Non-Invasive Liver Fibrosis Scores can Predict Hepatic Metastasis in Colorectal Cancers

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ABSTRACT

It was aimed to investigate the relationship between liver fibrosis and liver metastasis by using AST to Platelet Ratio Index (APRI) and Fibrosis4 (FIB4) non-invasive hepatic fibrosis scorings at the time of diagnosis in patients with nonmetastatic colorectal cancers (CRC) at diagnosis. A total of 1452 patients with colorectal cancer who were followed up between 2015-2020 were retrospectively reviewed. Seven hundred and fifty eight patients were included in the study. Fifty four patients who devoloped liver metastatis were compared with 704 patients who did not develop metastasis, the mean APRI score and mean FIB4 score at the time of diagnosis was determined to be significantly higher in the group with liver metastasis. The area under the curve (AUC) for the APRI score was 0.735 and the optimum sensitivity for detecting liver metastasis was 75.9%, while the optimal specificity was 65.1% and for the FIB4 score, AUC was 0.738, the optimum sensitivity for detecting liver metastasis was 74.1% and the specificity was 67.4%. When multivariate logistic regression analysis was conducted, FIB4 score, APRI score, Tstage, and Nstage were found as independent predictive factors in predicting liver metastasis It has been demonstrated that the group that may develop liver metastasis among patients with non-metastatic CRC at the time of diagnosis could be predicted by using the noninvasive liver fibrosis markers FIB4 and APRI scores. Moreover, it has been shown that these two scorings are also independent predictive markers. Based on this, shorter surveillance intervals may be an option in the group with higher FIB4 and APRI scores at the time of diagnosis.

Keywords: Colorectal cancer, Liver fibrosis, Liver metastasis

INTRODUCTION

Although colorectal cancers (CRC) are the 4th most common cancer, they are the 2nd in cancer-related death.[1] Metastasis develops in nearly 50-60% of patients diagnosed with CRC, and 80-90% of these patients also have unresectable liver metastasis.[2,3] Metastasis mostly develops as metachronous following locoregional CRC treatment, and the liver is the most common site of metastasis.[4] Besides, 20-34% of patients with CRC are diagnosed with synchronous liver metastases.[5] Overall survival is lower in unresectable liver metastases. The TNM staging system is at the forefront in predicting the prognosis of the disease. Yet, even among patients with the same stage, large differences have been revealed in clinical outcomes. Thus, there is a need for novel classifications and biomarkers that predict liver metastasis and recurrence.

Extracellular matrix alterations in the microenvironment of the liver tissue might be effective in the occurrence of metastasis and recurrence.[6] Remodeling in the extracellular matrix is particularly common during fibrosis. It leads to functional changes in biochemical and biomechanical properties and ultimately enables activation of pathogenic signaling pathways in the emerging microenvironment and more tissue remodeling.[7,8]

Albeit the relationship between tumor progression and fibrosis has been demonstrated in some studies, the mechanisms have not been fully elucidated yet, and the role of fibrosis in the metastatic spread of primary tumors remains unclear.[9] The relationship between fibrosis and cancer has been previously investigated in hepatocellular cancers, cancers that develop based on radiotherapy-induced fibrosis, and cancers forming in scar tissue.[10] The relationship between liver metastasis developing in CRC and liver fibrosis draws attention as an intriguing domain, and discussions on this issue remain on the agenda.[10,11]

Liver biopsy is the preferred invasive method for detecting fibrosis; however, due to its limitations, non-invasive alternative diagnostic techniques such as elastography or serological markers are increasingly used in the early detection of the fibrosis grade. AST to Platelet Ratio Index (APRI) and Fibrosis 4 (FIB4) are non-invasive scoring methods that are based on blood parameters in detecting liver fibrosis.[11,12] The mentioned hepatic fibrosis scoring is cost-effective and easily computable parameters and can be used easily. Hence, in the study, it was aimed to investigate the relationship between liver fibrosis and liver metastasis by using APRI and FIB4 non-invasive hepatic fibrosis scorings at the time of diagnosis in patients with non-metastatic CRC at diagnosis.

