J Breast Cancer. 2020 Jun;23(3):246-258
https://doi.org/10.4048/jbc.2020.23.e32
pISSN 1738-6756·eISSN 2092-9900

Journal of Breast Cancer JBC

Original Article

Assessment of the Predictive Role of Serum Lipid Profiles in Breast Cancer Patients Receiving Neoadjuvant Chemotherapy

Fanli Qu [1,*], **Rui Chen** [2,*], **Yang Peng** [1], **Ying Ye** [1], **Zhenrong Tang** [1], **Yihua Wang** [1], **Beige Zong** [1], **Haochen Yu** [1], **Shengchun Liu** [1]

[1]Department of Breast Surgery, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
[2]Department of Breast Surgery, Affiliated Hospital of Zunyi Medical College, Zunyi, China

Received: Sep 9, 2019
Accepted: Apr 18, 2020

Correspondence to
Shengchun Liu
Department of Breast Surgery, The First Affiliated Hospital of Chongqing Medical University, No.1 Youyi Road, Yuzhong District, Chongqing 400016, China.
E-mail: liushengchun@hospital.cqmu.edu.cn

*These authors contributed equally to this work.

ORCID iDs
Fanli Qu
https://orcid.org/0000-0002-6908-0630
Rui Chen
https://orcid.org/0000-0001-9702-2799
Yang Peng
https://orcid.org/0000-0002-4146-8369
Ying Ye
https://orcid.org/0000-0002-6886-8602
Zhenrong Tang
https://orcid.org/0000-0003-4706-926X
Yihua Wang
https://orcid.org/0000-0002-9024-0811
Beige Zong
https://orcid.org/0000-0003-0667-1721
Haochen Yu
https://orcid.org/0000-0003-4600-4085

ABSTRACT

Purpose: Effective predictors of the response to neoadjuvant chemotherapy (NAC) are still insufficient. This study aimed to investigate the predictive value of serum lipid profiles for the response to NAC in breast cancer patients.
Methods: A total of 533 breast cancer patients who had received NAC were retrospectively studied. The pretreatment of serum lipids, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and lipoprotein-α, and clinicopathological characteristics were collected to assess their predictive roles.
Results: Breast cancer patients had significantly lower TC, TG, HDL-C, and LDL-C levels than normal individuals. Among these indicators, TG and LDL-C levels and HDL-C level increased and decreased significantly after NAC, respectively. In estrogen receptor (ER)-positive patients, increased LDL-C level was associated with better outcomes. Moreover, the receiver operating characteristic curve analyses suggested that TG and HDL-C levels at diagnosis can be used as predictors of the response to NAC only in the ER-positive subgroup. According to univariate analyses, patients with low TG level (< 1.155 mmol/L) or high HDL-C level (≥ 1.305 mmol/L) in the ER-positive subgroup had more favorable clinical responses than the other patients in the subgroup. Furthermore, according to multivariate analyses, a high HDL-C level (≥ 1.305 mmol/L, $p = 0.007$) was an independent predictor of NAC efficacy.
Conclusion: High HDL-C level (≥ 1.305 mmol/L) before NAC and increased LDL-C level after NAC were associated with the better treatment response in ER-positive breast cancer patients. These results are potentially considered beneficial in establishing treatment decisions.

Keywords: Breast neoplasms; Drug therapy; Lipids; Lipoproteins; Neoadjuvant therapy

INTRODUCTION

Breast cancer is the most common malignant tumor in women, and it has the second highest cancer-related death rate [1]. Neoadjuvant chemotherapy (NAC), which offers an alternative treatment to adjuvant chemotherapy with the same therapeutic effect, has become a standard treatment for locally advanced breast cancer to reduce the extent of operation [2]. Furthermore, NAC can be considered an in vivo chemosensitivity test for tumor therapy

Shengchun Liu
https://orcid.org/0000-0003-0257-1336

Funding

This study was supported by the National Natural Science Foundation of China (NSFC) (NSFC No. 81472658) and Chongqing Science and Technology Committee Fund (csct2015shmszx0269).

Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

Conceptualization: Qu F, Chen R, Peng Y, Tang Z; Data curation: Qu F, Peng Y, Ye Y, Tang Z, Wang Y, Zong B; Formal analysis: Qu F, Chen R; Funding acquisition: Liu S; Investigation: Qu F, Chen R, Peng Y, Ye Y, Wang Y; Methodology: Qu F, Chen R, Peng Y, Ye Y, Zong B, Yu H; Project administration: Liu S; Software: Qu F, Chen R, Tang Z, Wang Y, Yu H; Supervision: Liu S; Validation: Chen R; Writing - original draft: Qu F; Writing - review & editing: Chen R, Liu S.

because the treatment response of each individual tumor can be evaluated directly by pathological assessment [3]. Biomarkers that can predict the response would be crucial in the clinical setting and could be used to select patients who benefit most from NAC. However, effective predictors of the response to NAC are still insufficient.

Obesity is defined as a body mass index (BMI) ≥ 30.0 kg/m^2 [4], and previous studies have suggested that it is directly associated with the risk of developing several kinds of cancer, including breast cancer [5]. Obesity is usually accompanied by elevated levels of serum lipids, such as triglycerides (TG), very low-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B. However, the association between breast cancer and plasma lipids or lipoproteins (LPs) is currently controversial. Some studies have demonstrated no significant differences in total cholesterol (TC), TG, and LDL-C levels between breast cancer patients and normal subjects [6]. Moreover, a large-scale prospective study of Korean adults found a positive association between cholesterol levels and breast cancer incidence [7]. In contrast, some other studies have shown an inverse association [8,9].

