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Fatty Liver in Hormone Receptor-Positive Breast Cancer and Its Impact on Patient's Survival

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Conflict of Interest
The authors declare that they have no competing interests.

ABSTRACT

Purpose: Long-term estrogen inhibition may cause fatty liver disease (non-alcoholic fatty liver disease; NAFLD) among other adverse conditions such as osteoporosis, climacteric symptoms, thromboembolism, dyslipidemia, and metabolic syndrome. The prevalence of NAFLD among breast cancer patients ranges from 2.3%–45.2%. This study aimed to determine the risk factors for newly developed NAFLD among breast cancer patients after hormonal treatment and whether it influences survival outcomes.
Methods: This retrospective study investigated hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (HR+/HER2−), nonmetastatic breast cancer patients diagnosed between January 2010 and December 2018. All patients received adjuvant hormonal treatment for at least 6 months. Clinical data on metabolic profile indicators such as body mass index (BMI), waist circumference, serum cholesterol, triglycerides, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), diabetes, and presence of metabolic syndrome (MetS) were collected. In total, 160 eligible patients with complete covariate data and survival follow-up were included.
Results: NAFLD was diagnosed in 35% of patients. There were significant associations of being overweight (BMI ≥ 25 kg/m^2), waist circumference > 80 cm, triglycerides ≥ 150 mg/dL, HDL-C ≤ 50 mg/dL, LDL-C < 150 mg/dL, and presence of MetS with the development of NAFLD. However, unlike other factors, MetS and HDL-C were not independently associated with NAFLD. Patients with breast cancer who developed NAFLD had longer disease-free survival (DFS). The median DFS was not reached in the NAFLD group, whereas it was 59.3 (45.6–73.0) months in the non-NAFLD group. No worsening of overall survival was observed in patients with breast cancer and NAFLD.
Conclusion: The development of NAFLD during treatment in patients with HR+/HER2− breast cancer was associated with several independent risk factors: being overweight, waist circumference, triglycerides, and LDL-C. Interestingly, breast cancer patients with NAFLD during treatment had longer DFS than those without NAFLD.

Author Contributions

Conceptualization: Taroeno-Hariadi KW, Aryandono T; Data curation: Taroeno-Hariadi KW, Putra YR, Hardianti MS; Formal analysis: Taroeno-Hariadi KW, Putra YR; Methodology: Taroeno-Hariadi KW, Hardianti MS, Aryandono T; Software: Taroeno-Hariadi KW; Supervision: Choridah L, Hardianti MS, Aryandono T; Validation: Choridah L, Widodo I, Aryandono T; Visualization: Taroeno-Hariadi KW; Writing - original draft: Taroeno-Hariadi KW, Widodo I; Writing - review & editing: Taroeno-Hariadi KW, Putra YR, Choridah L, Widodo I, Hardianti MS, Aryandono T.

Keywords: Aromatase inhibitors; Breast neoplasms; Fatty liver; Non-alcoholic fatty liver disease; Tamoxifen

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a common clinicopathological result of chronic liver disease that is not caused by alcohol intake [1]. NAFLD affects 20%–30% of the general population and can be characterized by a wide spectrum of conditions such as noninflammatory intracellular fat deposition (marked by isolated steatosis) to nonalcoholic steatohepatitis (NASH; characterized by severe steatosis, inflammatory necrosis, and various degrees of fibrosis) [2]. NAFLD occurs due to the dysregulation of hepatic cholesterol homeostasis and accumulation of free cholesterol, free fatty acids, and triglycerides in the liver [3]. Furthermore, NAFLD is associated with insulin resistance, diabetes mellitus, metabolic syndrome, and abdominal obesity [2]. Increasing number of reports have suggested that NAFLD can implicated in the pathology of cardiovascular, pulmonary, and kidney diseases as well as cancers [2,4,5]. NAFLD is associated with a higher incidence rate of hepatic cellular carcinoma, colorectal cancer, and breast cancer [6,7].

