Original Article

Investigation of the Relationship between Endometrial Cancer and Liver Fibrosis-4 Score

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Abstract

Objectives: We investigated the relationship between the degree of fibrosis and endometrial cancer (EC) by calculating the fibrosis-4 (FIB-4) score, a noninvasive marker for measuring the severity of liver fibrosis.
Materials and Methods: Liver function tests, platelet (PLT) values, abdominal ultrasonography (USG), and magnetic resonance imaging (MRI) reports were analyzed retrospectively before, after, and at diagnosis in patients with EC.
Results: The study included 38 patients diagnosed with EC. The median FIB-4 score was calculated as 1.15 (minimum: 0.46–maximum: 3.72). When endometroid (type 1 EC) and nonendometroid (type 2 EC) were compared, the FIB-4 score was higher in type one patients (1.16 [0.46–3.72] and 1.01 [0.53–2.96], respectively). However, there was no significant difference between the two groups (P = 0.961). There was no significant difference between the groups in terms of aspartate aminotransferase, alanine aminotransferase, and PLT parameters before diagnosis, at the time of diagnosis, and after treatment. Gamma-glutamyl transferase (GGT) level was significantly higher in the type 1 group in the prediagnosis period (P = 0.016). In the posttreatment period, GGT was higher in the type 2 group (P = 0.020). For PLT level, there was a statistically significant difference between all three periods only in the type 1 group (P < 0.001).
Conclusion: FIB-4 score was higher in patients with type 1 EC, which is more associated with obesity and hormones. In addition, prediagnostic values of GGT and PLT were statistically significantly higher in the type 1 group. Our study needs further studies to support FIB-4 score and biochemical GGT and PLT as biochemical markers in patients with type 1 EC.

Keywords: Endometrial cancer, fatty liver disease, fibrosis-4 score, gamma-glutamyl transferase, liver fibrosis, new cancer control strategy, platelet

Introduction

Approximately 142,000 women worldwide develop endometrial cancer (EC) each year and an estimated 42,000 women die from it, making EC globally the seventh most common malignant disease.[1] Endometrioid type adenocarcinoma (Type 1) accounts for 75%–80% of EC, while nonendometrioid histopathologic types such as serous or clear cell or undifferentiated carcinoma or carcinosarcoma (type 2) constitute the other subtypes.[2]

Exposure to unmet estrogen, excessive fat consumption, and obesity are the important risk factors in the etiology of EC.[3,4] Body mass index (BMI) of at least 25 kg/m^2 is present in almost 50% of women with EC. BMI above 25 kg/m^2 doubles a woman's risk of EC, which triples above 30 kg/m^2.[3]

Obesity is the most common risk factor for EC and atypical endometrial hyperplasia.[5] Fibrosis-4 (FIB-4), a noninvasive marker, is used to detect obesity-related fatty liver and liver fibrosis. It has been reported that the FIB-4 score can predict the risk of hepatocellular carcinoma (HCC) in patients in addition to evaluating liver fibrosis. Studies have reported that high FIB-4 score is strongly associated with the development of other cancers, especially HCC.[6] Although the associated cancer type

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has been attributed to HCC, it has been suggested that patients with high FIB-4 scores are more likely to develop advanced colorectal neoplasms compared to healthy controls. Although the association between fatty liver disease and the development of colorectal cancers has been confirmed, the relationship with other extrahepatic cancers remains under investigation.[7,8]

Early studies on obesity-related sedentary life and cancer showed that prolonged sitting was independently associated with the risk of colorectal, endometrial, ovarian, and prostate cancer.[9] As a result, obesity is a common problem in today's society and the relationship between obesity and cancer has been associated with many types of cancer. Fib-4 score is the strongest predictor of long-term clinical outcomes of obesity-induced fatty liver and liver fibrosis. Although EC is one of the cancers whose relationship with obesity has been identified, the relationship between EC and Fib 4 score has not been investigated. The conceptualization of the issue and the measurement criteria developed with the problems brought along by sedentary behavior are necessary to increase the validity of future studies. The most valuable of these measurements is the FIB-4 score. In our study, we investigated the evaluation of hepatic steatosis with FIB-4 score in the absence of fatty liver and other known liver diseases (alcoholic and viral hepatitis) and its association with EC.