PATIENTS and METHODS

One thousand four hundred and fifty two patients with colorectal cancer who were followed up in our oncology center between 2015 and 2020 were retrospectively reviewed. Patients with non-metastatic colorectal cancer at the time of diagnosis, aged 18 years and over and without secondary malignancy were included in the study, while patients with an active infection, steroid use, active infection with hepatotropic viruses such as HBV, HCV, as well as those with anemia such as iron deficiency, and vitamin B_{12} deficiency and those with chronic liver disease at the time of the diagnosis were excluded from the study. Seven hundred and fifty eight patients who met these criteria were included in the study. Diagnosis dates, ages, operation status, tumor location, adjuvant treatments, and disease course of the patients were retrospectively reviewed from their files. Blood hemogram and biochemistry values at the time of diagnosis were recorded retrospectively. Survival data were determined by reviewing the central registry system.

To determine the degree of liver fibrosis, FIB4 and APRI were applied in this analysis. The FIB4 score was calculated according to Sterling's formula[11], as follows:

Sterling's formula= age (years)×AST (IU/L)/ platelet count (10^9/L)×(ALT1/2(IU/L).

$$\text{Sterling's formula} = \frac{\text{Age (years)} \times \text{AST (IU/L)}}{\text{Platelet count } (10^9/\text{L}) \times \text{ALT1/2(IU/L)}}$$

The APRI score was calculated as Wai's formula[12]: ((AST/Upper limit of Normal)/platelet count (10^9/L)×100).

$$\text{Wai's formula} = \frac{\text{AST/Upper limit of Normal}}{\text{Platelet count } (10^9/\text{L}) \times 100)}$$

Ethical Approval: This study was conducted in compliance with the ethical principles according to the Declaration of Helsinki, and it was approved by the local Institutional Review Board. Health Sciences University, Dr. A.Y. Training and Research ethics committee approval was obtained for our study with the decision number 2021-06/1233 on 23.06.2021.

Statistical Analyses

Statistical analyzes were performed via the software of SPSS 25.0 (SPSS, Chicago, IL, USA). Mann-Whitney U test was used for comparison of nonparametric data, and Student T-test was used for comparison of parametric data. Chi-Square or Fisher's Exact test was used for comparison of categorical data. Kaplan-Meier method was used for survival analysis and the Log-Rank test was used for intergroup comparisons. Prognostic factors impacting overall survival were identified by conducting multivariate analysis with the Cox proportional hazards model. The results were considered statistically significant at $p< 0.05$.

Table 1. Baseline characteristics of the patients

Variables	n	%
Age (years)	62 (25-96)	
Gender		
Male	445	58.7%
Female	313	41.3%
Location		
Right sided colon	122	16.1%
Left sided colon	233	30.8%
Transvers colon	39	5.1%
Rectum	364	48%
TNM Stage		
Stage 1	77	10.2%
Stage 2	298	38.3%
Stage 3	307	40.5%
Unknown	76	10%
T Stage		
T1	17	2.2%
T2	93	12.3%
T3	385	50.8%
T4	123	16.2%
Unknown	140	18.5%
N Stage		
N0	349	46%
N1	200	26.4%
N2	82	10.8%
Unknown	127	16.8%
Histological Type		
Adenocarcinoma	684	90.2%
Mucinous	74	9.8%
Surgery		
Yes	676	89.1%
No	82	10.9%
Adjuvant Chemotheraphy		
Yes	537	70.8%
No	221	29.2%
Neoadjuvant Chemotheraphy (Rectum)		
Yes	242	66.5%
No	122	33.5%

RESULTS

In the study, the median age of 758 patients who were non-metastatic at the time of diagnosis was 62 (range: 25-96) and 58.7% (n= 445) of the patients were male. Most of the patients were with left colon (30.8% (n= 233)) and rectum (48% (n= 364)) localization. T3 and T4 of patients were 50.8% and 16.2%, respectively, while those with N0 and N1 were 46% and 16.2%, respectively. At the time of diagnosis, 40.5% (n= 307) of the patients were stage III and 39.3% (n= 298) stage II. Of the patients, 89.1% (n= 676) were operated, while 10.9% (n= 82) were not operated. While 70.8% (n= 537) of the patients received adjuvant therapy, 29.2% (n= 221) did not receive adjuvant therapy. 66.5% (n= 242) of the patients with rectal carcinoma received neoadjuvant therapy. Regarding their pathology, 90.2% (n= 684) were adenocarcinoma and 9.8% (n= 74) were mucinous carcinoma (Table 1).