Serum lipid and LP levels fluctuate during the process of chemotherapy [10]. Patients who respond favorably to chemotherapy display significant increases in their serum TC and LDL-C levels [11]. Hence, serum lipids and LPs may become potential predictors of chemotherapy response. However, there are few studies in this field, and whether serum lipid profiles can be used as predictors of NAC response is still unclear. In this study, the differences in serum lipid profiles between the normal and breast cancer groups and the associations between serum lipid profiles and breast cancer characteristics were investigated. More importantly, the association between serum lipid profiles and the response to NAC in breast cancer patients was systematically investigated.

METHODS

Study population

From January 2012 to March 2018, 533 primary breast cancer patients who were treated with NAC and surgery at the breast cancer center of The First Affiliated Hospital of Chongqing Medical University were recruited; all the patients were confirmed to have invasive cancer by biopsy. All patients met the following inclusion criteria: 1) female sex; 2) no history of breast cancer or other invasive malignancies; 3) no administration of lipid-lowering drugs or corticosteroids within 1 year; 4) no administration of human epidermal growth factor 2 (HER2)-targeted therapy before surgery; 5) administration of chemotherapy comprising at least 3 cycles of docetaxel (75 mg/m^2), epirubicin (75 mg/m^2), and cyclophosphamide (500 mg/m^2), each 21 days before surgery; and 6) fasting blood lipid levels measured before treatment. This study was authorized by the Ethics Committee of The First Affiliated Hospital of Chongqing Medical University (approval No. 2020-59). Written informed consent was obtained from all patients.

A total of 1,600 individuals who received a routine medical examination at our Health Checkup Center during the same period were included in the normal group. This group was 3 times larger than the breast cancer group. Serum lipids and LPs can be significantly affected by age and BMI; thus, the normal group comprised age-, weight-, height-, and BMI-matched women. Among them, individuals with history of cancer and individuals taking lipid-lowering drugs or corticosteroids within 1 year of their examination were excluded.

Blood sample collection and serum lipid and lipoprotein assays

Lipid profiles were tested along with routine preoperative plasma examinations at diagnosis and after NAC. Briefly, subjects were fasted for at least 6 hours before blood sample collection. Blood was collected into coagulant-coated tubes, and a fully automatic biochemical analyzer (Roche c701, Basel, Switzerland) was used to analyze TC, TG, high-density lipoprotein cholesterol (HDL-C), LDL-C, and lipoprotein (LP)-α levels.

Based on the receiver operating characteristic (ROC) curves, clinical response was used to establish the values of optimal serum lipid and LP levels. The optimal cutoff value was established using the Youden index. The results of the overall ROC curve analysis suggested that the cutoff values were 4.075 mmol/L for TC, 1.205 mmol/L for TG, 1.305 mmol/L for HDL-C, 3.695 mmol/L for LDL-C, and 95.75 mg/L for LP-α (**Figure 1**).

Immunohistochemistry and molecular typing

Estrogen receptor (ER), progesterone receptor, HER2 statuses, and the Ki67 index were assessed in each patient before NAC administration. ER and progesterone receptor expression were considered positive if greater than 1% of the tumor cells exhibited nuclear staining. If HER2 was evaluated as 3+ by immunohistochemical staining or recorded over 2.0-fold growth by fluorescence in situ hybridization, the HER2 expression was considered positive [12]. The Ki67 value was defined as the proportion of positively stained cells (500–1,000) among the total number of cancer cells in the invasive front of the tumor [13]. All results were assessed by 2 pathologists independently. The breast cancer tumors were classified into molecular subtypes, including luminal (HR+/HER2−), luminal/HER2 (HR+/HER2+), HER2 (HR−/HER2+), and TNBC (HR−/HER2−) subtypes, according to the immunohistochemical expression of ER, progesterone receptor, and HER2 before NAC.