Materials and Methods

Four hundred female patients diagnosed with EC who applied to the radiation oncology outpatient clinic of our university hospital between September 2013 and May 2023 were retrospectively evaluated and 38 patients who met the study criteria were included in the study. Hospital archives were scanned and patient data were retrieved from the hospital computer system. Inclusion criteria: Female patients diagnosed with EC who applied to our clinic. Exclusion criteria: Excessive alcohol consumption (alcohol intake ≥30 g/day for men and ≥20 g/day for women); positive serology for hepatitis B virus surface antigen; hepatitis C virus (HCV) or HIV+ patients; missing data for abdominal USG (ultrasound) or metabolic parameters; previous cancer diagnosis; history of organ transplantation; evidence of liver cirrhosis on abdominal USG; chronic kidney disease with glomerular filtration rate <30 mL/min.

Patients with at least 1 year of follow-up postdiagnosis were included. Data relating to liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transferase [GGT], and platelet [PLT]), and to serum markers of hepatitis virus infection, including hepatitis B surface antigen and anti-HBs, anti-HCV, and anti-HIV antibodies, were retrieved. In addition to laboratory data, abdominal ultrasonography (USG) and (MRI) reports were analyzed. The symptoms of hepatic steatosis were recorded according to USG and MRI findings. Hepatic steatosis was classified as mild, moderate, or severe. Patients with a previous history of cancer or a diagnosis of distant metastatic cancer or a previous history of organ transplantation were excluded, as were chronic kidney disease patients with cirrhosis of the liver on abdominal USG and a glomerular filtration rate of <30 mL/min.

The severity of liver fibrosis was calculated using the noninvasive marker FIB-4 score formula: (age × AST)/(PLT count × ALT) 1/2. A score of ≤1.5 was considered to indicate no fibrosis, ≥3.25 to indicate marked fibrosis, and a range of 1.6–3.24 to indicate suspected fibrosis.[6,10] The primary end point of our study was to determine the relationship between the FIB-4 score, which is a marker of fatty liver disease and fibrosis, and EC.

This study was conducted in accordance with the ethical standards specified by the committee on human experimentation and the Helsinki Declaration. The study was conducted with the approval of Recep Tayyip Erdogan University Faculty of Medicine Ethics Committee (Number E-40465587-050.01.04-730, date September 20, 2023). Written consent was obtained from the patient.

Statistical evaluation

Coded data were analyzed using the SPSS (the Statistical Package for the Social Sciences) (Version 22 for Windows, SPSS Inc, Chicago, IL, USA) program. In statistical analyses, the conformity of all measured variables to normal distribution was evaluated with the "Shapiro–Wilk test." Continuous variables were expressed as mean ± standard deviation and median (minimum value–maximum value), whereas frequency data were expressed as number and percentage (%). Categorical data were compared using Pearson's Chi-square test and Fisher's exact test. Since continuous variables did not conform to normal distribution, Mann–Whitney *U*-test was used for intergroup comparisons and Friedmann test was used for intragroup comparisons, and Wilcoxon test was used where necessary. Kaplan–Meier survival analysis and log–rank (Mantel-Cox) analysis were applied for survival analysis. Statistical significance level was accepted as $P < 0.05$ in all tests.

Results

The mean age of the 38 EC patients included in the study was 60.5 ± 11.3 years. The most common age range was 60–69 years (31.6%). 63.2% of the EC patients were type 1 endometroid EC and 36.4% (14 patients) were type 2 nonendometrioid EC (subtypes; 26% serous and clear cell; 5.3% carcinosarcoma; and 5.3% mixed carcinoma). The most

common stage was 3C with a frequency of 42.1%. While 30 patients received adjuvant chemotherapy, all patients received external radiotherapy and/or brachytherapy. The characteristics of the patients regarding cancer diagnoses are presented in Table 1.

