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LDL-c as a predictor of hormonal status and determining factor for therapy of breast cancer patients

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Abstract

Background: Immunohistochemical testing is important in determining clinical diagnosis and therapy, and is useful as a prognostic and predictive factor, but it is not easy to do and is not always available. Breast cancer patient with higher low-density-lipoprotein cholesterol [LDL-c]. level tends to have larger tumor size, higher grade, higher proliferation rate, positive Human Epidermal growth factor Receptor-2 (HER2-neu) and occasionally come at late stage. High LDL-c receptors are found on the surface of breast cancer cells, where cancer cells will take up cholesterol in serum, and a metabolite of 27-hydroxycholesterol cholesterol will affect Estrogen Receptor-α.

Methods: Analytical observational study by cross sectional method, during July 2020 – November 2020, at Oncology Clinic Dr. Soetomo Hospital Surabaya with a total sample size of 42. The data obtained were analyzed using the SPSS version 23.0 program, regression test and Chi-Square were performed for characteristic analysis and Chi-Square Fischer's Exact Test were performed for correlation test between lipid profiles with hormonal status.

Results: The mean value of LDL-c was 117.88 ± 33.89 mg/dL. In the analysis of the correlation between LDL-c and hormonal status, it was found that the majority of patients who had positive hormonal status had LDL-c levels of ≤160 mg/dL with p value = 0.049. ROC analysis shown LDL-c cut-off point of 132 mg/dL, p value = 0.034 (OR 5.031, 95% CI 1.159-21.848), sensitivity 46.7% and specificity 83.35%.

Conclusion: There is a statistically significant relationship between LDL-c levels and hormonal status with the cut-off point of 132 mg/dL. The increase in LDL-c in serum increases the tendency of negative hormonal status, therefore LDL-c levels can be considerate in determining the therapy for breast cancer patients.

Keywords: LDL-c; Hormonal status; Immunohistochemistry; Breast cancer

1. Introduction

Breast cancer has 4 clinical subtypes based on the molecular subtypes, which are luminal A, luminal B, HER2 and basal type [1]. Classifying tumor according to its histopathology, stage and molecular subtype using immunohistochemical evaluation is important in determining the correct corresponding diagnosis and therapy and is also useful to be utilized as a prognostic and predictive factor [2,3]. Patients with positive hormonal receptor status examinations (estrogen and progesterone receptors) will get advantage from hormonal therapy [4,5]. Unfortunately, immunohistochemical testing to determine the molecular subtypes of breast cancer is generally not easy to do and is not always available in all health care centers [6]. A study on 1779 subjects in 2016 found that women with obesity, metabolic syndrome,

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hyperinsulinemia, or insulin resistance were at greater risk of developing breast cancer [7]. Patients with obesity tend to experience metabolic syndromes such as glucose intolerance, lower high-density-lipoprotein cholesterol [HDL-c]., higher LDL-c, high triglyceride levels, and hypertension [8]. Breast cancer patients with high LDL-c levels tend to have the characteristics of having a larger tumor size, a higher degree of cancer cell differentiation, a higher proliferation rate, positive HER2-neu status and is often found at an advanced stage [9]. High LDL-c receptors are found on the surface of breast cancer cells, where cancer cells will take up cholesterol in serum, and 27-hydroxycholesterol cholesterol metabolites will affect ER-α, Liver X Receptor, PI3K/AKT, Plasminogen Activator Inhibitor-1 thus stimulating cell proliferation, epithelial-mesenchymal transition, angiogenesis and invasion, migration and metastasis of breast cancer cells [9,10]. In *in-vitro* studies, LDL-c was found to influence the proliferation of cancer cells with negative Estrogen Receptors [ER]. [11]. A nested case-control study with 287 samples between 1994 and 1998, found that 27 hydroxycholesterol [27-HC]. levels were associated with the ER-β marker in breast cancer and 27-HC levels associated with circulating cholesterol levels. However, from previous epidemiological studies, found there was no association between cholesterol levels and breast cancer risk [12,13]. In vitro research in 2017, found an effect of 27-HC in upregulating the ER-β receptors on prostate cancer cells, but similar results were not found on the ER-α receptors on breast cancer cells. The presence of receptor upregulation increases the effect of 27-HC on modulation of estrogen receptors [14]. LDL-c examination is an easy and inexpensive clinical laboratory examination, and is available in almost all health care centers with clinical laboratories. Examination the correlation of LDL-c levels to the hormonal status of breast cancer patients is an important step in the evaluation to further determine the useful aspects of the LDL-c test in determining the hormonal status of breast cancer patients.