Patients with breast cancer commonly develop NAFLD during the course of their disease. The incidence of NAFLD in breast cancer is approximately 2.3%–45.2% [8-10]. NAFLD seems to be associated with a patient's metabolic profile and is influenced by breast cancer treatment, causing insulin resistance and cardiovascular complications [11]. Long-term estrogen inhibition with selective estrogen receptor modulators (SERMs) has been reported to cause NAFLD [12]. The incidence of fatty liver with tamoxifen (Tam) use is higher than that for aromatase inhibitor (AI) use [13]. However, the impact of NAFLD development in breast cancer patients after hormonal treatment has not yet been elucidated.

This study aimed to explore the prevalence, risk factors, and prognostic impact of NAFLD among nonmetastatic, hormone receptor (HR)-positive, human epidermal growth factor receptor (HER2)-negative or HR+/HER2− breast cancer patients who received adjuvant hormonal treatment.

METHODS

Ethics approval and patient selection

The Medical and Health Research Ethics Committee of the Faculty of Medicine, Universitas Gadjah Mada, approved this study (ref. No: KE/FK/1082/EC/2019). We retrospectively investigated HR+/HER2− nonmetastatic female breast cancer patients diagnosed between January 2010 and December 2018. Written informed consent was obtained from all the patients to access their medical data. Patients who received adjuvant hormonal treatment including Tam, AI, or Tam followed by AI (Tam + AI) for at least 6 months were included. These patients were only included if they also had metabolic and anthropometric data at their initial visit and had regular visits for clinical surveillance. Data on metabolic profile indicators such as body mass index (BMI), waist circumference, serum cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), diabetes mellitus, and metabolic syndrome (MetS) were collected. MetS was defined according to the modified National Cholesterol Education Program Adult

Treatment Panel III (NCEP ATP III) for Asians [14,15]. Metabolic data were collected only for the first visit or before hormonal treatment.

The presence of any three of the following five metabolic criteria was defined as MetS: 1) high waist circumference (male > 90 cm, female > 80 cm); 2) elevated triglycerides or use of medication for hypertriglyceridemia (triglyceride ≥ 150 mg/dL); 3) low HDL-C (male ≤ 40 mg/dL, female ≤ 50 mg/dL); 4) hyperglycemia (fasting glucose level ≥ 100 mg/dL); and 5) hypertension or use of medication for hypertension (systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg).

Fatty liver was qualitatively diagnosed using conventional ultrasonography (USG), based on the increased echogenicity of the liver parenchyma as compared to the right kidney cortex, as well as visibility and sharpness of the diaphragm and liver veins [16]. All patients underwent baseline breast imaging, abdominal USG, chest radiography, and bone survey. NAFLD diagnosed during adjuvant hormonal treatment was analyzed based on patient characteristics, metabolic risk factors, and type of hormonal treatment. Patients with NAFLD at baseline, previously documented liver disease, incomplete covariate data, incomplete clinical, histological, and imaging data for tumor assessment, or those who declined cancer treatment before completing 85% of the planned dosage, had double malignancy, or had severe comorbidities were excluded from the analysis.

Recurrence and survival data

Recurrence was assessed during surveillance at 6 month-intervals by clinical examination and breast and abdominal USG. Chest X-ray, mammography, and bone surveys were performed yearly according to the clinical protocol in our hospital. Recurrence event was defined as the reappearance of cancer or metastases detected by clinical, imaging, or cytologic procedures. Death status was collected from hospital death certificates or from the patient's family information.

Disease-free survival (DFS) was calculated from the date of pathology result of the primary tumor until the date of the earliest documented recurrence or metastasis, death from any cause, or until the end of follow-up. Overall survival (OS) was calculated from the date of pathology result of the primary tumor until the date of death or until the end of follow-up. The last date of follow-up for survival (end of study) was December 31, 2019. DFS and OS were analyzed based on newly developed NAFLD.

