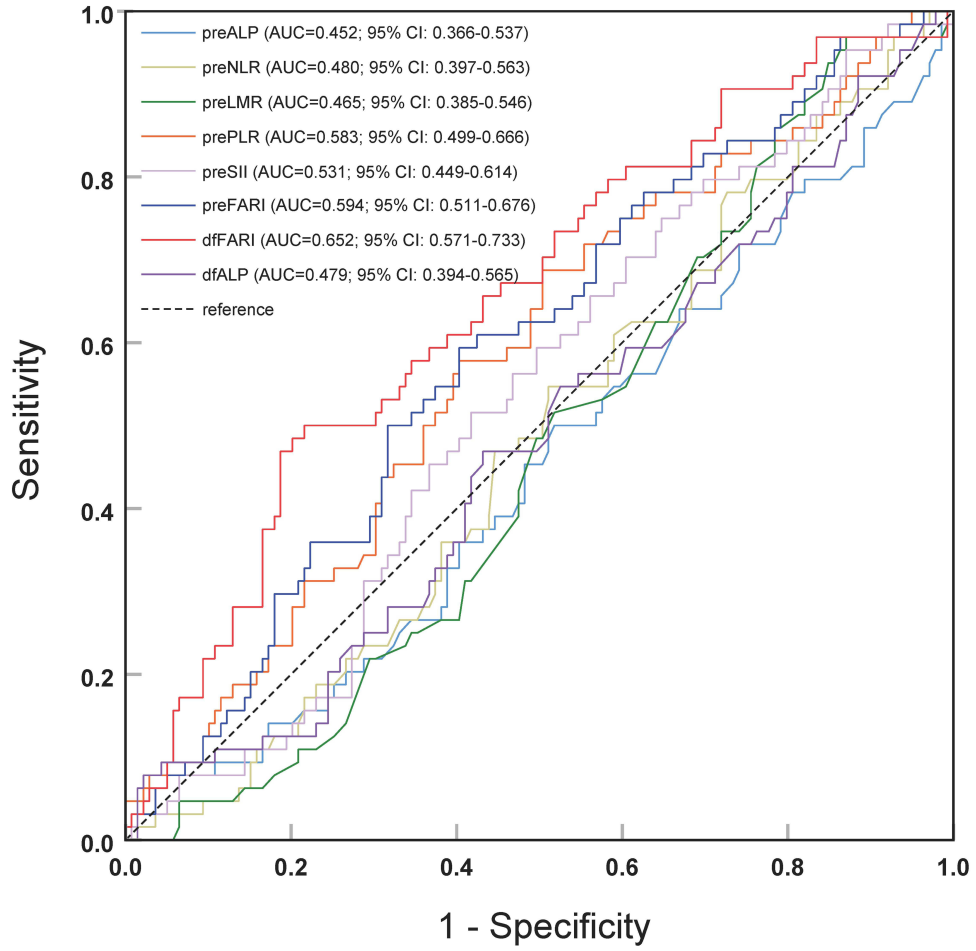

Figure 2 ROC curves for serum markers to discriminate patients' response to NAC.

Kaplan-Meier Survival Analysis

First, we confirmed that patients with good response to NAC have favorable MFS and DFS than patients with poor response (Figure 3A and B). Therewith, we compared the survival outcomes between subgroups (high-preFARI vs low-preFARI; high-preALP vs low-preALP) to verify the predictive performance of FARI and preALP. The Log rank test demonstrated that patients with high preFARI have superior MFS and DFS (Figure 3C and D). With regard to the preALP, the analysis was conducted on 148 patient cohorts, which only included patients with elevated ALP before NAC. As a result, patients with high preALP (>224 U/L) have shorter MFS and DFS than those with low preALP (≤224 U/L) (Figure 3E and F).