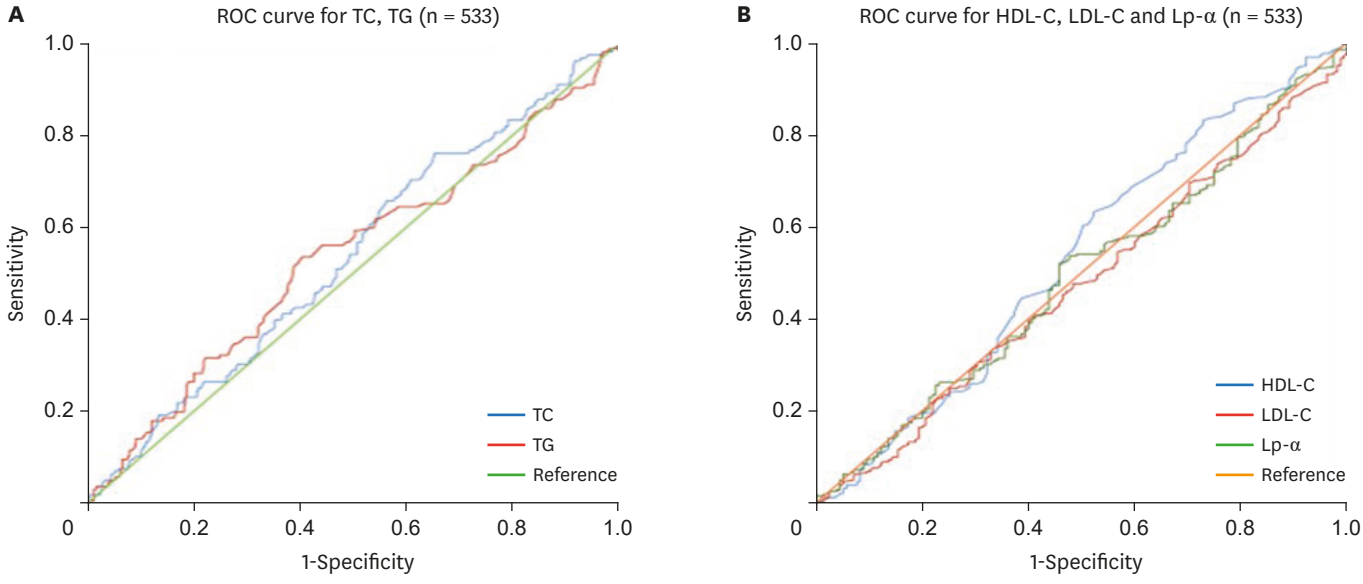

Figure 1. ROC curve analysis for the predictive role of serum lipid profiles. (A) ROC curve for TC, TG (n = 533). (B) ROC curve for HDL-C, LDL-C, and LP-α (n = 533). ROC = receiver operating characteristic; AUC = areas under the ROC curves; TC = total cholesterol; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LP-α = lipoprotein-α.

https://doi.org/10.4048/jbc.2020.23.e32

Evaluation of the response to neoadjuvant chemotherapy

The effect of NAC on breast cancer was assessed using ultrasonography and magnetic resonance imaging before surgery. The comparison was made based on alterations in the primary lesions. According to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.1, treatment response is evaluated by physical and imaging examinations. A reduction in the sum of the diameters of the target lesions ≥ 30% was classified as a clinical partial response (PR). An increase in the sum of the diameters of the target lesions ≥ 20% was considered clinically progressive disease (PD). Tumors that did not sufficiently shrink to qualify for a PR but did not sufficiently increase to qualify for PD were classified as clinically stable disease (SD). The absence of any residual tumor lesions in any excised breast tissue or lymph nodes was defined as a pathological complete response (pCR) [14].

Statistical analyses

All statistical analyses were performed using the Statistical Package for the Social Sciences version 25.0 software (IBM Corp., Armonk, USA). The cutoff values for TC, TG, HDL-C, LDL-C, and LP-α were established by the ROC curve analysis. Student's *t*-test was used to compare quantitative parameters, and the chi-squared test was used to compare categorical variables. Multivariate analysis of prognostic factors was performed using a logistic regression analysis model. Hazard ratios were reported with corresponding 95% confidence intervals (CIs). A p-value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

The mean patient age at baseline was 49.0 ± 9.0 years (range, 20.0–77.0 years), and among the patients, 317 patients (59.5%) were premenopausal women. A total of 145 (27.2%) and 36 (6.8%) patients were overweight (BMI, 25.0–29.9 kg/m^2) and obese (BMI, ≥ 30.0 kg/m^2), respectively. Chemotherapy was administered for a median of 4 cycles (range, 3–8 cycles). The mean tumor diameters at baseline and after NAC were 4.19 ± 2.05 cm and 2.21 ± 1.90 cm, respectively. Additionally, more than half of the patients (53.5%) had node-positive disease at diagnosis. Among the 533 NAC-treated patients, the proportions of ER-, progesterone receptor-, and HER2-positive patients were 62.5% (n = 333), 49.0% (n = 261), and 41.3% (n = 220), respectively, and 73.4% (n = 391) of all patients had Ki67 expression ≥ 14%. According to the RECIST guidelines, 57 (10.7%), 321 (60.2%), 147 (27.6%), and 8 (1.5%) patients who received NAC were classified into pCR, PR, SD, and PD, respectively. The characteristics of these patients are detailed in **Table 1**.

Assessment of the associations between serum lipid profiles and breast cancer

Selected characteristics and serum lipid and LP levels for the breast cancer patients and normal individuals are summarized in **Table 2**. There was no significant difference between the breast cancer group and the normal group in the baseline values of age, height, weight, BMI, and LP-α level. However, the mean TC, TG, HDL-C, and LDL-C levels in the breast cancer group were 4.57 mmol/L (p < 0.001), 1.35 mmol/L (p = 0.003), 1.43 mmol/L (p < 0.001), and 2.85 mmol/L (p < 0.001), respectively, and these levels were significantly lower than those in the normal group.

As shown in **Table 3**, we next assessed the associations between serum lipid profiles and clinicopathological characteristics in breast cancer patients. Lipids and LPs were divided into high and low levels according to the appropriate cutoff value. There was a significant positive

https://doi.org/10.4048/jbc.2020.23.e32

Table 1. Characteristics of all patients (n = 533)

Parameters	Values
Age (year)	
< 55.0	387 (72.6)
≥ 55.0	146 (27.4)
Menopause	
Yes	216 (40.5)
No	317 (59.5)
BMI (kg/m^2)	
< 25.0	320 (60.0)
25.0–29.9	145 (27.2)
≥ 30.0	36 (6.8)
Unknown	32 (6.0)
Chemotherapy cycles	
3	10 (1.9)
4	476 (89.3)
5–8	47 (8.8)
Subtype of cancer	
Ductal	522 (97.9)
Lobular	9 (1.7)
Others	2 (0.4)
Tumor size (cm)	
< 2.0	40 (7.5)
2.0–4.0	278 (52.2)
> 4.0	215 (40.3)
Clinical nodal status	
Positive	285 (53.5)
Negative	248 (46.5)
Histological grade	
I	13 (2.4)
II	293 (55.0)
III	80 (15.0)
Unknown	147 (27.6)
ER status*	
Positive	333 (62.5)
Negative	200 (37.5)
Progesterone receptor status*	
Positive	261 (49.0)
Negative	272 (51.0)
HER2 status	
Positive	220 (41.3)
Negative	274 (51.4)
Unknown	39 (7.3)
Ki67	
< 14	142 (26.6)
≥ 14	391 (73.4)
Response evaluation	
pCR	57 (10.7)
PR	321 (60.2)
SD	147 (27.6)
PD	8 (1.5)
Responder (pCR and PR)	378 (70.9)
Non-responder (SD and PD)	155 (29.1)