Statistical analysis

Independent t-test and χ^2 test were used to compare continuous and categorical data, respectively. Multivariate logistic regression analysis was used to identify potential independent risk factors that contributed to the development of NAFLD. Kaplan-Meier survival curve and Cox regression hazard model were applied to show the effect of NAFLD on prognosis of HR+/HER2− breast cancer. All statistical analyses were conducted using SPSS version 23 (IBM Corp., Armonk, USA).

RESULTS

A total of 1,612 HR+/HER2− breast cancer cases were diagnosed between January 2010 and December 2018. However, only 160 (9.93%) patients were eligible for the analysis (**Figure 1**). As compared to the larger (1,612 cases) HR+/HER− breast cancer cohort, the 160 eligible

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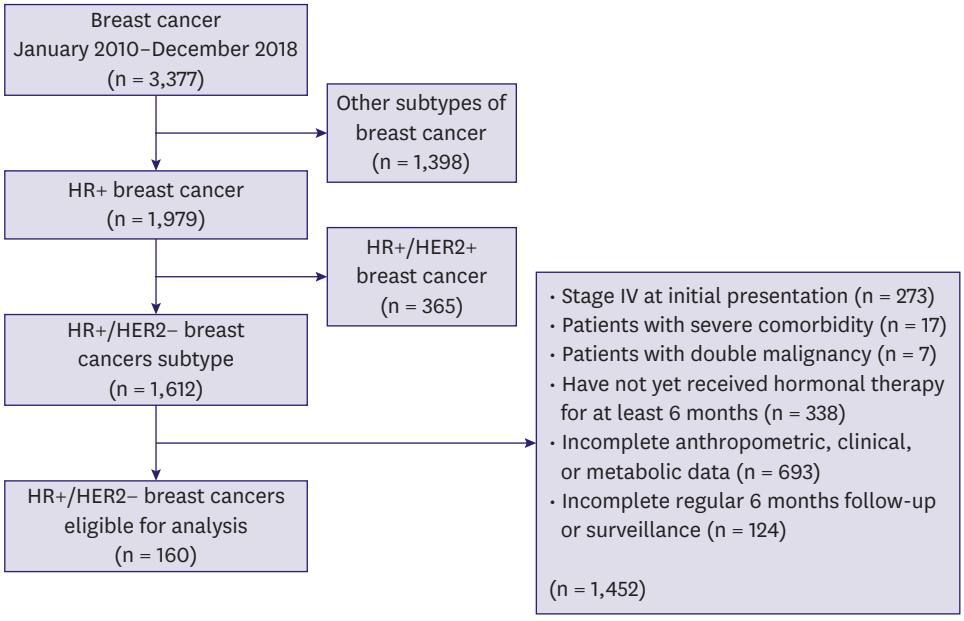

Figure 1. Flowchart for patient selection.
HR = hormone receptor; HER2 = human epidermal growth factor receptor.

HR+/HER2– cases had a less aggressive phenotype. Nodes 0 and 1 were more common in our samples than in the larger cohort ($p < 0.001$), as were early-stage patients. Ductal invasive types were more common in our sample compared to the larger cohort, as shown in **Supplementary Table 1**.

The median age at diagnosis was 49 years (range, 32–74 years). The median follow-up time was 46.3 months (range, 7.8–116.7 months of observation).

Tam was used in 77 (48.1%) patients, whereas Tam + AI was used in 29 (18.1%) patients, and AI was used in 54 (33.8%) patients. MetS was detected in 87 (54.4%) patients, whereas obesity was detected in 15 (9.4%). Seventy-four patients (46.3%) had a BMI ≥ 25 kg/m^2. NAFLD was diagnosed in 56 patients (35.0%). The mean onset of NAFLD after hormonal therapy was 23.5 ± 17.8 months. The baseline characteristics of HR+/HER2– breast cancer patients who developed NAFLD compared to those who did not develop NAFLD are described in **Table 1**. Being overweight, presence of MetS or its component, and having low LDL were more common in patients who developed NAFLD during treatment (**Table 1**).