Univariable and Multivariable Analyses

In terms of MFS, univariate analysis showed that the gender (HR: 0.551, 95% CI: 0.327–0.929; p=0.025), tumor diameter (HR: 1.914, 95% CI: 1.211–3.025; p=0.005), necrosis rate (HR: 1.994, 95% CI: 1.157–3.437; p=0.013), preFARI (HR: 0.473, 95% CI: 0.296–0.756; p=0.002), preALP (HR: 3.323, 95% CI: 1.977–5.587; p<0.001), and preNLR (HR: 1.98, 95% CI: 1.039–3.775; p=0.038) were significantly associated with MFS. Further, we performed a multivariate analysis on the factors with p<0.1 in the univariate analysis. Multivariate analysis confirmed that tumor diameter (HR: 2.173, 95% CI: 1.314–3.592; p=0.002), necrosis rate (HR: 1.908, 95% CI: 1.087–3.348; p=0.024), preALP (HR: 1.997, 95% CI: 1.128–3.535; p=0.018) and preFARI (HR: 0.470, 95% CI: 0.285–0.777; p=0.003) were independent predictors of MFS (Figure 4A). The high preFARI level is associated with longer MFS. Similar findings were observed in the COX regression analysis for DFS (Figure 4B). The results showed that the high-preFARI (HR:

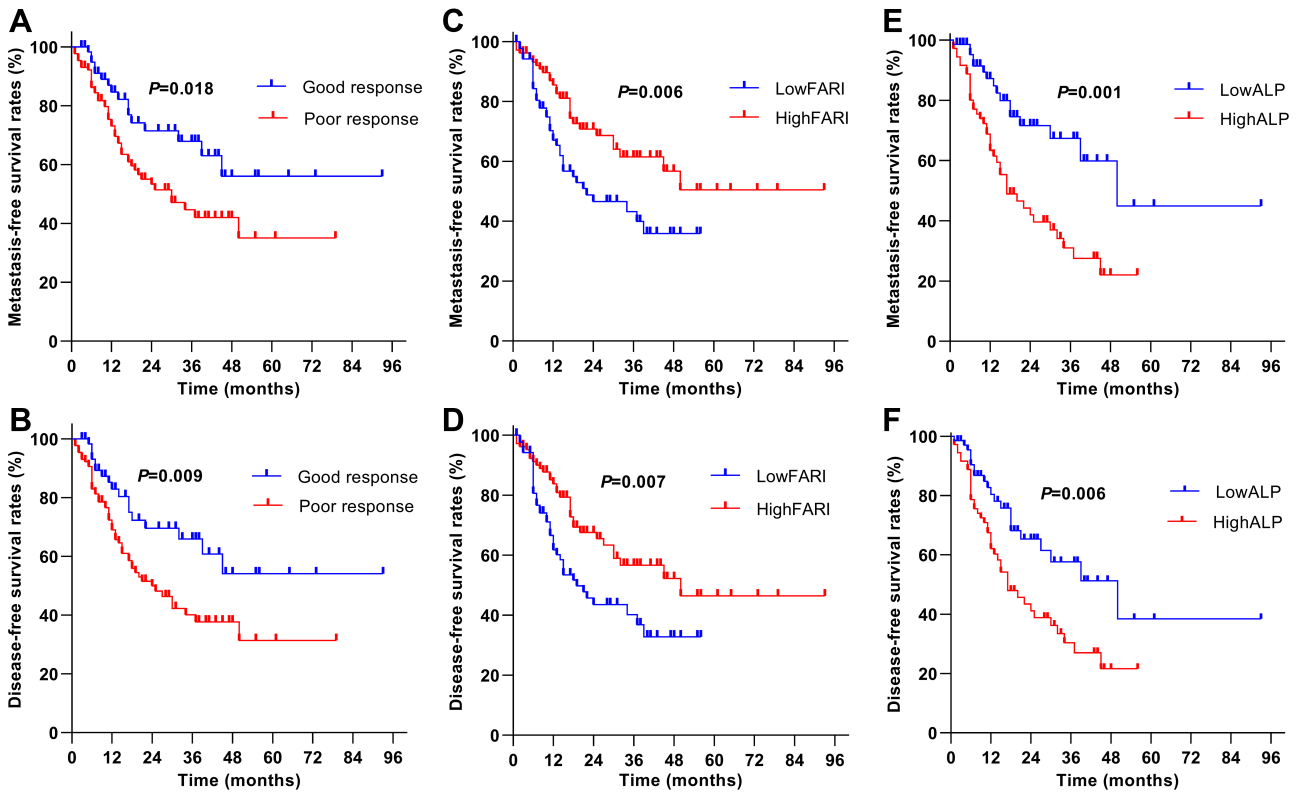

Figure 3 Survival analysis of osteosarcoma patients according to different variables. Kaplan-Meier survival curves of MFS (**A**) and DFS (**B**) in the two response groups, MFS (**C**) and DFS (**D**) in the high and low FARI groups, MFS (**E**) and DFS (**F**) in the high and low ALP groups.
Abbreviations: MFS, metastasis-free survival; DFS, disease-free survival; FARI, the fibrinogen–albumin ratio index.

0.410, 95% CI: 0.258–0.652; $p<0.001$), good response (necrosis rate ≥90%; HR: 1.931, 95% CI: 1.128–3.306; $p=0.016$), female (HR: 0.565, 95% CI: 0.342–0.935; $p=0.026$), and small tumor diameter (<10; HR: 2.857, 95% CI: 1.185–4.498; $p<0.001$) were significantly associated with favorable DFS.

Construction of the Nomogram Prediction Model

A nomogram model was constructed based on independent influencing factors (tumor response, preFARI, preALP, tumor diameter, and gender) selected in the above analysis to predict 1-, 3- and 5-year survival rates for osteosarcoma. By Harrell's C-statistic test, the nomogram model showed significant performance for predicting MFS (C-index=0.748; se = 0.028, Figure 5A) and DFS (C-index = 0.727, se = 0.030; Figure 5B). Each level of each variable was assigned a grade score, and the total scores of individuals were calculated accordingly based on the scores corresponding to different values of each variable, and then the 1-, 3- and 5-year survival rates of individuals obtained. The higher total score represents longer MFS and DFS. For example, if the patient is a female, with tumor diameter <10 cm, poor response and preFARI ≤6.1%, the probability of 1-year, 3-year and 5-year DFS is estimated to be 75%, 47% and 35%, respectively (Figure 5C).

Discussion

In this study, the roles of FARI in patients with osteosarcoma around the knee were investigated. The results suggested that a higher level of FARI was observed in the large-tumor and good response group. And pretreatment FARI (preFARI) exhibited better performance in predicting tumor response to chemotherapy and showed a significant association with both MFS and DFS, indicating that it is an independent prognostic factor. To our knowledge, this was the first study to assess the predictive value of FARI for the effectiveness of NAC for osteosarcoma.

Consistent with previous studies reporting that the higher FARI was correlated with larger tumors,[15,21,23,26,32] we also found a higher level of FARI in tumor size ≥10 cm group. Regarding tumor stage, high FARI levels were associated with