Throughout the follow-up period, liver metastasis developed in 54 patients (7.1%). In terms of TNM stages, no significant difference was determined between the group with liver metastasis and the group without liver metastasis (p= 0.373). No significant difference was detected between the groups in terms of tumor location and liver metastasis development (p= 0.882). When these 54 patients were compared with 704 patients who did not develop metastasis, the mean APRI score at the time of diagnosis was determined to be significantly higher in the group with liver metastasis (0.3796 ± 0.0479 vs. 0.2246 ± 0.0086; respectively, p< 0.001) (Figure 1a). On the other hand, mean FIB4, which is another fibrosis score, was found to be significantly higher among the group with liver metastasis (1.9630 ± 1.3051 vs. 1.1947 ± 1.031; respectively, p< 0.001) (Figure 1b) (Table 2). Liver metastasis was found to be significantly higher among male patients compared to female patients (8.76% vs. 4.79%; respectively, p= 0.036). While the APRI score was significantly higher in male patients compared to females (0.2494 vs. 0.2128; p= 0.045, respectively), no significant difference was determined between the groups in terms of FIB4 score (1.2958 vs. 1.1853; p= 0.176, respectively). Liver metastasis was found to be significantly higher in patients with T4 tumors compared to other T-stage patients (p< 0.001). Similarly, liver metastases developed significantly more in patients with stage T3 compared to those with T1-2 (p= 0.018). No significant difference was determined between T1 and T2. Liver metastasis was significantly higher in the lymph node-positive group (p< 0.001).

The mean follow-up period of the study was 29.41 (range: 1-182) months. The median duration until metastasis occurred in the group with liver metastasis was 10 (6.43-13.56) months. In the study, the median OS of the whole group was 84 months

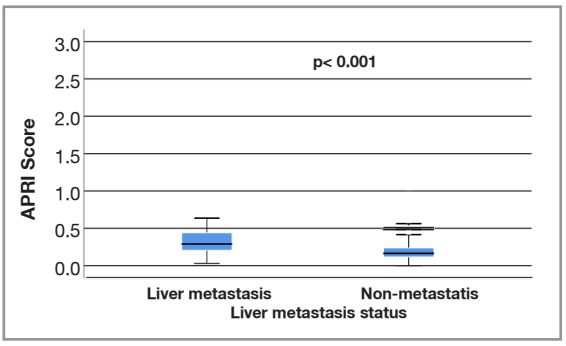

Figure 1a. Comparison for APRI score with liver metastasis and non-metastasis

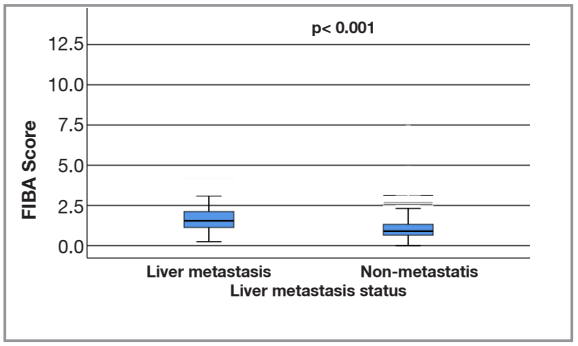

Figure 1b. Comparison for FIB4 score with liver metastasis and non-metastasis

(70.40-97.59) and the 3-year OS was 82%. In the group without liver metastasis, the median OS was 85 months (67.93-102.06) and 3-year OS was 85.8%, whereas in the group with liver metastasis, the median OS was 31 months (20.77-41.17) and 3-year OS was 46% (p< 0.001). A significant negative correlation was found between Median OS and APRI score (r= –0.106; p= 0.0024. Likewise, a significant negative correlation was found between the FIB4 score and the median OS (r= –0.185; p< 0.001).