Risk factors for NAFLD

There were significant associations between being overweight (odds ratio [OR], 3.526; 95% confidence interval [CI], 1.780–6.985; $p < 0.001$), waist circumference ≥ 80 cm (OR, 6.111; 95% CI, 2.407–15.518; $p = 0.001$), triglyceride level ≥ 150 mg/dL (OR, 2.793; 95% CI. 1.405–5.551; $p = 0.003$), HDL-C ≤ 50 mg/dL (OR, 2.245; 95% CI, 1.158–4.355; $p = 0.016$), LDL-C ≥ 150 mg/dL (OR, 0.491; 95% CI, 0.248–0.974; $p = 0.040$) and NAFLD development (**Table 2**). MetS was associated with NAFLD (OR, 3.446; 95% CI, 1.700–6.987; $p = 0.001$). Tam use increased the risk of NAFLD but this was not statistically significant (OR, 1.439; 95% CI, 0.71–2.190; $p = 0.310$).

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Table 1. Baseline characteristics based on groups developed NAFLD and no-NAFLD

Characteristics	NAFLD (n = 56)	No NAFLD (n = 104)	p^*
Age (yr)	49.70 ± 7.786	50.92 ± 8.842	0.385
Tumor size			
T1	9 (16.1)	16 (15.4)	0.807
T2	20 (35.7)	42 (40.4)	
T3	20 (35.7)	30 (28.8)	
T4	7 (12.5)	16 (15.4)	
Nodal			
N0	39 (69.6)	61 (58.7)	0.301
N1	10 (17.9)	30 (28.8)	
N2	7 (12.5)	11 (10.6)	
N3	0 (0)	2 (1.9)	
Grade			
Grade 1–2	43 (48.9)	18 (41.9)	0.451
Grade 3	45 (51.1)	25 (58.1)	
Ki-67			
< 20%	18 (64.3)	14 (87.5)	0.096
≥ 20%	10 (35.7)	2 (12.5)	
BMI (kg/m^2)			
≥ 25	37 (66.1)	37 (35.6)	**< 0.001**
< 25	19 (33.9)	67 (64.4)	
Menopause	17 (30.4)	38 (36.5)	0.430
Pre-menopause	39 (69.6)	66 (63.5)	
Waist (cm)			
≥ 80	50 (89.3)	60 (57.7)	**< 0.001**
< 80	6 (10.7)	44 (42.3)	
Cholesterol (mg/dL)			
≥ 200	29 (51.8)	47 (45.2)	0.462
< 200	27 (48.2)	56 (54.8)	
Triglyceride (mg/dL)			
≥ 150	27 (48.2)	26 (25.0)	**0.003**
< 150	29 (51.8)	78 (75.0)	
HDL-C (mg/dL)			
≤ 50	31 (55.4)	37 (35.6)	**0.016**
> 50	25 (44.6)	67 (64.4)	
LDL-C (mg/dL)			
≥ 150	32 (57.14)	76 (73.1)	**0.040**
< 150	24 (42.86)	28 (26.9)	
Fasting glucose (mg/dL)			
≥ 100	37 (66.1)	68 (65.4)	0.93
< 100	19 (33.9)	36 (34.6)	
Hypertension			
Yes	28 (50.0)	57 (54.8)	0.561
No	28 (50.0)	47 (45.2)	
MetS			
Yes	41 (73.2)	46 (44.2)	**< 0.001**
No	15 (26.8)	58 (55.8)	
Chemotherapy			
Yes	51 (91.1)	102 (98.1)	0.052
No	5 (8.9)	2 (1.9)	
Adjuvant hormone			
Tam	30 (53.6)	47 (45.2)	0.544
Tam + AI	10 (17.8)	19 (18.3)	
AI	16 (28.6)	38 (36.5)	
Mean onset of NAFLD after adjuvant hormone	23.55 ± 17.800		

Values are expressed as number (%) or mean ± standard deviation.
NAFLD = non-alcoholic fatty liver disease; Ki-67 = proliferation index; BMI = body mass index; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; MetS = metabolic syndromes; Tam = tamoxifen; AI = aromatase inhibitor; Tam + AI = tamoxifen for 2 years followed by AI.
*Calculated with Pearson χ^2 test; $p < 0.05$ was considered as statistically significant (bold-faced).