Values are presented as number (%).
BMI = body mass index; ER = estrogen receptor; HER2 = human epidermal growth factor 2; pCR = pathologic complete response; PR = partial response; SD = stable disease; PD = progressive disease.
*Positive ≥ 1%.

association between TG and BMI ($p < 0.001$), while HDL-C was negatively associated with BMI ($p < 0.001$). Moreover, high lipid level was associated with older age (TC, $p < 0.001$; TG, $p = 0.003$; HDL-C, $p = 0.026$; and LDL-C, $p = 0.005$) and menopausal status (TC, $p < 0.001$;

https://doi.org/10.4048/jbc.2020.23.e32

Table 2. Selected demographic characteristics and levels of serum lipid profiles in the study and the normal group at baseline

Characteristics	Breast cancer group (n = 533)	Normal group (n = 1,600)	*p*-value
Age (yr)	49.39 ± 8.97	49.71 ± 10.51	0.523
Height (cm)	155.37 ± 6.61	155.58 ± 5.00	0.456
Weight (kg)	58.54 ± 8.76	58.66 ± 6.06	0.729
BMI (kg/m^2)	24.30 ± 3.75	24.23 ± 2.23	0.639
TC (mmol/L)	4.57 ± 0.88	5.06 ± 0.90	< 0.001
TG (mmol/L)	1.35 ± 0.99	1.52 ± 1.16	0.003
HDL-C (mmol/L)	1.43 ± 0.38	1.50 ± 0.32	< 0.001
LDL-C (mmol/L)	2.85 ± 0.75	3.08 ± 0.79	< 0.001
LP-α (mg/L)	211.48 ± 273.74	207.00 ± 268.99	0.740

Data are shown as mean ± standard deviation.
BMI = body mass index; TC = total cholesterol; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LP-α = lipoprotein-α.

Table 3. Clinical characteristics of patients according to the different levels of serum lipid profiles

Characteristics	TC (n = 533)		*p*-value	TG (n = 533)		*p*-value	HDL-C (n = 533)		*p*-value	LDL-C (n = 533)		*p*-value	LP-α (n = 533)		*p*-value
	< 4.075 (n = 168)	≥ 4.075 (n = 365)		< 1.205 (n = 297)	≥ 1.205 (n = 236)		< 1.305 (n = 213)	≥ 1.305 (n = 320)		< 3.695 (n = 454)	≥ 3.695 (n = 79)		< 95.750 (n = 265)	≥ 95.750 (n = 268)	
Age (yr)			< 0.001			0.003			0.026			0.005			0.373
< 55	144	243		231	156		139	178		340	47		197	190	
≥ 55	24	122		66	80		74	142		114	32		68	78	
Menopause			< 0.001			0.002			0.026			< 0.001			0.139
Yes	43	173		103	113		74	142		169	47		99	117	
No	125	192		194	123		139	178		285	32		166	151	
BMI (kg/m^2)			0.120			< 0.001			< 0.001			0.888			0.644
< 25	110	210		203	117		103	217		272	48		166	154	
≥ 25	50	131		79	102		98	83		153	28		90	91	
Subtypes of cancer			0.847			0.180			0.495			0.376			0.222
Ductal	164	358		292	230		209	313		443	279		259	263	
Lobular	3	6		3	6		4	5		9	0		6	3	
Others	1	1		2	0		0	2		2	0		0	2	
Tumor size (cm)			0.199			0.437			0.038			0.769			0.848
< 2	14	26		21	19		15	25		34	6		19	21	
2–4	78	200		149	129		98	180		234	44		136	142	
> 4	76	139		127	88		100	115		186	29		110	105	
Histological grade			0.449			0.730			0.598			0.522			0.642
I	6	7		7	6		6	7		12	1		5	8	
II	93	200		168	125		115	178		249	44		147	146	
III	29	51		42	38		36	44		65	15		42	38	
Molecular subtype*			0.642			0.035			0.680			0.060			0.153
Luminal	68	130		102	96		78	120		169	29		96	102	
Luminal/ HER2	28	65		64	29		34	59		83	10		39	54	
HER2	34	89		64	59		49	74		97	26		70	53	
TNBC	25	54		45	34		36	43		72	7		42	37	

TC = total cholesterol; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LP-α = lipoprotein-α; BMI = body mass index; HER2 = human epidermal growth factor 2; TNBC = triple negative breast cancer.
*Luminal: HR+/HER2−, luminal/HER2: HR+/HER2+, HER2: HR−/HER2+, TNBC: HR−/HER2−.