When the ROC analysis was performed in the study, the area under the curve (AUC) for the APRI score was 0.735 and the optimum sensitivity was 75.9%, while the optimal specificity was 65.1% and the ideal cut-off value corresponding to these values was 0.2054 (Figure 2a); For the FIB4 score, AUC was 0.738, the optimum sensitivity was 74.1% and the specificity was 67.4%, while the ideal cut-off value corresponding to these values was calculated as 1.2586 (Figure 2b). When multivariate logistic regression analysis was conducted, FIB4 score, APRI score, T-stage, and N-stage were found as independent predictive factors in predicting liver metastasis (p1= 0.015, p2< 0.001, p3< 0.001, p4= 0.047, respectively) (Table 3).

DISCUSSION

In the study, APRI score, FIB4 score as well as T and N stage, which are non-invasive fibrosis markers in patients with non-metastatic colorectal cancer at the time of diagnosis, were found to be independent predictive factors in terms of predicting patients who may develop liver metastasis. Moreover, a negative correlation was demonstrated between fibrosis scores and survival.

Similar to other studies, in the presented study,

Table 2. Comparison of liver metastatised and non-metastatised patients

		Liver Metastasis	Non-metastasis	P value
Patients (n)		54	704	
Age (median)	62 years (36-83)	62 years (24-96)	0.936	
Location	Right sided colon	9	113	
	Left sided colon	19	214	0.882
	Transvers colon	2	37	
	Rectum	24	340	
Stage (n)	1	4	80	
	2	20	299	0.373
	3	28	299	
	Unknown	2	74	
APRI score (mean)	0.3796±0.0479	0.2246±0.0086	< 0.001	
FIB4 score (mean)	1.9630±1.3051	1.1947±1.0310	< 0.001	

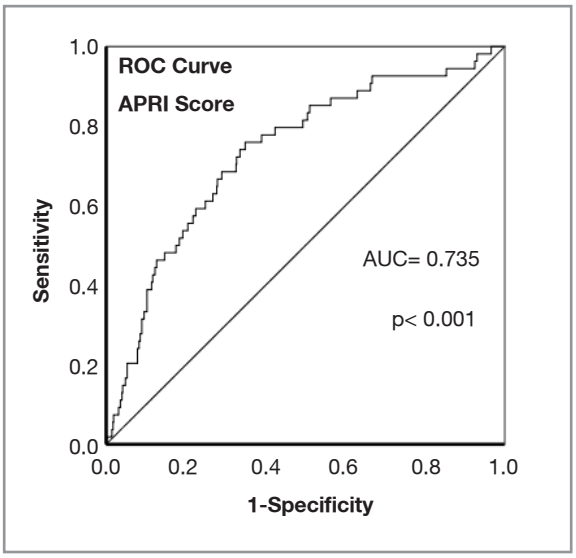

Figure 2a. Liver fibrosis APRI score nomogram measured by ROC curves for liver metastasis

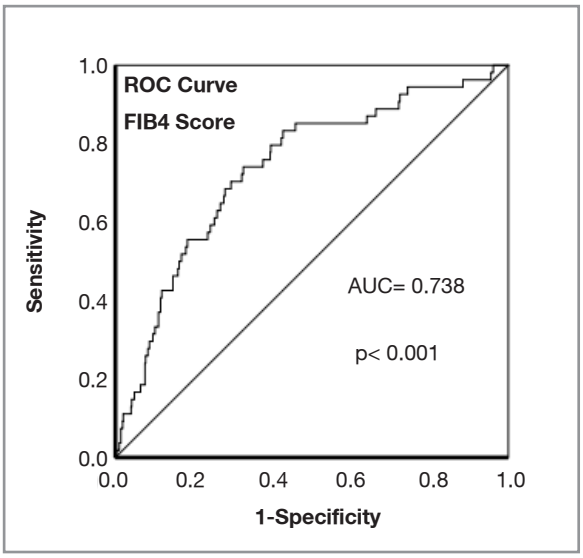

Figure 2b. Liver fibrosis APRI score nomogram measured by ROC curves for liver metastasis

