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ORIGINAL ARTICLE

Fibrosis- 4 index and survival in early breast cancer patients

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ABSTRACT

Background: The objective of this study is to assess the correlation between survival outcomes and fibrosis-4 (FIB-4) index in patients with non-metastatic breast cancer treated with anthracyclines

Methods: This study was conducted on individuals with non-metastatic breast cancer who were treated with at least one dose of anthracycline from 2018 to 2023. The FIB-4 index was calculated based on the following parameters: age, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) serum levels, and platelet count for each patient before anthracycline treatment.

Results: A total of 208 patients were included in the study. Patients below 35 years of age (n=28) and those above 65 years of age (n=11) were excluded from the study as the FIB-4 index is less reliable in these age groups. Patients were then divided into two subgroups, low and high, according to the pre-defined cut-off value of 1.45, which is obtained from the primary reference. In univariate analysis, hemoglobin (p=0.03), FIB-4 index (p=0.02), and diagnosis at stage (p=0.01) were statistically related to overall survival (OS). In multivariate analysis, patients with higher FIB-4 index (HR: 4.36, 95% CI 1.38-13.78 p=0.012), anemia (HR: 3.32, 95% CI 1.32-8.34, p=0.011), and stage 3 (HR: 4.53, 95% CI 1.22-16.76, p=0.024) had decreased OS. An additional aim was to evaluate the association between anthracycline-induced cardiotoxicity and the FIB-4 index. Our study showed no relationship (p=0.738).

Conclusions: The FIB-4 index, a marker easily obtained through routine biochemistry testing at low cost, could serve as an independent predictor of OS patients with non-metastatic breast cancer treated with anthracyclines. Routine lab tests performed for cancer patients may help clinicians identify high-risk patients in whom closer follow-up or protective measures should be considered.

Keywords: breast cancer, fibrosis-4 index, anthracyclines, survival

INTRODUCTION

Breast cancer is the most common tumour in women worldwide, accounting for approximately 40% of all cancer cases. Nearly 2.5 million people are diagnosed with breast cancer each year [1]. The incidence of breast cancer is increasing, especially in high-income countries. This may be due to a sedentary lifestyle, such as less physical activity, and an unhealthy diet [2]. Fortunately, 70-80% of patients are diagnosed at a non-metastatic stage, which is likely to be curable [3,4].

Breast cancer is a heterogeneous disease, with both diagnostic and prognostic features exhibiting significant variability [5]. For instance, key molecular features such as HER2 status [6], hormone receptor status [7], and BRCA mutations all impact treatment decisions. It is important to note that patients who present with similar molecular features may display different clinical outcomes. As a consequence, treatment and prognosis are not exclusively guided by molecular features, but also by other clinical

factors, which is why it is important to define new prognostic factors [8].

The fibrosis-4 (FIB-4) index is a non-invasive tool to assess liver fibrosis [9]. Noninvasive tests like simple laboratory tests are becoming important to predict the histology of the liver and the prognosis of many diseases [10]. For instance, an increased FIB4 index is associated with mortality in cardiovascular diseases and rheumatoid arthritis [11,12]. Furthermore, the FIB-4 index has been demonstrated to be related to hepatocellular carcinoma and gastric cancer [13,14]. However, the prognostic impact of using the FIB4 index for patients with breast cancer is not well understood yet. Therefore, we hypothesized that the FIB4 index is associated with an adverse prognosis in patients with non-metastatic breast cancer treated with anthracycline.

This study aims to define the correlation between survival outcomes and the FIB-4 index in patients with non-metastatic breast cancer treated with anthracycline.

MATERIALS AND METHODS

Patients

We conducted a retrospective study of patients with non-metastatic breast cancer who received at least 1 cycle of anthracycline-based chemotherapy in Hacettepe University Hospital between 2018 and 2023. Patients below 35 (n=28) and above 65 (n=11) were excluded as these groups' FIB-4 index is less reliable. Patients who did not have at least one of the FIB4 index components (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count) were excluded from this study (n=14).

Definition of FIB-4 index

The FIB-4 index was calculated based on the following parameters: age, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) serum levels, and platelet count. The FIB-4 index was calculated for each patient before anthracycline treatment using the following formula:

$$\text{FIB4 Index} = \frac{\text{Age(years)} \times [\text{Aspartate Aminotransferase(AST)(IU}/L)]}{\text{Platelet Count}\left(10^9/L\right) \times \sqrt{\text{Alanine Aminotransferase(ALT)(IU}/L)}}$$

The pre-defined cut-off value was used to categorize patients as having either a high or low FIB-4 index [9].

Definition of anthracycline cardiotoxicity

Cardiotoxicity was defined as the presence of systolic dysfunction according to LVEF criteria of the European Society of Cardiology (ESC) or diastolic dysfunction according to the criteria of the American Society of Echocardiography (ASE) [15,16].

Data collection

We gathered comprehensive data on each patient from their medical records, including information on their age, gender, medical history, other health conditions they had, the specific treatment they were receiving, and results from their baseline laboratory tests, such as complete blood count, albumin, creatinine, and liver function tests. This information was collected before any chemotherapy treatment was administered.