HDL-C, $p = 0.026$; TG, $p = 0.002$; and LDL-C, $p < 0.001$). Additionally, only TG was significantly associated with molecular subtype ($p = 0.035$). Regarding pretreatment tumor size, only HDL-C was significantly associated with tumor size ($p = 0.038$). There were no statistically significant associations between the subtypes of cancer and histological grade and lipids.

https://doi.org/10.4048/jbc.2020.23.e32

Assessment of the associations between serum lipid profiles and the treatment response to neoadjuvant chemotherapy

The ROC curves were used to identify the predictive value of serum lipids and LPs. The results of the overall ROC curve analysis suggested that the areas under the ROC curves (AUCs) of TC, TG, HDL-C, LDL-C, and LP-α were 0.536 (p = 0.186 [95% CI, 0.483–0.590]), 0.535 (p = 0.202 [95% CI, 0.480–0.591]), 0.533 (p = 0.237 [95% CI, 0.476–0.589]), 0.473 (p = 0.332 [95% CI, 0.420–0.527]), and 0.493 (p = 0.787 [95% CI, 0.439–0.546]), respectively (**Figure 1**), suggesting that neither serum lipids nor serum LPs could be used as predictors of the response to NAC. As shown in **Figure 2**, a subgroup analysis based on ER status showed that the AUCs of TG and HDL-C were 0.572 (p = 0.041 [95% CI, 0.502–0.614]) and 0.580 (p = 0.023 [95% CI, 0.509–0.650]), respectively, suggesting that TG and HDL-C levels at diagnosis might be used as predictors of the response to NAC in the ER-positive subgroup. Consistently, none of the serum lipid or LP levels in the ER-negative subgroup could be used for prediction. Moreover, in the ER-positive subgroup, 1.155 mmol/L and 1.305 mmol/L were the optimal cutoff values for pretreatment TG and HDL-C levels, respectively, for predicting the response to NAC. The positive predictive values of TG and HDL-C were 78.1% and 77.1%, respectively, and the negative predictive values of TG and HDL-C were 37.7% and 38.3%, respectively.

After NAC, serum lipid profiles were available in 372 of the included patients. As shown in **Supplementary Table 1**, TG and LDL-C levels significantly increased after NAC. On the contrary, the level of HDL-C decreased. Additionally, our analysis suggested that treatment response was associated with LDL-C level change during NAC in ER-positive breast cancer patients (**Supplementary Table 2**).

Evaluation of the predictive value of the pretreatment serum lipid profiles in the estrogen receptor-positive subgroup

The χ^2 test was used to assess the associations between clinicopathological parameters and the clinical response to NAC. Patients who were premenopausal (p = 0.022) and younger (< 55 years, p = 0.002) or with larger tumor sizes (> 4 cm, p = 0.023) had more favorable clinical responses compared to patients who were postmenopausal and older or with smaller tumor sizes. Additionally, low TG level (< 1.155 mmol/L) and high HDL-C level (≥ 1.305 mmol/L) also demonstrated positive associations with clinical response, while the clinical nodal status, HER2 status, Ki67 status, and BMI of the patients did not demonstrate a positive association (**Table 4**). According to a multivariate analysis, younger age (< 55 years, p = 0.002), larger tumor size (> 4 cm, p = 0.016), and high HDL-C level (≥ 1.305 mmol/L, p = 0.007) were independent predictive factors of the efficacy of NAC (**Table 5**).

DISCUSSION

NAC has been shown to be as efficacious as adjuvant chemotherapy [15], but the response to NAC varies. If patients achieve pCR after NAC, the long-term survival rates would be improved. However, a proportion of patients who are treated with NAC cannot benefit from NAC and are exposed to the toxicity of chemotherapeutic drugs [16]. Therefore, identifying the predictive biomarkers of the response to NAC in breast cancer has important clinical significance. Several studies have shown an association between obesity and the risk of breast cancer [4,5]. Furthermore, some studies have revealed that serum lipid and LP levels at diagnosis could be prognostic factors for breast cancer [11,17]. However, whether serum lipid and LP levels can be used as predictors of the response to NAC in breast cancer patients is still unknown.