ages of diagnosis ranged mostly in the 6th-7th decades.[13] In the study, stage and location distribution were determined to be similar to other studies.[14] While de-novo liver metastasis occurs with an incidence of 20-34% in colorectal cancers, metastasis develops in nearly half of the patients.[2-5] The most common site of metastasis is the liver. In this study, the lower incidence of metastasis development may be due to the shorter follow-up period, and the rate of metastatic patients likely increases when the follow-up period is longer. In CRC, the development of metastasis decreases survival rates. Albeit TNM staging gives an idea about the risk of disease progression, liver metastasis develops in some patients at the same stage, whereas in others it does not. This finding has also been demonstrated in a previous study.[15] Similarly, in the present study, TNM staging was determined to be similar, when the group with the development of liver metastasis was compared with the group that had not. As can be concluded from here, it suggests that TNM staging is not a good selector (marker) for predicting liver metastasis.

Table 3. Multivariate analysis of the effect of APRI score FIB4 score, stage and gender

	HR (95%CI)	p
APRI Score		
Low	Reference	< 0.001
High	10.231 (4.469-23.423)	
T Stage		
T1-2	Reference	< 0.001
T3-4	2.796 (1.566-4.711)	
FIB4 Score		
Low	Reference	0.015
High	3.096 (1.244-7.706)	
N Stage		
Negative	Reference	0.047
Positive	1.563 (1.005-2.430)	
TNM Stage		
Stage 1-2	Reference	0.160
Stage 3	1.276 (0.685-2.379)	
Gender		
Female	Reference	0.135
Male	0.567 (0.269-1.194)	

The relationship between hepatic fibrosis and liver metastasis has been assessed in several studies. In one of these studies, it has been revealed that liver metastases decrease as hepatic fibrosis decreases.[16] Fibrosis that occurs for hepatocyte regeneration is mediated by cytokines such as TGF beta and hepatocyte growth factor.[16] These cytokines could also be an alternative mechanism for liver metastasis by increasing the invasion of cancer cells.[17] As shown in the present study, although the more frequent occurrence of liver metastases on the basis of fibrosis can be explained by these mechanisms, further studies are still needed. Although the well-known and widely used prognostic factors for CRC patients, such as tumor histology,

perineural invasion, and vascular invasion, were valuable predictive factors for predicting recurrence patterns in previous studies, they failed to predict organ-specific metastasis.[18-20] One of the most remarkable findings in the presented study is that APRI and FIB4 scores, which are non-invasive liver-specific fibrosis scores, can predict liver metastases with good sensitivity and specificity rates. In another study, similar to our study, a significant correlation was found between non-invasive liver fibrosis scores and predicting liver metastasis in patients who were initially non-metastatic.[14] In the study, the rate of liver metastasis was detected to be higher in male patients compared to women. This situation may have been caused by the significantly higher APRI score obtained in our male patients. Furthermore, similar to other studies, rather than TNM staging, T stage and N stage alone gave more successful results in the study in predicting liver metastasis.[14]

In the study, a negative prognostic relationship was observed between fibrosis score and overall survival. Likewise, a negative correlation was determined between the FIB4 score and survival in another study in which the relationship between fibrosis and survival was assessed, but unlike that study, this negative correlation was also observed with the APRI score in our study.[14] Similar to these studies, another study has demonstrated that survival decreases as fibrosis increases.[21] This situation can be explained by the decrease in liver reserve in patients with fibrosis and the decrease in overall survival due to the more frequent development of metastasis in the fibrotic background.

The limitations of our study include the fact that it is a retrospective single-centered study, the absence of invasive methods to confirm fibrosis, the inability to reach some data through reviewing patient files, while the sufficient sample size and the fact that it based on real-life data stand out as the strengths of our study.

In conclusion, it has been demonstrated that the group that may develop liver metastasis among patients with non-metastatic CRC at the time of diagnosis could be predicted by using the non-invasive liver fibrosis markers FIB4 and APRI scores. Moreover, it has been shown that these two scorings are also independent predictive markers. Based on this, shorter surveillance intervals may be an option in the group with higher FIB4 and APRI scores at the time of diagnosis. Further studies with longer follow-up periods are needed to better reveal these relationships.

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