2. Material and methods

This cross-sectional analytic observational study altogether with the samples used for this study were all obtained from breast cancer patients at the Oncology Clinic of Dr. Soetomo Public Hospital, Surabaya during July 2020 - November 2020. Patients with a diagnosis of breast cancer who had not undergone breast surgery, had undergone a mastectomy or breast tumor biopsy in less than 1 month, and had never received prior chemotherapy to being included in the study. Patients using lipid lowering agent therapy, undergoing herbal treatment to reduce cholesterols levels, experienced recurrence, and with histopathological results other than breast carcinoma, such as sarcomas, phyllodes and lymphoma in the breast were excluded from the study. The lipid panel was examined using direct colorimetric method with Siemens Dimension EXL-200 and the results were triglycerides, total cholesterol, HDL-c and LDL-c. The lipid panel data were stratified with a limit of 200 mg/dL for total cholesterol and triglycerides, 40 mg/dL for HDL-c and 160 mg/dL for LDL-c. Hormonal status was determined from immunohistochemical examination with interpretation according to the Allred scoring system. The data obtained were analyzed with the SPSS version 23.0 program. Data regarding the hormonal status in each sample will be grouped based on age, obesity status and histopathological type, then regression and Chi-Square tests are carried out. Data regarding total cholesterol, triglycerides, HDL-c, LDL-c/HDL-c ratio and LDL-c to hormonal status will be analyzed using the *Chi-Square – Fischer's Exact* test.

3. Results

The study was conducted for 5 months starting from July 2020 to November 2020, with 42 subjects being eligible and included in the study. The study subjects consisted of 42 women (100%) whose patient characteristics are being described in the Table 1.

The research subjects consisted of 42 women (100%) with the most age being 35-50 years, 26 patients (61.9%) followed by 13 patients (31%) aged > 50 years and 3 patients < 35 years old (7.1%). Based on the type of anatomical pathology, the most common was ductal carcinoma, namely 29 patients (69%) followed by other types of carcinoma as many as 9 patients (21.4%) and lobular carcinoma by 4 patients (9.5%). Based on the characteristics of Body Mass Index [BMI]. the most were found in normal conditions, namely 29 patients (69%) followed by overweight as many as 9 patients (21.4%) and 4 patients (9.5%) who were obese. The research subjects who are under 35 years of age with negative hormonal status consisted of 1 subject and 2 subjects with positive hormonal status. Subjects who are between 35-50 years old with negative hormonal status consisted of 8 subjects and who are the hormonal status positive consisted of 18 subjects. In addition, subjects who are more than 50 years old with negative hormonal status consisted of 6 subjects and positive hormonal status consisted of 7 subjects. Subjects with the result of ductal carcinoma in anatomical pathology examination with negative hormonal status consisted of 11 subjects and 18 subjects with positive hormonal status. Lobular carcinoma with negative hormonal status consisted of 1 subject and 3 subjects with positive hormonal status. The data showed subjects with normal BMI and negative hormonal status consisted of 8 subjects and 21 subjects with positive hormonal status. The subject who are the BMI overweight and negative hormonal status

consisted of 5 subjects and 4 subjects with positive hormonal status. Subjects who are BMI obesity with negative hormonal status consisted of 2 subjects and with positive hormonal status consisted of 2 subjects.