The histopathologic features of type 1 and type 2 are compared in Table 2. In type 2, both the mean age and the number of patients aged 70 years and older were higher. However, this difference was not statistically significant. When the patient groups were compared in terms of stage, 70.8% of type 1 patients were in Stage 3 and above, whereas 42.9% of type 2 patients were in Stage 3 and above. However, the difference between them was not statistically significant [$P = 0.089$, Table 2].

There were no patients in the study group with FIB-4 ≥3.25, which is an indicator of significant fibrosis. The rate of FIB-4 ≤1.5 (no fibrosis) was 76.3% (29 patients), while FIB-4:1.5–3.25 (probable fibrosis) was 23.7% (nine patients). When the groups were compared according to fibrosis status, 20.8% of type 1 and 28.6% of type 2 patients had probable fibrosis, but the difference between the groups was not significant [$P = 0.58$, Table 2].

Table 1: Characteristics of the patients

Variables	*n* (%)
Age (years), mean±SD (minimum–maximum)	60.5±11.3 (35–87)
Age groups (years)	
30–39	2 (5.3)
40–49	5 (13.2)
50–59	11 (28.9)
60–69	12 (31.6)
≥70	8 (21.1)
Cancer type	
Endometroid type endometrial cancer type 1	24 (63.2)
Nonendometroid histopathological types type 2	14 (36.8)
Stage classification	
1A	5 (13.2)
1B	9 (23.7)
2A	1 (2.6)
3A	2 (5.3)
3C	16 (42.1)
4A	1 (2.6)
4B	4 (10.5)
Presence of distant metastasis	
Yok	34 (89.5)
Var	4 (10.5)
Classification of hepatosteatosis (USG-MRI)	
Normal	19 (50.0)
Grade 1	7 (18.4)
Grade 2	10 (26.3)
Grade 3	2 (5.3)

SD: Standard deviation, USG-MRI: Ultrasonography-magnetic resonance imaging

The median FIB-4 score of EC patients was calculated as 1.15 (minimum: 0.46–maximum: 3.72). When type 1 and type 2 EC were compared, this value was higher in type 1 patients (1.16 [0.46–3.72] and 1.01 [0.53–2.96], respectively). However, there was no significant difference between the two groups [$P = 0.961$, Table 3]. The distribution of FIB-4 score according to groups is shown in Figure 1.

There was no significant difference between the groups in terms of AST, ALT, and PLT parameters measured before, at the time of diagnosis and after treatment ($P > 0.05$ for all comparisons). While GGT level was significantly higher in the type 1 group in the prediagnosis period ($P = 0.016$), in the posttreatment period, it was higher in the type 2 group ($P = 0.020$). The difference between GGT measurements at the time of diagnosis was not significant ($P = 0.288$). In intragroup comparison, there was no significant difference in AST, ALT, and GGT parameters measured before diagnosis, at the time of diagnosis and after treatment in each group [$P > 0.05$, Table 3].

For PLT level, there was a statistically significant difference between all three periods only in the type 1 group ($P < 0.001$). Advanced analysis revealed that the difference was due to the posttreatment PLT level being significantly lower than both prediagnosis and at-diagnosis PLT levels ($P = 0.001$ and $P = 0.002$, respectively). There was no significant difference between PLT levels before and at the time of diagnosis [$P = 1.00$, Table 3].