https://doi.org/10.4048/jbc.2020.23.e32

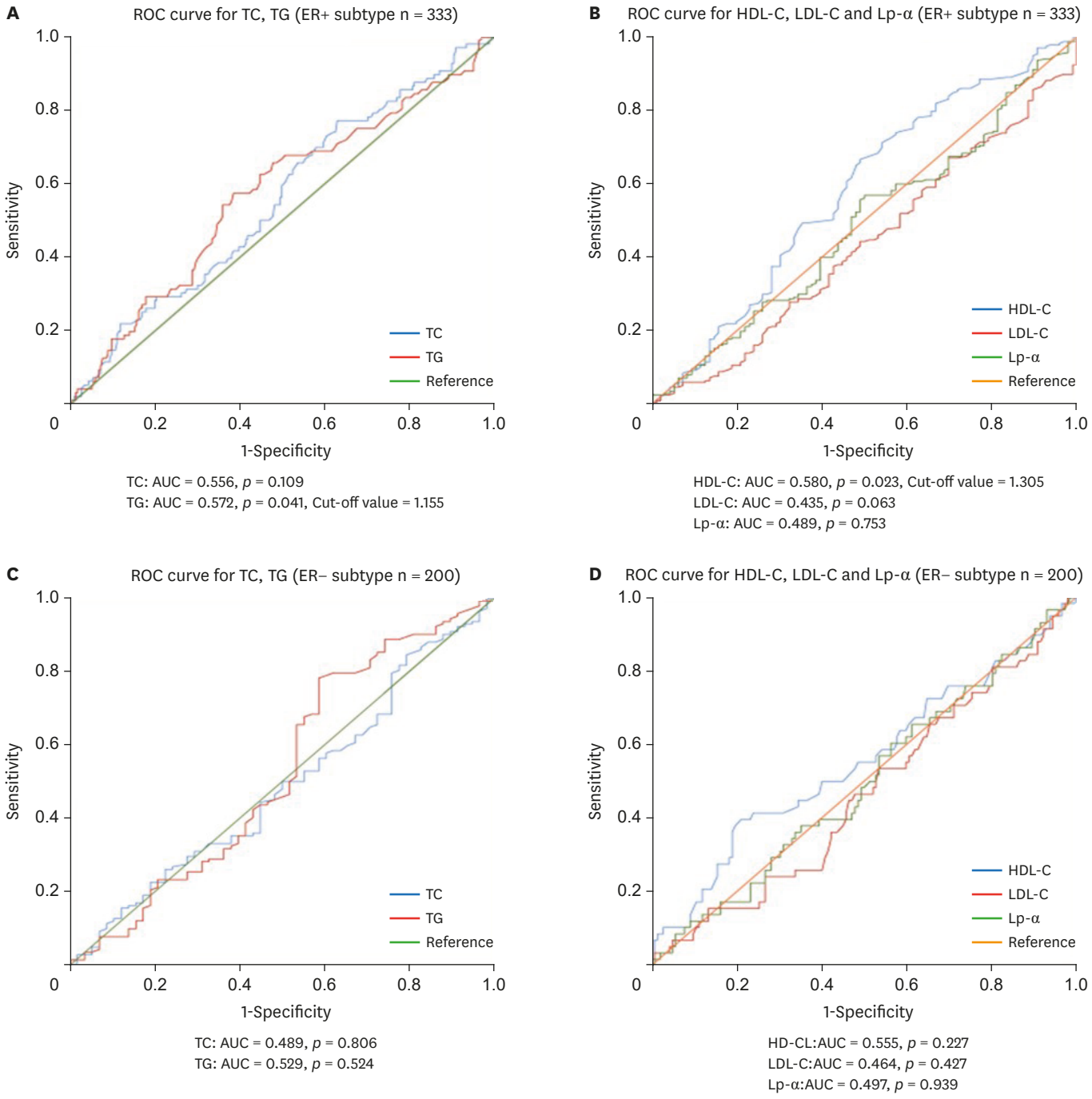

Figure 2. ROC curve analysis for the predictive role of serum lipid profiles between 2 different ER subtypes. (A) ROC curve for TC, TG (ER+ subtype n = 333). (B) ROC curve for HDL-C, LDL-C, and LP-α (ER+ subtype n = 333). (C) ROC curve for TC, TG (ER− subtype n = 200). (D) ROC curve for HDL-C, LDL-C, and LP-α (ER− subtype n = 200).
ROC = receiver operating characteristic; AUC = areas under the ROC curves; ER = estrogen receptor; TC = total cholesterol; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LP-α = lipoprotein-α.

Several previous studies have revealed significant dyslipidemia in breast cancer patients. A large-scale prospective study enrolled 1,189,719 Korean adults and revealed a positive association between cholesterol levels and increased breast cancer incidence [7]. In contrast, some other studies have shown an inverse association [8,9]. In the present study,

https://doi.org/10.4048/jbc.2020.23.e32

Table 4. Univariate analysis of baseline characteristics according to response to NAC (ER+ subgroup n = 333)

Characteristics	Clinical response		*p*-value
	cRes*	Non-cRes†	
Age (yr)			0.002
< 55.0	183	58	
≥ 55.0	54	38	
Menopause			0.022
Yes	77	44	
No	160	52	
Tumor size (cm)			0.023
< 2.0	16	12	
2.0–4.0	125	59	
> 4.0	96	25	
Clinical nodal status			0.650
Yes	125	48	
No	112	48	
HER2 status			0.715
Positive	77	28	
Negative	142	57	
Ki67 expression (%)			0.067
< 14	67	37	
≥ 14	170	59	
BMI (kg/m^2)			0.256
< 25.0	142	53	
≥ 25.0	74	37	
TG			0.002
< 1.155	146	41	
≥ 1.155	91	55	
HDL-C			0.003
< 1.305	79	49	
≥ 1.305	158	47	

NAC = neoadjuvant chemotherapy; ER = estrogen receptor; HER2 = human epidermal growth factor 2; BMI = body mass index; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol.
*cRes: pCR and PR; †Non-cRes: PD and SD.

Table 5. Multivariate analysis of baseline characteristics according to response to NAC (ER+ subgroup n = 333)

Characteristics	Clinical response		
	Hazard ratio	95% CI	*p*-value
Age	0.485	0.199–1.181	0.111
Menopause	0.965	0.412–2.262	0.918
Ki67 expression	0.717	0.424–1.212	0.214
Tumor size	0.508	0.292–0.882	0.016
TG	0.663	0.391–1.125	0.128
HDL-C	0.478	0.279–0.819	0.007

NAC = neoadjuvant chemotherapy; ER = estrogen receptor; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; CI = confidence interval.

we compared serum lipid and LP levels in the breast cancer and normal groups, and our data suggested that the mean TC, TG, HDL-C, and LDL-C levels in the breast cancer group were significantly lower than those in the normal group. These observations were consistent with the findings of some previous works [8,9]. The above inconsistent results may be associated with the differences in the age, ethnicity, and menstrual status of the subjects. Additionally, lower TC and LDL-C levels are commonly observed in other types of cancer, including hematopoietic, lung, prostate, and oral cancers [18-21]. The possible reason is that malignant tumors have protean physiological effects, which may include depression of the serum cholesterol level [22]. In several experimental studies, malignant cells were found to be able to consume HDL-C through scavenger receptor class B, type I [23]. This receptor could be partly responsible for the reduced HDL-C serum levels in cancer patients. Moreover, breast cancer cells have been shown

https://doi.org/10.4048/jbc.2020.23.e32

to have increased uptake of LDL-C through highly expressed LDL receptors [24]. The high expression of these receptors may affect LDL-C removal and result in decreased LDL-C serum levels in cancer patients. However, the underlying mechanisms for the declined TC and TG serum levels in breast cancer patients remain unclear.