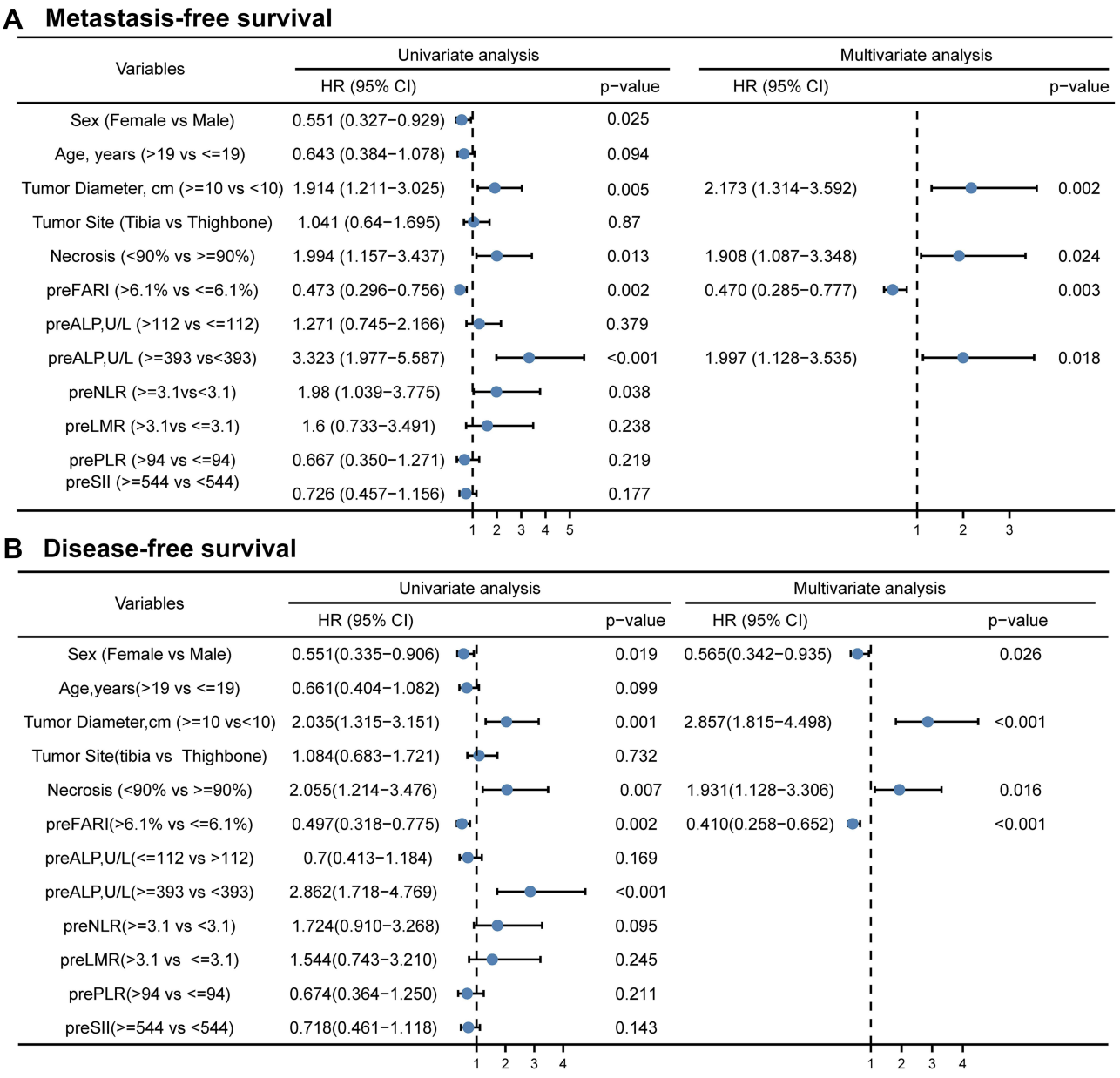

Figure 4 Univariate and multivariate analyses for metastasis-free survival (**A**) and disease-free survival (**B**).

advanced stage of colorectal, breast, and soft tissue sarcoma,[15,21,23,26,32] but not related to hepatocellular cancer,[22] indicating the association might vary depending on different cancer stage criteria. In the cohort of this study, no significant difference was observed between stage IIA and IIB. This might be due to unique Enneking stage criteria in bone cancer, which stratify disease by the pathological grade, the anatomic setting, and the presence of metastasis, without considering tumor size.[33]