Table 1 Characteristics of Age, Results of Anatomical Pathology, and BMI of Research Subjects

Subject Characteristics		**Negative Hormonal Status**	**Positive Hormonal Status**	**Total**	**P value**	**OR (95% CI)**
Age	< 35 years old	1	2	3	0.637	NA
		6.7%	7.4%	7.1%		
	35-50 years old	8	18	26		
		53.3%	66.7%	61.9%		
	>50 years old	6	7	13		
		40%	25.9%	31.0%		
Results of Anatomical Pathology	Ductal carcinoma	11	18	29	0.867	NA
		73.3%	66.7%	69.0%		
	Lobular carcinoma	1	3	4		
		6.7%	11.1%	9.5%		
	Other type carcinoma	3	6	9		
		20%	22.2%	21.4%		
BMI	Normal	8	21	29	0.255	NA
		53.3%	77.8%	69.0%		
	Overweight	5	4	9		
		33.3%	14.8%	21.4%		
	Obesity	2	2	4		
		13.3%	7.4%	9.5%		

Based on the characteristics of the serum lipid profile, normal HDL-c levels were 37 patients (88.1%), normal triglyceride levels were 39 patients (92.0%), normal total cholesterol levels were 30 patients (71.4%), and LDL-c/HDL-c ratio > 2,426 as many as 23 patients (54.8%).

In the analysis of the relationship between total cholesterol and hormonal status, it was found that the majority of patients with positive hormonal status had total cholesterol levels ≤200 mg/dL) with p value = 0.292 (OR 2.333; 95% CI 0.590-9.227). In the analysis of the relationship between triglycerides and hormonal status, it was found that the majority of patients who had positive hormonal status had triglyceride levels ≤200 mg/dL with p value = 0.541. In the analysis of the correlation between HDL-c and hormonal status, it was found that the majority of patients with positive hormonal status had HDL-c levels > 40 mg/dL with p value = 0.142. In the analysis of the correlation between the LDL-c/HDL-c ratio with hormonal status, it was found that the majority of patients with positive hormonal status had a LDL-c/HDL-c ratio ≤ 2.426 with p value = 0.337 (OR 2.154; CI 95% 0.580-8,001). The mean value of LDL-c was 117.88 ± 33.89 mg/dL, with a maximum value of 229 mg/dL and a minimum of 64 mg/dL. Most of the patients had positive hormonal status, as many as 27 patients (64.28%). The correlation between cholesterol levels and hormonal status of breast cancer patients was tested using the chi-square test (Table 2), it was found that there was a significant correlation between cholesterol levels and hormonal status of breast cancer patients with p value = 0.049 (OR 5,333; CI 95% 1,095-25,985).

Table 2 Correlation between Lipid Panels on Hormonal Status

Subject Characteristics		Negative Hormonal Status	Positive Hormonal Status	Total	*P value*	*OR (95% CI)*
Total Cholesterol	≤200 mg/dL	9	21	30	0.292	2.333 (0.590-9.227)
		60.0%	77.8%	71.4%		
	>200 mg/dL	6	6	12		
		40.0%	22.2%	28.6%		
Triglycerides	≤200 mg/dL	15	24	39	0.541	NA
		100%	88.9%	92.9%		
	>200 mg/dL	0	3	3		
		0.0%	11.1%	7.1%		
HDL-c	>40 mg/dL	15	22	37	0.142	NA
		100%	81.5%	88.1%		
	≤ 40 mg/dL	0	5	5		
		0.0%	18.5%	11.9%		
LDL-c/HDL-c ratio	≤ 2.426	5	14	19	0.337	2.154 (0.580-8.001)
		33.3%	51.9%	45.2%		
	> 2.426	10	13	23		
		66.7%	48.1%	54.8%		
LDL-c	>160 mg/dL	6	3	9	0.049	5.333 (1.095-25.985)
		40.0%	11.2%	21.4%		
	≤ 160 mg/dL	9	24	33		
		60.0%	88.8%	78.6%		

Table 3 Correlation between LDL-c level at cut-off value and hormonal status

Subject		Negative Hormonal Status	Positive Hormonal Status	Total	*P value*	*OR (95% CI)*
LDL-c	≤132 mg/dL	8	23	31	0,034	5.031 (1.159-21.848)
		53.3%	85.2%	73.8%		
	>132 mg/dL	7	4	11		
		46.7%	14.8%	26.2%		
Total		15	27	42		
		100%	100%	100%		

From the results of the analysis on the ROC (Figure 1), the cut-off point of the LDL-c level was 132 mg/dL, where the LDL-c level of more than 132 mg/dL correlated with a tendency to negative hormonal status with p value = 0.034 (OR 5.031, 95% CI 1.159-21.848) and LDL-c levels > 132 mg / dL had a tendency to negative hormonal status by 5.031 times with a sensitivity of 46.7% and specificity of 83.35% (Table 3).