In this study, we also assessed the associations between serum lipid profiles and breast cancer characteristics, and our data showed that the TG level was significantly associated with the molecular subtype ($p = 0.035$). Among the other molecular subtypes, the luminal subtypes accounted for the highest proportion among high TG level patients (≥ 1.205 mmol/L), which was consistent with the results of Hilvo's study [3]. This association may be attributed to an increased level of circulating estradiol and a reduced level of sex hormone-binding globulin by the conversion of androgens to estrogen in the adipose tissue [25].

Our further analysis focused on evaluating the predictive value of serum lipids and LPs for the response to NAC in different ER subtypes. According to our results, TG and HDL-C could be used as predictors of the response to NAC only in ER-positive subtype breast cancer. With ROC curves, we identified 1.155 mmol/L and 1.305 mmol/L as the best cutoff values for the pretreatment TG and HDL-C levels, respectively. These values are all within the normal ranges. Furthermore, the results of the univariate analyses also showed that both low TG level (< 1.155 mmol/L) and high HDL-C level (≥ 1.305 mmol/L) demonstrated positive associations with response in the ER-positive subgroup, as expected. A high HDL-C level (≥ 1.305 mmol/L, $p = 0.007$ [95% CI, 0.279–0.819]) was identified as an independent predictor of the efficacy of NAC by multivariate analyses. Since the AUC of HDL-C was 0.580 (less than 0.6), this result needs further studies to confirm. However, these indicators were not predictive of the response to NAC in the ER-negative breast cancer subgroup. Another finding was that the change of LDL-C level was associated with treatment response only in the ER-positive subgroup. The possible causes of the differences between the ER-positive and ER-negative subgroup are tumor heterogeneity and different signaling pathways caused by chemotherapy. These findings are consistent with our previous results that serum lipid levels were significantly associated with the luminal subtypes. To the best of our knowledge, this is the first systematic study to assess the association between obesity and its associated metabolism and NAC. Our results demonstrated that HDL-C but not BMI can be used as a predictor of NAC. High HDL-C levels at baseline improve the therapeutic effect of NAC by increasing the production of anti-inflammatory cytokines, which prevents oxidative membrane damage and affects androgen, estrogen, insulin, and insulin-like growth factor-1 levels [9,26].

Chemotherapy is considered to be one of the causes of endocrine and metabolic functional changes in cancer survivors, which may be associated with the development of metabolic syndrome [27]. Our analysis showed significant changes in TG, LDL-C, and HDL-C levels after NAC. Previous studies of the alterations in serum lipid and LP levels in cancer patients undergoing chemotherapy have reported inconsistent magnitudes and directions [10,28,29]. An experimental study found that these different alterations may be due to different chemotherapeutic agents having varied effects on lipid metabolism genes [30].

The main limitation of our study was that our data were collected from a retrospective study in a single center and lacked valid external validation. Additionally, HER2-positive patients had not received targeted therapy due to financial issues. Our analysis of the association between HER2 status and NAC response might be affected. Consequently, further prospective studies are required.

https://doi.org/10.4048/jbc.2020.23.e32

In conclusion, this study suggested that breast cancer patients have lower TC, TG, HDL-C, and LDL-C levels than normal subjects and that the luminal subtypes accounted for the highest proportion among patients with high TG levels. Further, TG, LDL-C, and HDL-C levels in breast cancer patients could be affected by NAC. Moreover, high HDL-C level (≥ 1.305 mmol/L) before NAC and increased LDL-C level after NAC were associated with the better treatment response in ER-positive breast cancer patients. Therefore, the monitoring and regulation of serum lipid profiles are significantly important for breast cancer patients receiving NAC.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Comparison of status of serum lipid profiles pre and post NAC

Click here to view

Supplementary Table 2

Changes* in lipid profiles between pre and post NAC according to patient outcomes between 2 different ER subtypes (n = 371)

Click here to view

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7-30.
PUBMED | CROSSREF
2. Kaufmann M, von Minckwitz G, Mamounas EP, Cameron D, Carey LA, Cristofanilli M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012;19:1508-16.
PUBMED | CROSSREF
3. Hilvo M, Gade S, Hyötyläinen T, Nekljudova V, Seppänen-Laakso T, Sysi-Aho M, et al. Monounsaturated fatty acids in serum triacylglycerols are associated with response to neoadjuvant chemotherapy in breast cancer patients. Int J Cancer 2014;134:1725-33.
PUBMED | CROSSREF
4. Picon-Ruiz M, Morata-Tarifa C, Valle-Goffin JJ, Friedman ER, Slingerland JM. Obesity and adverse breast cancer risk and outcome: mechanistic insights and strategies for intervention. CA Cancer J Clin 2017;67:378-97.
PUBMED | CROSSREF
5. Neuhouser ML, Aragaki AK, Prentice RL, Manson JE, Chlebowski R, Carty CL, et al. Overweight, obesity, and postmenopausal invasive breast cancer risk: a secondary analysis of the women's health initiative randomized clinical trials. JAMA Oncol 2015;1:611-21.
PUBMED | CROSSREF
6. Zhao Y, Wang H, Pan YY, Li N, Bian C. Association of lipid profile levels in premenopausal and postmenopausal women with breast cancer: a meta-analysis. Int J Clin Exp Med 2016;9:552-63.
7. Kitahara CM, Berrington de González A, Freedman ND, Huxley R, Mok Y, Jee SH, et al. Total cholesterol and cancer risk in a large prospective study in Korea. J Clin Oncol 2011;29:1592-8.
PUBMED | CROSSREF
8. Kucharska-Newton AM, Rosamond WD, Mink PJ, Alberg AJ, Shahar E, Folsom AR. HDL-cholesterol and incidence of breast cancer in the ARIC cohort study. Ann Epidemiol 2008;18:671-7.
PUBMED | CROSSREF
9. Kim Y, Park SK, Han W, Kim DH, Hong YC, Ha EH, et al. Serum high-density lipoprotein cholesterol and breast cancer risk by menopausal status, body mass index, and hormonal receptor in Korea. Cancer Epidemiol Biomarkers Prev 2009;18:508-15.
PUBMED | CROSSREF