Survival analysis

In the follow-up of 38 patients with EC, 5 (13.2%) died and 33 (86.8%) patients were still alive and the mean survival time was 88.6 months (standard error (SE): 6.2; 95% confidence interval [CI]: 76.3–100.8). The mean survival time was 94.7 months (SE: 6.1; 95% CI: 82.7–106.8) in type 1 and 61.5 months (SE: 8.4; 95% CI: 45.0–78.0) in type 2 patients. In the survival analysis, although survival was longer in the Type 1 group, there was no statistically significant difference

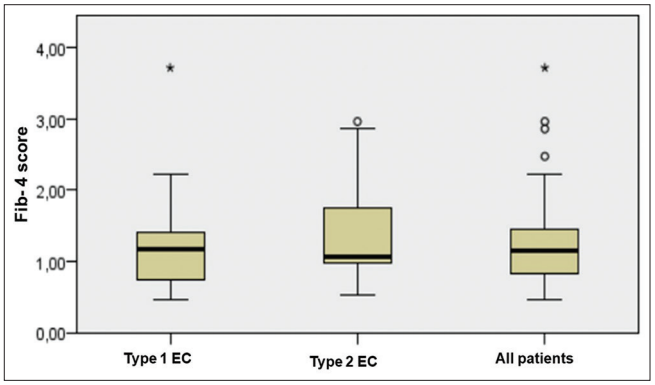

Figure 1: Distribution of fibrosis-4 score according to groups. EC: Endometrial cancer, FIB: Fibrosis

Table 2: Comparison of some parameters of type 1 and type 2 endometrial cancer

Variables	Endometroid type 1 endometrial carcinoma (*n*=24), *n* (%)	Nonendometroid type 2 endometrial carcinoma (*n*=14), *n* (%)	*P*
Age (mean±SD)			
All cases	58.5±12.2	64.1±9.0	0.150
≥70 (%)	12.5	35.7	0.392
Stage (TNM)			
II and below	7 (29.2)	8 (57.1)	0.089*
III and above	17 (70.8)	6 (42.9)	
Tumor (T stage)			
T2 and below	16 (66.7)	11 (78.6)	0.488**
T3 and above	8 (33.3)	3 (21.4)	
Nodal involvement (N stage)			
N0	10 (41.7)	9 (64.3)	0.179*
N+	14 (58.3)	5 (35.7)	
Metastasis (M stage)			
M0	22 (91.7)	12 (85.7)	0.616**
M1	2 (8.3)	2 (14.3)	
Hepatosteatosis grade			
Normal	11 (45.8)	8 (57.1)	0.278*
Grade 1	3 (12.5)	4 (28.6)	
Grade 2	8 (33.3)	2 (14.3)	
Grade 3	2 (8.3)	0	
Fibrosis			
No fibrosis	19 (79.2)	10 (71.4)	0.58
Suspected fibrosis	5 (20.8)	4 (28.6)	

*Pearson Chi-square test, **Fisher's exact test. SD: Standard deviation, TNM: Tumor-node-metastasis

between the two groups (long-rank [Mantel-Cox]: 1.23 $P = 0.26$) [Figure 2].

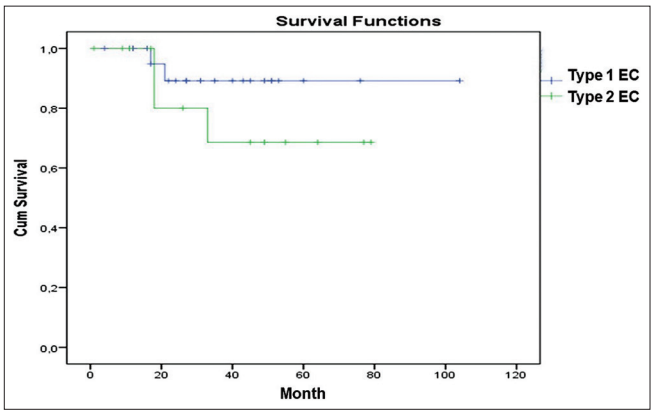

Figure 2: Survival in endometrial cancer patients according to cancer type. EC: Endometrial cancer

Discussion

The typical age-incidence curve for EC shows that most cases are diagnosed after menopause, with the highest incidence around the seventh decade of life. The mean age of the patients in our study was 60.5 ± 11.3 years. The most common age range was 60–69 years. In EC type 2, both the mean age and the number of patients aged 70 years and older were higher. The rate of EC type 1 is reported to be around 80% in the literatüre.[2] In our study, 63.2% consisted of type 1 cases. Type 2 rate was found to be higher in our study compared to the literature.