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Table 2. The risk factors for NAFLD

Risk Factor	Univariate			Multivariate		
	OR	p^*	95% CI	OR	$p^\dagger$	95% CI
BMI (kg/m²)						
≥ 25	**3.526**	**< 0.001**	1.780–6.985	**2.270**	**0.047**	1.012–5.093
< 25						
Menopause	0.760	0.430	0.380–1.520			
Pre-menopause						
Waist (cm)						
≥ 80	**6.111**	**< 0.001**	2.407–15.518	**4.138**	**0.009**	1.428–11.992
< 80						
Cholesterol (mg/dL)						
≥ 200	1.253	0.462	0.654–2.402			
< 200						
Triglyceride (mg/dL)						
≥ 150	**2.793**	**0.003**	1.405–5.551	**2.253**	**0.036**	1.054–4.865
< 150						
HDL-C (mg/dL)						
≤ 50	**2.245**	**0.016**	1.158–4.355	1.295	0.521	0.587–2.858
> 50						
LDL-C (mg/dL)						
≥ 150	**0.491**	**0.040**	0.248–0.974	**0.309**	**0.005**	0.137–0.697
< 150						
Fasting glucose (mg/dL)						
≥ 100	0.970	0.93	0.489–1.924			
< 100						
Hypertension						
Yes	1.213	0.561	0.633–2.325			
No						
Hormone treatment						
Tam						
AI	0.695	0.309	0.344–1.404			
Hormone treatment						
Tam						
Tam + AI	0.825	0.424	0.338–2.012			

NAFLD = non-alcoholic fatty liver disease; OR = odd ratio; CI = confidence interval; BMI = body mass index; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; Tam = tamoxifen; AI = aromatase inhibitor; Tam + AI = tamoxifen for 2 years followed by AI.
*Footnote mark is calculated with Pearson χ^2 test; †calculated by regression logistic, method backward LR; $p < 0.05$ is considered as statistically significant (bold-faced).

Multivariate logistic regression determined the independent risk factors for NAFLD: being overweight (OR, 2.270; 95% CI, 1.012–5.093; $p = 0.047$), waist circumference > 80 cm (OR, 4.138; 95% CI, 1.428–11.992; $p = 0.009$), LDL-C < 100 mg/dL (OR, 3.233; 95% CI, 1.435–7.284; $p = 0.005$), and triglyceride level ≥ 150 mg/dL (OR, 2.265; 95% CI, 1.054–4.865; $p = 0.036$) (**Table 2**).

Only seven patients with breast cancer received hormone treatment without chemotherapy. The risk of NAFLD for patients who received only hormone treatment without adjuvant chemotherapy was greater (hazard ratio [HR], 5.000; 95% CI, 0.938–26.665; $p = 0.060$) than for those receiving both treatments. However, the number of patients was too small to obtain reliable results.

NAFLD and survival in HR+/HER2–, nonmetastatic breast cancer

Interestingly, there were fewer progression events in patients with NAFLD than in non-NAFLD patients (10 vs. 45 events). The median DFS of HR+/HER2– breast cancer patients without NAFLD was 59.3 months (45.6–73.0), whereas in patients who developed NAFLD, the