The relationship between FARI and treatment response was investigated in a handful of reports,[32,34] in which low pretreatment FARI levels were more likely to be observed in good-response patients with colorectal cancer.[32,34] In contrast to these published results, we found the higher FARI levels in good-response patients than those in poor-response patients. This discrepancy might result from the following aspects: 1) age: the median age was 60 in other reports,[32,34] while the median age was 17 in our cohort; 2) response evaluation system: tumor regression grade (TRG) was used in colorectal cancer,[32] while tumor necrosis rate was applied in the present study.[30]

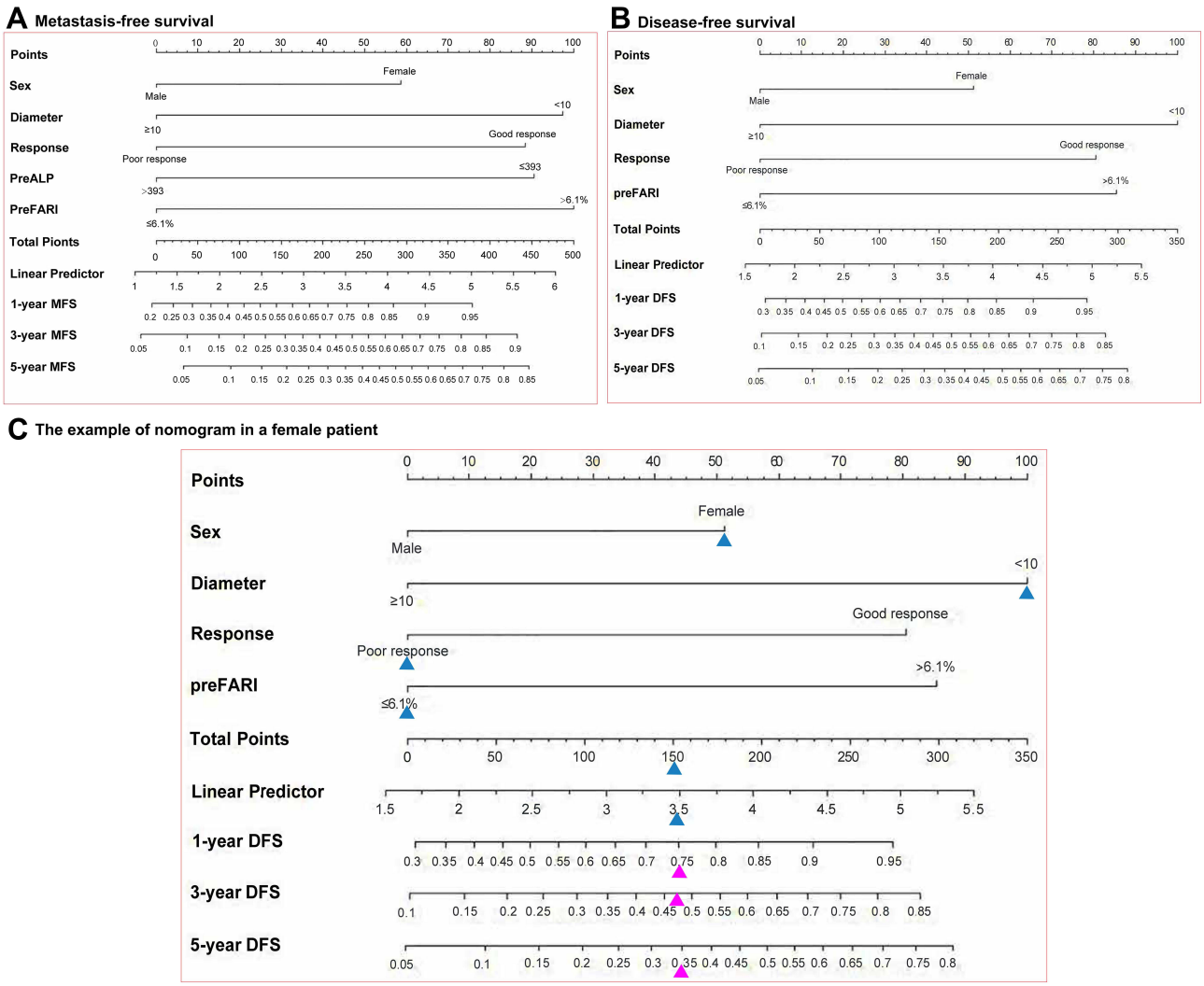

Figure 5 Nomogram to predict the probabilities of metastasis-free survival (**A**) and disease-free survival (**B**) of osteosarcoma. The example of nomogram in a female patient (**C**).