It is known that unmet estrogen, excessive fat consumption and overweight (BMI at least 25 kg/m^2) are important risk factors in the etiology of type 1 EC.[3,4] Obesity is a risk factor for EC even if circulating estrogen concentrations are normal.[11] Obesity and associated fatty liver disease are thought to be associated with cancer development.[9] Studies have reported that high FIB-4 score, which is a sign of liver fibrosis, is strongly associated with the development of all cancers and especially HCC.[6] Although the associated cancer type has been attributed to HCC, it has been suggested that these patients are more likely to develop advanced colorectal neoplasms than healthy controls. Although the association between fatty liver disease and the development of colorectal cancers has been confirmed, the association with other extrahepatic cancers has not been clearly demonstrated.[7,8]

The FIB-4 score is a noninvasive tool used to assess liver fibrosis, a common complication of nonalcoholic fatty liver disease.[12] The score is calculated using age, AST levels, and PLT counts and has been shown to be a reliable method to detect fibrosis in the liver.[13] In our study, the FIB-4 score of EC patients was calculated as 1.15 (minimum: 0.46–maximum: 3.72). When type 1 and type 2 EC were compared,

Table 3: Comparison of fibrosis-4 score in relation to cancer type and some biochemical parameters among and within groups according to treatment periods

Parameters	Type 1 ($n=24$), median (minimum–maximum)	Type 2 ($n=14$), median (minimum–maximum)	*P*
FIB-4 score			
Prediagnosis	1.16 (0.46–3.72)	1.01 (0.53–2.96)	0.961*
ALT (U/L)			
Prediagnosis	16.5 (7–46)	14.6 (8–29)	0.897*
Moment of diagnosis	19.9 (7–40)	15.1 (4–47)	0.446*
After treatment	22.6 (7–70)	22.5 (6–96)	0.936*
P	0.305**	0.361**	
AST (U/L)			
Prediagnosis	19.1 (11–37)	21.7 (13–52)	0.628*
Moment of diagnosis	24.1 (11–107)	18.9 (11–35)	0.784*
After treatment	17.5 (7–40)	19 (14–189)	0.355*
P	0.371**	0.083**	
GGT (U/L)			
Prediagnosis	34.3 (12–210)	28.7 (11.0–67)	0.016*
Moment of diagnosis	31.2 (10–86)	46.0 (11.6–283)	0.288*
After treatment	39.2 (14–256)	126.5 (11–1374)	0.020*
P	0.648**	0.500**	
Platalet (10^3/IU)			
Prediagnosis (a)	355.0 (148–2155)	263.6 (135–351)	0.207*
Moment of diagnosis (b)	257.3 (168–428)	275.3 (123–530)	0.253*
After treatment (c)	219.6 (117–362)	209.9 (115–316)	0.166*
P	<0.001**	0.065**	
	a–b: 1.00***		
	a–c: 0.001***		
	b–c: 0.002***		

*Mann–Whitney *U*-test, **Friedmann test, ***Wilcoxon test. AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, PLT: Platelet

the FIB-4 score was found to be lower in type 1 patients who were more obese: 1.16 (0.46–3.72) versus (1.01) (0.53–2.96), respectively. However, there was no significant difference between the two groups ($P = 0.961$). The FIB-4 score may help identify patients at high risk for the development of cirrhosis, HCC and other liver-related conditions. It has also been suggested that there is a link between fatty liver disease and EC.[14] Several studies have demonstrated this association, with one retrospective cohort study showing higher rates of EC in patients with fatty liver disease.[14] These findings suggest that the FIB-4 score may be a useful tool in identifying patients at risk for the development of EC and other related conditions.