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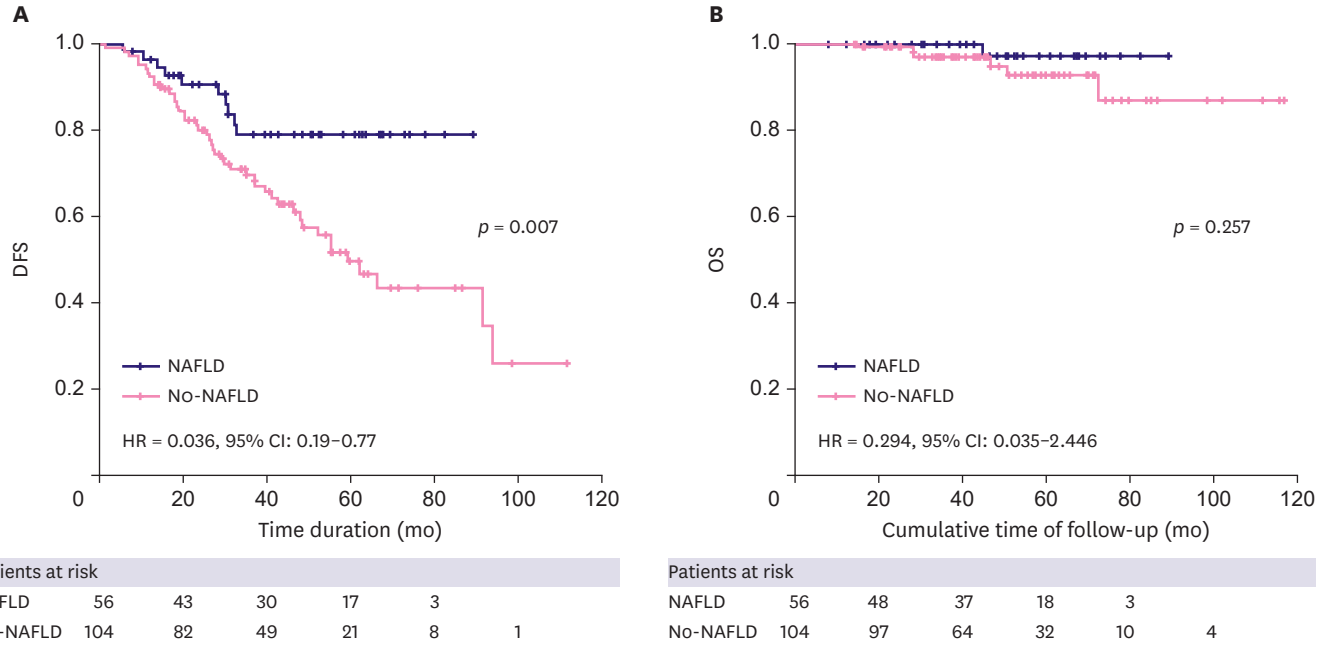

Figure 2. DFS and OS according to the development of NAFLD during treatment.
(A) The median DFS was 59.3 months (95% CI, 45.5–73.0) in the non NAFLD group; whereas in the NAFLD group the median DFS was not reached (HR, 0.386; 95% CI, 0.19–0.77; p = 0.007). (B) The survival estimation of breast cancer patients who developed NAFLD was not different from that of non-NAFLD patients: mean survival was 108.23 ± 3.525 months vs. 87.79 ± 1.283 months. The median survival estimation of both groups was not reached (HR for OS, 0.294; 95% CI, 0.035–2.446; p = 0.257).
DFS = disease-free survival; OS = overall survival; NAFLD = non-alcoholic fatty liver disease; CI = confidence interval; HR = hazard ratio.

median DFS was not reached. The HR for NAFLD to relapse or progress was 0.386 (95% CI, 0.19–0.77; p = 0.007) (**Figure 2**).

There was no significant difference in OS based on NAFLD development among breast cancer patients (HR, 0.294; 95% CI, 0.04–2.45; p = 0.26) (**Figure 2**).

Compared to other conventional prognostic factors such as age, tumor size, node involvement, and Ki-67 level, newly developed NAFLD was associated with longer DFS (HR, 0.386; 95% CI, 0.194–0.770; p = 0.007). A higher histological grade (grade 3) was associated with shorter DFS (HR, 2.286; 95% CI, 1.199–4.359; p = 0.011) (**Table 3**). Multivariate analysis confirmed that NAFLD (HR, 0.359; 95% CI, 0.180–0.716; p = 0.004) and higher histological grade (HR, 2.482; 95% CI, 1.300–4.739; p = 0.006) were independent factors for DFS.