Statistical analysis

Statistical analyses were performed using SPSS V.24. All data are expressed as either median (IQR) for continuous variables or the number of patients (percentage) for categorical variables. Groups were compared using the chi-square test for categorical variables and Mann–Whitney U test or the Kruskal-Wallis test for quantitative variables. The overall survival (OS) time was defined as the period from treatment initiation to the last follow-up and/or death. Survival analyses were conducted using Kaplan–Meier analyses, and comparisons of survival times between prognostic subgroups were done using the log-rank test. The significant predictors of OS were evaluated by multivariate analysis using Cox's proportional hazards model. Variables showing associations at a significance level of α=0.25 in univariable analysis were selected for inclusion in the multivariable model. Covariates were also selected according to the results of previous research. A type-1 error level of <5% was used to infer statistical significance.

RESULTS

Baseline characteristics

This study included 208 patients. The median follow-up was 46 (IQR=25-61) months. The median age was 49 (IQR=43- 55), and 206 (99%) patients were women. Demographic and clinicopathologic characteristics of the study population are presented in Table 1.

Table 1. Baseline Characteristics of breast cancer patients treated with anthracycline therapy

	All patients (n=208)	Low FIB-4 index (n=189)	High FIB4- index (n=19)
Median Age (IQR)	49 (43-55)	48 (43-54)	57 (54-60)
Sex			
Male	2 (1.0%)	2 (1.1%)	0
Female	206 (99.0%)	187 (98.9%)	19 (100%)
Anthracycline dosage (mg/m²) (IQR)	235 (230-240)	235 (229-239)	235 (228-240)
Histologic Subtype			
Ductal Carcinoma	168 (80.8%)	152 (80.4 %)	16 (84.2%)
Lobular Carcinoma	18 (8.7%)	16 (8.5 %)	2 (10.5%)
Mix	20 (9.6%)	19 (10.1 %)	1 (5.3%)
Missing Data	2 (1.0%)	2 (1.1%)	0
TNM Stage			
Stage 2	88 (42.3 %)	83 (43.9 %)	5 (26.3 %)
Stage 3	118 (56.7 %)	104 (55.0 %)	14 (73.7 %)
Missing Data	2 (1.0 %)	2 (1.1 %)	0
Hormone Receptor Status			
Positive	151 (72.6%)	140 (74.%1)	11 (57.9%)
Negative	55 (26.4%)	47 (24.9%)	8 (42.1%)
Missing Data	2 (1.0%)	2 (1.1%)	0
HER2 status			
Positive	96 (46.2%)	89 (47.1%)	7 (36.8%)
Negative	110 (52.9%)	98 (51.8%)	12 (63.2%)
Missing Data	2 (1.0%)	2 (1.1%)	0
Hemoglobin (g/dl)			
<12 g/dL	34 (16.3%)	33 (17.5%)	1 (5.3%)
≥ 12 g/ dL	174 (83.7%)	156 (82.5%)	18 (94.7%)
Cardiovascular disease			
Yes	43 (20.7%)	38 (20.1%)	5 (26.3%)
No	165 (79.3%)	151 (79.9%)	14 (73.7%)
Cardiotoxicity			
Yes	181 (87.0%)	164 (86.8%)	17 (89.5%)
No	27 (13.0%)	25 (13.2%)	2 (10.5%)
Body Mass Index (kg/m²)			
< 25	58 (27.9%)	55 (29.1%)	3 (15.8%)
≥ 25	150 (72.1%)	134 (70.9%)	16 (84.2%)
Median Platelet Count (10³/L) (IQR)	283 (241-329)	285 (242-329)	262 (235-337)
Median ALT (IU/L) (IQR)	17 (13-25)	17 (13-25)	17 (11-24)
Median AST (IU/L) (IQR	19 (17-24)	20 (17-24)	19 (17-21)

FIB-4: FIBrosis-4, IQR: Interquartile range, HER2: Human epidermal growth factor receptor 2, ALT: Alanine transaminase, AST: Aspartate aminotransferase

Association of FIB-4 index with patient outcomes

In univariate analysis, hemoglobin (p=0.03), FIB-4 index (p=0.02), and TNM stage (p=0.01) were statistically related to overall survival. In multivariate analysis, patients with higher FIB-4 index (p=0.012 HR: 4.36 95% CI 1.38-13.78), anemia (p=0.011 HR: 3.32 95% CI 1.32-8.34), and stage 3 (p=0.024 HR:4.53 95% CI 1.22-16.76) had decreased overall survival (OS) (Table 2 and Figure 1)

FIB-4 index and anthracycline-induced cardiotoxicity

We discovered no connection between the FIB-4 index and cardiotoxicity associated with anthracycline. (p=0.738)