We found that preFARI exhibited more reliable and greater predictive ability than ALP and other markers like NLR, LMR, PLR, and SII. ALP is the most common marker in osteosarcoma, but it is elevated in 60% of patients.[35–37] In our study, ROC analysis showed that FARI had a better performance than ALP in predicting tumor response to chemotherapy, suggesting that combined serum markers might be superior to a single serum item as a predictor.

In this study, the cut-off value for preFARI was set at 6.1%, while in previous studies, the cut-off value was 6 to 11,[22,23,26,34,38,39] and reasons of this difference caused might be due to different study participants among these researches. Surprisingly, we found that the high-FARI (>6.1%) group showed a favorable MFS and DFS than the low-FARI group. These results were totally opposite to previous reports, in which the high-FARI group had unfavorable survival than the low-FARI group.[22,23,26,34,38,39] To validate our findings, we provided comparisons of MFS and DFS based on gender, tumor size, tumor response, and ALP. These results were strongly consistent with large cohort studies in osteosarcoma[6–8,40,41] and previous studies from our institute,[42] indicating that data from the cohort of this study was reliable and replicable. Therefore, the opposing result of FARI might be due to different tumor types, even including operable soft tissue sarcoma.[26]

Finally, prognostic factors were evaluated using univariate and multivariate Cox regression analysis, which were applied to construct nomograms. The constructed nomograms were used to assess the 1-, 3- and 5-year MFS and DFS based on the identified prognostic factors. In our study, four independent prognostic factors for MFS (sex, tumor diameter, chemotherapy

response, preFARI and preALP) were identified, which also significantly impact DFS, except for preALP. To test the reliability of the nomogram for prediction prognosis, we used Harrell's C-statistic to test the accuracy of the prediction model. The C-index, index of concordance, evaluates the predictive accuracy of a model by assessing how well the model's predictions match the actual observations.[43,44] The C-indexes for MFS and DFS were 0.7478 (se = 0.02751) and 0.7265 (se = 0.02792), respectively, indicating good performances of the nomograms.

Several limitations associated with the present study warrant mention. First, this study is a single-center retrospective study with a limited sample size, leading to selection bias. Second, information on the operation approach and adjuvant therapy was incomplete, which could lead to potential biases, and inflammatory markers associated with C-reactive protein were not analyzed in this study as that data was not collected during routine preoperative examinations. Moreover, we did not perform an overall survival analysis due to the reluctance of families of deceased patients (the majority of the deceased were children, and the parents did not want to look back again and answer any questions at the time of telephone follow-up). Therefore, further studies are needed to confirm the results of this study.

Conclusions

In summary, preFARI and dfFARI have remarkable performance in predicting tumor response to neoadjuvant chemotherapy, and preFARI is an independent prognostic marker for metastasis-free and disease-free survival in osteosarcoma patients. Thus, FARI contributes to clinical decision-making and treatment optimization, serving as a promising predictive marker for NAC in osteosarcoma patients. Validation studies or large prospective studies are necessary to further validate our findings.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Informed Consent

The study was approved by the Institutional Review Board of Shanghai Jiao Tong University Affiliated Sixth People's Hospital (Approval no. 2021-080). All participants were informed as to the purpose of this study and that this study complied with the Declaration of Helsinki.

Consent for Publication

All of the authors have agreed to the publication of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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