Due to the imbalanced number of patients receiving adjuvant hormone therapy alone compared to adjuvant chemotherapy followed by hormone therapy, we performed a sub-analysis by sorting out all patients who received adjuvant hormone therapy alone (7 patients). In the remaining 153 patients who received chemotherapy followed by hormone therapy, the association between NAFLD and progression was consistent (HR, NAFLD for DFS, 0.437; 95% CI, 0.215–0.887; p < 0.022). We also filtered out those who progressed earlier than 24 months (45 patients) to eliminate patients who had events before developing NAFLD and found that in the remaining 115 patients, the effect of NAFLD on DFS in HR+/HER2− breast cancer was consistent (HR, 0.332; 95% CI, 0.126–0.823; p < 0.025).

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Table 3. Survival analysis of variables related to DFS and OS

Variable	DFS				OS	
	Univariate		Multivariate		Univariate	
	HR (95% CI)*	p*	HR (95% CI)†	p†	HR (95% CI)*	p*
Age (yr)						
≤ 50	1 (reference)		-		1 (reference)	
≥ 50	1.414 (0.831–2.406)	0.201	-	-	0.879 (0.196–3.932)	0.866
NAFLD						
No developed	1 (reference)		1 (reference)		1 (reference)	
Developed	0.386 (0.194–0.770)	**0.007**	0.359 (0.180–0.716)	**0.004**	0.294 (0.035–2.446)	0.257
Tumor size						
T1–T2	1 (reference)		-		1 (reference)	
T3–T4	1.589 (0.929–2.717)	0.091	-	-	2.768 (0.534–14.271)	0.224
Node involvement						
N0–N1	1 (reference)		-		1 (reference)	
N2–N3	1.540 (0.774–3.066)	0.219	-	-	1.122 (0.135–9.324)	0.915
Grade (available in 131 patients)						
G1–G2	1 (reference)		1 (reference)		1 (reference)	
G3	2.286 (1.199–4.359)	**0.011**	2.482 (1.300–4.739)	**0.006**	161,409 (0.00–)	0.947
Unknown	1.821 (0.839–3.952)	**0.130**	1.930 (90.888–4.198)	**0.097**	105,663 (0.00–)	0.949
Ki-67 (available in 44 patients)						
< 20%	1 (reference)		-		1 (reference)	
≥ 20%	3.004 (0.750–12.030)	0.120	-	-	329,555 (0.000–)	0.948
Unknown	1.868 (0.666–5.239)	0.235	-	-	13,656 (0.00–)	0.961

NAFLD = non-alcoholic fatty liver disease; DFS = disease-free survival; OS = overall survival; HR = hazard ratio; CI = confidence interval; T = tumor; N = node involvement; G = histological grade; Ki-67 = proliferation index.
*Univariate, †multivariate, data are analyzed by binomial Cox proportional hazard model; $p < 0.05$ is considered as statistically significant (bold-faced).

DISCUSSION

NAFLD that develops during hormonal treatment in HR+ breast cancer is associated with visceral obesity and metabolic abnormalities. However, in this study, breast cancer patients who developed NAFLD had good prognosis.

NAFLD prevalence has been increasing worldwide [17] and is higher in breast cancer patients, compared to the normal population, depending on the modalities used to diagnose NAFLD [18]. In this study, the prevalence of NAFLD was 35% in patients with breast cancer who received hormonal therapy. Similar results have been reported in previous studies [19].

Visual assessment of NAFLD in this study was performed using USG as part of the routine surveillance for breast cancer progression. Bedside USG is easy to use, noninvasive, and a readily available diagnostic tool but it has some limitations such as being subject to interobserver variability and low sensitivity if steatosis is < 20% [20,21]. However, when fat accumulation in the liver > 20%, bedside USG has 90% sensitivity in diagnosing NAFLD [20]. Liver biopsy, which is the gold standard test but also more invasive, is not routinely performed during surveillance for breast cancer patients for the diagnosis of steatohepatitis and NASH. Thus, the prevalence of NAFLD in this study was higher than that reported in previous studies that used liver biopsy to diagnose NAFLD [22].