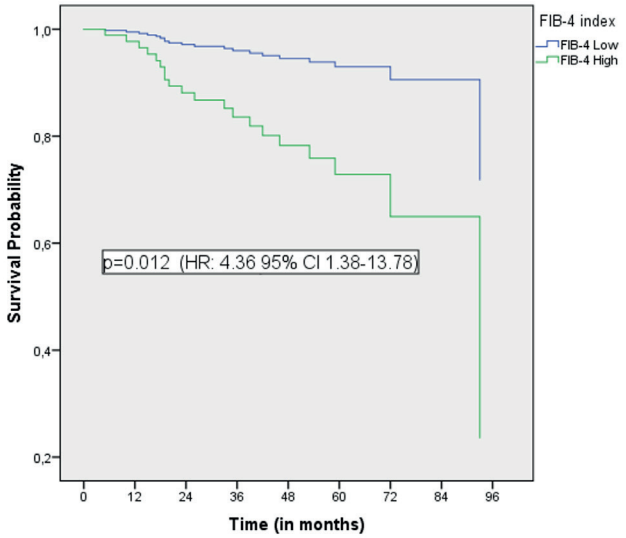

Figure 1. Survival outcomes in patients with non-metastatic breast cancer treated with anthracycline

Table 2. Univariate and multivariate Cox regression analysis of covariates associated with overall survival

	Overall Survival	
	Univariate analysis p-value	**Multivariate analysis-p (HR, 95 %CI)**
Median Age (IQR)	0.21	0.29
Anthracycline dosage (mg/m²) (IQR)	0.18	0.92
Hemoglobin (g/dl) <12 g/dL ≥ 12 g/ dL	*0.03*	*0.011* *(HR: 3.32 95%CI 1.32-8.34)*
Cardiovascular disease Yes No	0.58	(-)
Body Mass Index (kg/m²) < 25 ≥ 25	0.22	0.43
FIB-4 index Low (< 1.45) High (≥ 1.45)	*0.02*	*0.012* *(HR: 4.36 95% CI 1.38-13.78*
Cardiotoxicity Yes No	0.70	*(-)*
TNM Stage at diagnosis Stage 2 Stage 3	*0.010*	*0.024* *(HR: 4.53 95% CI 1.22-16.76)*

DISCUSSION

This study demonstrates a significant association between the FIB-4 index and survival in non-metastatic breast cancer patients treated with anthracycline. This study showed that the FIB-4 index and hemoglobin level were independent indicators of better OS.

We found no relationship between the FIB-4 index and anthracycline-related cardiotoxicity. (p=0.738). Similarly, no relationship was detected between anthracycline dose and the overall survival of patients (p=0.92). This might be due to the characteristics of the study population, which did not include other cancers (such as lymphoma and sarcoma). Furthermore, the anthracycline dose we used (Median dose: 235mg/m^2) might be lower to detect cardiovascular morbidity. However, further prospective trials are needed to demonstrate the relationship between FIB-4 index, survival outcomes, and anthracycline-induced cardiotoxicity.

It is known that the FIB-4 index can be used as an inflammatory marker and assist in defining patients with higher risk. For example, it was shown that the FIB-4 index can predict mortality in patients with rheumatologic disease [12,17]. Although the inflammatory process is important in cancer patients, the relationship between FIB-4 score and breast cancer has not been widely assessed. On the other hand, Xu et al. [13] showed that patients with gastric cancer and higher FIB-4 index had shorter OS (HR: 4.65; 95% CI 1.07-4.29; P = 0.031). Association was identified between elevated levels of the FIB-4 index and colorectal cancer patients in terms of decreased recurrence-free survival (RFS) and overall survival (OS) [18]. Similarly, an elevated FIB-4 score was related to the development of hepatocellular cancer in patients with pre-existing liver disease [19-21].

The FIB-4 index may be a helpful method for identifying high-risk patients who will be treated with anthracyclines. Nevertheless, the FIB-4 index may not be a reliable indicator for patients below 35 or above 65 [22]. Consequently, the interpretation of the FIB-4 index must be considered with caution. One of its advantages is that the FIB-4 index can be easily calculated without additional intervention. Most patients already undergo baseline laboratory tests, making the process easy for patients and clinicians [23]. Moreover, the FIB-4 index provides information before chemotherapy is initiated. Overall, the FIB-4 index is a useful method to define prognosis.

Our study has some limitations. Firstly, our study is retrospective and our patient number is relatively small. Secondly, we only included patients with breast cancer. Therefore, the interpretation of the results on all cancers needs to be taken cautiously. Furthermore, other inflammatory parameters, such as pro-inflammatory cytokines, immunoglobulins, complement proteins, and CRP, were not included in the study as they are not routinely measured at our institution. Lastly, no association was found between cumulative doxorubicin dose and the risk of cardiotoxicity, which could be due to the relatively lower doses used in most patients. Despite these limitations, we showed that there is a significant relationship between the FIB-4 index and overall survival in patients with non-metastatic breast cancer treated with anthracycline.

In conclusion, this study indicates that the FIB-4 index can be easily calculated before treatment with laboratory tests and is linked to the overall survival of non-metastatic breast cancer patients.

Author contribution

Study conception and design: OB, MT and TKŞ; data collection: OB and NG; analysis and interpretation of results: OB and SA ; draft manuscript preparation: OB and LK . All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Clinical Research Ethics Committee (Protocol no. 2024/13-15-30.07.2024).

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Conflict of interest

The authors declare that there is no conflict of interest.

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