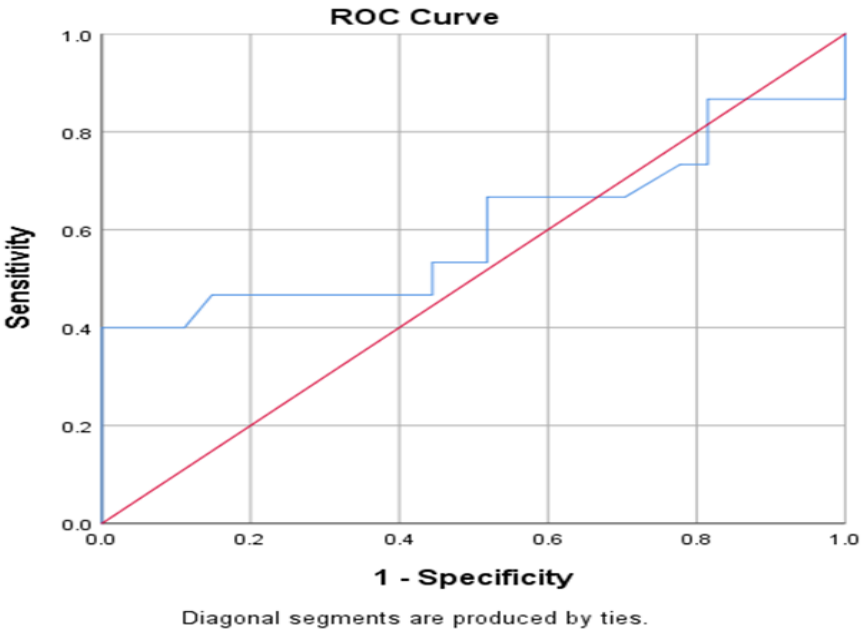

Figure 1 ROC analysis between LDL-c level and hormonal status

4. Discussion

The age range of our patients were between 35-50 years, where 26 patients (61.9%) were in that range. This is in accordance with previous studies where the age of most breast cancer is in the age range of 35-50 years. The most common histopathological finding in our study was ductal carcinoma, accounted for 69%, where 64.9% of the hormonal status was luminal type. The results of this study are consistent with the study conducted by Yue et al. (2016), where the tumour subtypes were mostly dominated by positive hormonal status (luminal type) [15]. Based on the BMI characteristics, 29 patients (69%) had normal BMI. There was no significant relationship between obesity and hormonal status. This result is different from the literature review which stated that obesity causes a tendency of breast cancer patients with negative hormonal receptors by 2.2-fold (95% CI 0.9-5.8) [16]. Other literature also stated that women who were overweight or obese (having body mass index of more than 25 kg/m^2 was associated with a greater risk for developing invasive breast cancer compared to women who were not overweight or obese. Interestingly, in this literature the risk of having invasive breast cancer was predominantly higher in a case with ER-positive [17]. Although the effects of obesity on breast cancer risk or prognosis are multifactorial, several mechanism have been proposed. This may be related with obesity-induced hyperinsulinemia, increased levels of insulin-like growth factors, adipokines, increased inflammatory immune cells, and increased inflammatory cytokines in all subtypes of breast cancer [18]. Nevertheless, in this study we found no significant correlation between obesity and the hormonal status of breast cancer. Some differences from several literatures and our findings can be caused by socio-geographical differences between the two studies, where this condition can affect differences in diet and daily activities. In addition, race differences between these two studies can also be a cause of these differences. Nonetheless, study by Law et al., also stated that the mechanism by which obesity affect breast cancer can happen in all subtypes of breast cancer not necessarily a determinant of hormonal status of breast cancer [18].