Patients with fatty liver disease, especially those with high FIB-4 scores, may benefit from regular screening for EC.[15] Furthermore, lifestyle changes such as weight loss and exercise may help reduce the risk of both fatty liver disease and EC.[9,16] More research is needed to fully understand the relationship between these conditions and to develop effective prevention and treatment strategies. However, the use of the FIB-4 score as a noninvasive tool to assess liver fibrosis may help identify patients at high risk for the development of EC and other related conditions, allowing for earlier intervention and improved outcomes.

In our study, while GGT level was significantly higher in the type 1 group in the prediagnosis period ($P = 0.016$), it was higher in the type 2 group in the posttreatment period ($P = 0.020$). GGT is a liver enzyme that is often used as a biomarker for liver disease. However, it has also been suggested that high GGT levels may be a potential biomarker for cancer.[17] Several studies have shown that serum GGT levels are elevated in various solid tumors, including liver, pancreatic, and gynecologic cancers.[18,19] In addition, elevated GGT serum levels have been associated with increased cancer risk in women and worse prognosis in gynecologic cancers.[19]

In our study, there was a statistically significant difference in PLT level among all three periods only in the type 1 group ($P < 0.001$). Further analysis revealed that the difference was due to the fact that the posttreatment PLT level was significantly lower than both prediagnosis and at diagnosis. It is claimed that PLT levels may be an important biomarker for cancer diagnosis and follow-up.[20] Many studies have shown that elevated PLTs play an important role in promoting cancer growth and metastasis.[20] Thrombocytosis, conventionally defined as a PLT count ≥400,000, is a known prognostic biomarker in patients with cancer.[21] Thrombocytosis is common in advanced disease in patients with ovarian cancer,

EC and cervical cancer.[22] Although the value of PLT count as a biomarker of early stage cancer is still unclear,[23] the importance of monitoring PLT levels in cancer patients is well recognized. A meta-analysis including 11 studies suggested that a platelet count ≥400x103/mm3 was significantly associated with decreased overall survival in EC patients.[24]

In the literature, 5-year overall survival in EC is around 80% when all stages are considered together. In our study, the mean survival time was 88.6 months. The mean survival time was 94.7 months in type 1 patients and 61.5 months in type 2 patients. In the survival analysis, although survival was longer in the type 1 group, there was no statistically significant difference between the two groups. There is a significant prognostic difference between EC histologic types. The most common type 1 is hormone-sensitive and has a better prognosis, whereas type 2 tumors are high-grade and tend to recur even at an early stage and have a worse prognosis.

It has been reported that screening for EC makes no sense and screening is unlikely to reduce mortality from this disease. What is actually needed is the development of screening programs to identify women with tumors at low risk for EC. Furthermore, transvaginal ultrasonography and Pap smear or cytology from an endometrial brush are minimally invasive methods suitable for screening and have limited accuracy for diagnosing EC in an asymptomatic population.[25,26]

Early studies on obesity-related sedentary life and cancer showed that prolonged sitting was independently associated with colorectal, endometrial, ovarian, and prostate cancer risk.[9] Future research is expected to investigate whether reducing sedentary life is a new and feasible cancer control strategy.

Conclusion

In our study, FIB-4 score was higher in patients with type 1 EC, which is associated with obesity and hormones. In addition, prediagnostic values of GGT and PLT, which are prognostically important for many cancers, were statistically significantly higher in the type 1 group. These data suggest that FIB-4 score, GGT and PLT values can be used as biochemical markers for early diagnosis, especially in patients with type 1 EC.

The relationship between fatty liver and EC may be presented as a new applicable cancer control strategy to reduce fatty liver and fibrosis through FIB-4 score by reducing sedentary life and obesity.

Author contributions

The corresponding author (SYR) undertook the design of the project, selection of consenting patients, data collection and analysis (OY, HZY, and SM), literature review, manuscript writing, and submission of the manuscript for publication. SYR had final responsibility for the decision to submit the manuscript for publication. All authors have read and agreed to the final version of the manuscript.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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