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

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

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.
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) $\geq 30.0 \text{kg/m}^2$ [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.
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/m²) and obese (BMI, ≥ 30.0 kg/m²), 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
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, $p < 0.001$;
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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/m²)     | 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) < 4.075 | TC (n = 533) ≥ 4.075 | p-value | TG (n = 533) < 1.205 | TG (n = 533) ≥ 1.205 | p-value | HDL-C (n = 533) < 1.305 | HDL-C (n = 533) ≥ 1.305 | p-value | LDL-C (n = 533) < 3.695 | LDL-C (n = 533) ≥ 3.695 | p-value | LP-α (n = 533) < 95.750 | LP-α (n = 533) ≥ 95.750 | p-value |
|-----------------|-----------------------|-----------------------|---------|-----------------------|-----------------------|---------|--------------------------|--------------------------|---------|--------------------------|--------------------------|---------|--------------------------|--------------------------|---------|
| Age (yr)        | 0.001                 | 0.003                 | 0.260   | 0.001                 | 0.002                 | 0.005   | 0.373                    |                          |         |                          |                          |         |
| Menopause       | 0.001                 | 0.002                 | 0.001   | 0.001                 | 0.010                 | 0.001   | 0.001                    |                          |         |                          |                          |         |
| BMI (kg/m²)     | 0.170                 | 0.078                 | 0.250   | 0.088                 | 0.001                 | 0.001   | 0.001                    |                          |         |                          |                          |         |
| Subtypes of cancer | 0.847             | 0.495                 | 0.376   | 0.222                 |                       |         |                          |                          |         |                          |                          |         |
| Ductal          | 0.199                 | 0.437                 | 0.038   | 0.769                 | 0.848                 |         |                          |                          |         |                          |                          |         |
| Lobular         | 0.001                 |                       |         | 0.001                 | 0.001                 | 0.001   | 0.001                    |                          |         |                          |                          |         |
| Others          | 0.001                 | 0.001                 | 0.001   | 0.001                 | 0.001                 | 0.001   | 0.001                    |                          |         |                          |                          |         |
| Tumor size (cm) | 0.001                 | 0.001                 | 0.001   | 0.001                 | 0.001                 | 0.001   | 0.001                    |                          |         |                          |                          |         |
| Histological grade | 0.449              | 0.730                 | 0.598   | 0.522                 | 0.642                 |         |                          |                          |         |                          |                          |         |
| I               | 0.001                 | 0.001                 | 0.001   | 0.001                 | 0.001                 | 0.001   | 0.001                    |                          |         |                          |                          |         |
| II              | 0.001                 | 0.001                 | 0.001   | 0.001                 | 0.001                 | 0.001   | 0.001                    |                          |         |                          |                          |         |
| III             | 0.001                 | 0.001                 | 0.001   | 0.001                 | 0.001                 | 0.001   | 0.001                    |                          |         |                          |                          |         |
| Molecular subtype* | 0.642              | 0.035                 | 0.680   | 0.060                 | 0.153                 |         |                          |                          |         |                          |                          |         |
| Luminal         | 0.001                 | 0.001                 | 0.001   | 0.001                 | 0.001                 | 0.001   | 0.001                    |                          |         |                          |                          |         |
| Luminal/ HER2   | 0.001                 | 0.001                 | 0.001   | 0.001                 | 0.001                 | 0.001   | 0.001                    |                          |         |                          |                          |         |
| HER2            | 0.001                 | 0.001                 | 0.001   | 0.001                 | 0.001                 | 0.001   | 0.001                    |                          |         |                          |                          |         |
| TNBC            | 0.001                 | 0.001                 | 0.001   | 0.001                 | 0.001                 | 0.001   | 0.001                    |                          |         |                          |                          |         |

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.
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 χ² 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.
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,
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

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)                 |                   |         |
| < 55.0                   | 183               | 58      |
| ≥ 55.0                   | 54                | 38      |
| Menopause                |                   |         |
| Yes                      | 77                | 44      |
| No                       | 160               | 52      |
| Tumor size (cm)          |                   |         |
| < 2.0                    | 16                | 12      |
| 2.0–4.0                  | 125               | 59      |
| > 4.0                    | 96                | 25      |
| Clinical nodal status    |                   |         |
| Yes                      | 125               | 48      |
| No                       | 112               | 48      |
| HER2 status              |                   |         |
| Positive                 | 77                | 28      |
| Negative                 | 142               | 57      |
| Ki67 expression (%)      |                   |         |
| < 14                     | 67                | 37      |
| ≥ 14                     | 170               | 59      |
| BMI (kg/m²)              |                   |         |
| < 25.0                   | 142               | 53      |
| ≥ 25.0                   | 74                | 37      |
| TG                       |                   |         |
| < 1.155                  | 146               | 41      |
| ≥ 1.155                  | 91                | 55      |
| HDL-C                    |                   |         |
| < 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        | 0.299–0.882 | 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.
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 \( (\geq 1.205 \text{ mmol/L}) \), 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 \( (< 1.155 \text{ mmol/L}) \) and high HDL-C level \( (\geq 1.305 \text{ mmol/L}) \) demonstrated positive associations with response in the ER-positive subgroup, as expected. A high HDL-C level \( (\geq 1.305 \text{ mmol/L}, \ p = 0.007 \ [95\% \ CI, 0.279–0.819]) \) 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-I 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.
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

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

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