In term of total cholesterol levels, there was no statistically significant relationship between total cholesterol levels and hormonal status of breast cancer patients, p value = 0.292 (p> 0.05; OR 2.333; 95% CI 0.590-9.227). Total cholesterol produces a metabolite in the form of 27-HC. It is one of the most prevalent oxysterols, found to be an endogenous Selective Estrogen Receptor Modulator (SERM) and Liver X Receptor (LXR) antagonist [11]. 27-HC is mainly transported in esterified form where this metabolite acts as SERM in cancer cells which contribute to the development of breast cancer through a mechanism that promotes migration and invasion, through STAT-3/MMP9 and STAT-3/EMT, in both ER-positive and ER-negative breast cancer cells. 27-HC causes greater macrophage infiltration and exacerbation of inflammation in the regulation of hypercholesterolemia, thus providing a link between inflammation and cancer development [12,13].

In study conducted by Cedó et al. in 2019 stated that the first evidence for 27-HC's role in breast cancer began with the study that 27-HC played a role in stimulating the growth of cancer cell in ER-positive breast cancer cell and did not show a growth stimulation in ER-negative breast cancer cells. 27-HC also hasten the myeloid immune cell function. It increased the number of neutrophil but decreased the cytotoxic CD8+ T cells which responsible for controlling cancer cells. It was also stated that the discovery of 2-HC as an endogenous ER ligand which promotes the growth of ER-positive breast cancer could help explain why certain breast cancer patients with positive hormonal status are not responding well to aromatase inhibitors. In this case, 27-HC act as an alternate esterogenic ligand [11]. However, the correlation between total cholesterol as a precursor of 27-HC on hormonal status was not found in this study. The reason is probably due to the fact that in vitro findings may not represent the in vivo findings.

Beside total cholesterol, there was no correlation between triglyceride levels and hormonal status of breast cancer patients with p value = 0.541 (p> 0.05). Triglycerides are a form of blood cholesterol obtained from absorption of fat in the digestive tract. This form will still undergo further metabolism in the body to be able to affect cell metabolism. Triglycerides serve as an independent source for fatty acid oxidation, which is considered as an important process for cell proliferation and tumor growth. Triglycerides do not affect the development of hormonal status in breast cancer. This suggests that the dominant role in luminal type breast cancer is probably played by lipoproteins and not by triglycerides [19].

There was no relationship between HDL-c levels and hormonal status of patients, with a value of p value = 0.142 (p> 0.05). The results of this study are inconsistent with previous studies which showed that increased HDL-c increased the risk of positive Estrogen Receptor (ER) breast cancer [11].

HDL-c itself contains a single copy or multiple copies of apolipoprotein A-I, the most abundant HDL-c apolipoprotein. It plays role in promoting cholesterol release from cells. It possesses anti-inflammatory, antioxidant, and antiapoptotic properties. It also influences innate immunity [20]. In study conducted by Cedó et al., it was also stated the controversy in term of HDL-c levels and breast cancer risk. It was stated that in vitro analysis had shown that HDL stimulated proliferation in both ER-positive and ER-negative breast cancer. The controversy related with the role of HDL-c in hormonal breast cancer is that some studies stated that apoA-1 in HDL-c was inversely related with the development of breast cancer [21], but other study stated that it was positively associated with breast cancer [22]. It is important to note that clinical or methodological differences in study design, including variation in geographic area, menopausal status, number of cases, or length of follow-up, may explain the differences found in these studies.

There was no relationship between LDL-c/HDL-c ratio and hormonal status of breast cancer patients with a p value = 0.337 (p> 0.05; OR 2.154; 95% CI 0.580-8.001). This is consistent with a study by Furberg et al. (2005) where the LDL-c/HDL-c ratio is a strong predictor of estradiol concentration, so that this ratio is more sensitive as a marker of breast cancer risk rather than hormonal status in breast cancer, a LDL-c/HDL-c ratio ≥ 2.08 was found to be have more exposure to estradiol levels [8]. Circulating estradiol itself is thought to play a major role in the development of breast cancer not necessarily breast cancer in certain hormonal status. There is no significant correlation found in our study also provides an insight that LDL-c/HDL-c ratio is not a determinant for certain subtype of breast cancer.