10. Li X, Liu ZL, Wu YT, Wu H, Dai W, Arshad B, et al. Status of lipid and lipoprotein in female breast cancer patients at initial diagnosis and during chemotherapy. Lipids Health Dis 2018;17:91.
PUBMED | CROSSREF
11. Rodrigues Dos Santos C, Fonseca I, Dias S, Mendes de Almeida JC. Plasma level of LDL-cholesterol at diagnosis is a predictor factor of breast tumor progression. BMC Cancer 2014;14:132.
PUBMED | CROSSREF
12. Wolff AC, Hammond ME, Allison KH, Harvey BE, Mangu PB, Bartlett JM, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. J Clin Oncol 2018;36:2105-22.
PUBMED | CROSSREF
13. Dowsett M, Nielsen TO, A'Hern R, Bartlett J, Coombes RC, Cuzick J, et al. Assessment of Ki67 in breast cancer: recommendations from the international Ki67 in breast cancer working group. J Natl Cancer Inst 2011;103:1656-64.
PUBMED | CROSSREF
14. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
PUBMED | CROSSREF
15. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004;351:2817-26.
PUBMED | CROSSREF
16. Wei S, Liu L, Zhang J, Bowers J, Gowda GA, Seeger H, et al. Metabolomics approach for predicting response to neoadjuvant chemotherapy for breast cancer. Mol Oncol 2013;7:297-307.
PUBMED | CROSSREF
17. Li X, Tang H, Wang J, Xie X, Liu P, Kong Y, et al. The effect of preoperative serum triglycerides and high-density lipoprotein-cholesterol levels on the prognosis of breast cancer. Breast 2017;32:1-6.
PUBMED | CROSSREF
18. Lohe VK, Degwekar SS, Bhowate RR, Kadu RP, Dangore SB. Evaluation of correlation of serum lipid profile in patients with oral cancer and precancer and its association with tobacco abuse. J Oral Pathol Med 2010;39:141-8.
PUBMED | CROSSREF
19. Baroni S, Scribano D, Zuppi C, Pagano L, Leone G, Giardina B. Prognostic relevance of lipoprotein cholesterol levels in acute lymphocytic and nonlymphocytic leukemia. Acta Haematol 1996;96:24-8.
PUBMED | CROSSREF
20. Siemianowicz K, Gminski J, Stajszczyk M, Wojakowski W, Goss M, Machalski M, et al. Serum total cholesterol and triglycerides levels in patients with lung cancer. Int J Mol Med 2000;5:201-5.
PUBMED | CROSSREF
21. Henriksson P, Eriksson M, Ericsson S, Rudling M, Stege R, Berglund L, et al. Hypocholesterolaemia and increased elimination of low-density lipoproteins in metastatic cancer of the prostate. Lancet 1989;2:1178-80.
PUBMED | CROSSREF
22. Schatzkin A, Hoover RN, Taylor PR, Ziegler RG, Carter CL, Albanes D, et al. Site-specific analysis of total serum cholesterol and incident cancer in the national health and nutrition examination survey I epidemiologic follow-up study. Cancer Res 1988;48:452-8.
PUBMED
23. Danilo C, Gutierrez-Pajares JL, Mainieri MA, Mercier I, Lisanti MP, Frank PG. Scavenger receptor class B type I regulates cellular cholesterol metabolism and cell signaling associated with breast cancer development. Breast Cancer Res 2013;15:R87.
PUBMED | CROSSREF
24. Pires LA, Hegg R, Freitas FR, Tavares ER, Almeida CP, Baracat EC, et al. Effect of neoadjuvant chemotherapy on low-density lipoprotein (LDL) receptor and LDL receptor-related protein 1 (LRP-1) receptor in locally advanced breast cancer. Braz J Med Biol Res 2012;45:557-64.
PUBMED | CROSSREF
25. Renehan AG, Roberts DL, Dive C. Obesity and cancer: pathophysiological and biological mechanisms. Arch Physiol Biochem 2008;114:71-83.
PUBMED | CROSSREF
26. Furberg AS, Veierød MB, Wilsgaard T, Bernstein L, Thune I. Serum high-density lipoprotein cholesterol, metabolic profile, and breast cancer risk. J Natl Cancer Inst 2004;96:1152-60.
PUBMED | CROSSREF
27. de Haas EC, Oosting SF, Lefrandt JD, Wolffenbuttel BH, Sleijfer DT, Gietema JA. The metabolic syndrome in cancer survivors. Lancet Oncol 2010;11:193-203.
PUBMED | CROSSREF

28. Alexopoulos CG, Pournaras S, Vaslamatzis M, Avgerinos A, Raptis S. Changes in serum lipids and lipoproteins in cancer patients during chemotherapy. Cancer Chemother Pharmacol 1992;30:412-6.
PUBMED | CROSSREF

29. Raghavan D, Cox K, Childs A, Grygiel J, Sullivan D. Hypercholesterolemia after chemotherapy for testis cancer. J Clin Oncol 1992;10:1386-9.
PUBMED | CROSSREF

30. Sharma M, Tuaine J, McLaren B, Waters DL, Black K, Jones LM, et al. Chemotherapy agents alter plasma lipids in breast cancer patients and show differential effects on lipid metabolism genes in liver cells. PLoS One 2016;11:e0148049.
PUBMED | CROSSREF