Several risk factors are associated with newly developed NAFLD such as age, BMI, anthropometric size, dyslipidemia, MetS, and hormonal treatment for breast cancer [23-25]. In this study, further analysis revealed that being overweight, waist circumference > 80 cm, low LDL-C, and high triglyceride levels were associated with NAFLD. MetS, as a group of metabolic abnormalities, was not included in multivariate analysis which analyzed its

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metabolic components. Waist circumference directly indicates visceral obesity, whereas metabolic syndrome, dyslipidemia, and being overweight are closely associated with the same.

The median time for developing NAFLD is 1–3 years after the initiation of hormonal treatment [26], similar to our results. SERM or Tam contribute to newly developed NAFLD, similar to the effect of aromatase inhibitors [23,24]. The mechanisms by which SERM induces NAFLD have been described previously. Tam has been shown to increase hepatic fat accumulation by blocking estrogen, which disrupts hepatic lipid homeostasis, increases triglycerides, and lowers LDL-C [27]. Patients with breast cancer receiving Tam have higher triglyceride levels and lower LDL-C and cholesterol levels [27]. Aromatase inhibitors may also induce NAFLD; however, the underlying mechanisms are not known. Although several studies have revealed that Tam has a greater effect in promoting newly developed NASH than AI [13], the difference was not significant with our data. The use of only Tam increased the risk of NAFLD compared to Tam + AI but again the difference was not significant.

The effect of NAFLD on prognosis of breast cancer remains a concern. Previous studies have shown that NAFLD worsens the prognosis of breast cancer patients independent of stage, lymph node involvement, diabetes, and obesity [23,24]. In contrast, our findings showed that NAFLD improved the survival of early breast cancer patients, similar to the results of Zheng et al. [28].

Low levels of insulin-like growth factor-1 (IGF-1) in NAFLD [29] may contribute to longer DFS in breast cancer patients with NAFLD. The synthesis of IGF-1 is downregulated in NAFLD, and the level of IGF-1 is associated with the severity of NAFLD [29]. In the liver, IGF-1 decreases lipogenesis, triglyceride accumulation, and reactive oxygen species, improves insulin resistance and mitochondrial function, induces senescence of hepatic stellate cells (HSC), and inhibits the activation of HSCs and fibrosis, thereby protecting against steatohepatitis and NASH [30]. IGF-1 signaling through the IGF-1 receptor is functional in any type of breast cancer. IGF-1 promotes proliferation and is anti-apoptotic. Hence, it contributes to antiestrogen resistance, and low IGF-1 levels in NAFLD may improve antiestrogen action.

This study has several limitations. First, it was a retrospective study, which may have made selection bias inevitable. Second, using USG to diagnose NAFLD makes it impossible to determine severity of steatosis and degree of fibrosis which may influence the prognosis. The relatively small sample size, and less aggressive phenotypes compared to the entire HR+ breast cancer cohort due to incomplete retrospective variables and shorter follow-up made selection bias unavoidable, which may be a major limitation.

The study findings suggest that women with breast cancer who received hormonal therapy, who were overweight, had waist circumference ≥ 80 cm, had high triglyceride levels, and had low LDL-C levels had an increased risk of developing NAFLD. Developing NAFLD during hormonal treatment does not compromise survival. DFS of women who develop NAFLD during hormone treatment was longer compared to those who do not develop NAFLD. These results may have practical implications when treating such patients. Due to the complexity of possible mechanisms involved in the interplay between estrogen, lipid metabolism and growth factor signaling, it is important for clinicians who treat breast cancer patients with hormone therapy to continue hormone therapy, even when NAFLD is documented during treatment evaluation.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Comparison of the whole cohort and eligible sample of HR+/HER2– breast cancer

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