The relationship between LDL-c levels and hormonal status of breast cancer patients was tested using the Chi-Square test, it was found that there was a significant relationship between LDL-c levels and hormonal status of breast cancer patients with p value = 0.049 (p <0.05; OR 5,333; 95% CI 1,095-25,985) which means that there is a statistically significant relationship between LDL-c levels and hormonal status, where LDL-c ≤ 160 mg/dL will tend to have a positive hormonal status of 5.333 times compared to high cholesterol. The results of this study are in accordance with research from Cedó et al (2019) where High LDL-c was found to influence proliferation in ER-negative cells [11]. Cancer cells that proliferate will experience an increased need for cholesterol. An increase need of cholesterol by breast cancer tissue is demonstrated by an increase in LDL-R expression [23]. LDL-c primarily promotes proliferation and migration in ER-negative cells, but this is not evident in ER-positive cell lines. This difference between the two cell types is related to the greater ability of ER-negative cells to take up, store, and utilize exogenous cholesterol due to increased acyl-CoA: cholesterol acyltransferase 1 (ACAT-1) activity. ER-negative breast cancer cells through different mechanisms take up and store cholesterol. This explains the effect of a low-fat diet on ER-negative breast cancer recurrence [9,11].

The increase in LDL-c in serum plays a role in increasing free cholesterol levels in the intracellular area and will result in the build-up of ester cholesterol. The accumulation of ester cholesterol will trigger an increase in LDL-R expression, which is found to be more dominant in breast cancer cells with negative hormonal status. The cholesterol metabolite, in the form of 27-HC, was proven *in-vitro* to not be able to show a modulation effect of ER-α on breast cancer cells. This also increases the tendency of negative hormonal status to high cholesterol levels.

Based on study conducted by Antalis et al. in 2009, it was found that ER negative breast cancer cells are able to take up higher LDL-c in greater extent. This ability is associated with higher activity levels of ACAT1, higher mRNA protein, higher protein levels of CAV1, and lower de novo cholesterol synthesis [24]. The greater capability of basal-like ER negative breast cancer cells to make and store lipid is known as "lipid accumulating phenotype". This phenotype may develop in precursor cancer cells as a result of mutation or as a result of tumor hypoxia. In this case, this ability may enable cells to take high free fatty acids and LDL-c. The reason behind the more prominent effect of ER-negative breast cancer cell to proliferate under LDL may also be bridged by ACAT1. It was found that the mRNA expression of ACAT1 is increased in ER-negative breast cancer cell. Inhibition of ACAT1 itself may reduce the proliferation of LDL induced proliferation [11].

Cholesteryl ester accumulation due to increased LDL-c internalization which also happens in ER-negative breast cancer cells is associated with breast cancer proliferation and patients with higher LDL-R expression is found to be associated with a worse prognosis especially in patient who undergo systemic therapy. Overall triple-negative breast cancer patients with higher circulating LDL-c and higher expression of LDL-R are at risk disease progression and disease-free survival [11].

In this study, a cut-off point was obtained from the correlation between cholesterol levels and the hormonal status of tumour cells at a value of 132 mg/dL, where cholesterol levels > 132 mg/dL had a tendency to negative hormonal status by 5.031 times with a sensitivity of 46.7% and specificity 83.35%. The results of this study indicate that LDL-c level can be used as a consideration in determining the therapy for breast cancer patients. In the conditions where immunohistochemistry testing is not readily available, LDL-c levels ≤132 mg/dL can suggest the need for hormonal therapy, while LDL levels > 132 mg/dL propose the need for lipid lowering therapy.

5. Conclusion

High LDL level is significantly correlated with negative hormonal status in breast cancer patients; however, HDL-c, total cholesterol level, triglyceride level and LDL-c/HDL-c ratio is not significantly correlated with hormonal status of breast cancer. A cut-off value of 132 mg/dL, LDL-c > 132 mg/dL shows a tendency of a breast cancer to possess negative hormonal status by 5.031 times.

Compliance with ethical standards

Author Contribution

Conception and design: All authors; Administrative support: Reynard Budy Setiawan; Provision of study materials or patients: All authors; Collection and assembly of data: Reynard Budy Setiawan; Data analysis and interpretation: All authors; Manuscript writing: All authors; Final approval of manuscript: All authors.

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Disclosure of conflict of interest

All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

Statement of ethical approval

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Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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