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The Relationship Between Fatty Acid Synthetase Level and Histopathological Grading in Breast Cancer Patients

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ABSTRACT

Introduction: Breast cancer is the most prevalent cancer among women and a major cause of cancer-related deaths in women globally. Fatty acid synthetase (FASN) is a crucial enzyme in neoplastic lipogenesis. Increased FASN levels are frequently observed in various breast cancers; this enzyme contributes to metabolic oncogenic processes that are vital for the growth and survival of tumor cells. This study aims to explore the correlation between FASN levels and histopathological grading in breast cancer patients in Makassar.
Methods: This retrospective cohort study included 62 of luminal subtype invasive breast cancer patients from March to May 2024 at Wahidin Sudirohusodo Hospital, Makassar. Data were collected from medical records, and examination FASN levels was carried out using the ELISA method at Clinical Pathology Laboratory Faculty of Medicine Hasanuddin University Hospital. Statistical analysis were performed Fisher Extract and Mann-Withney test. ROC (Receiver Operating Characteristics) Curve were performed for determine FASN cut-off levels.
Results: A total of 62 patients with breast carcinoma were included in the study. Generally, patients in the histopathological grading group of IDC presented a moderate differentiation. There were 18 cases high FASN level among the patients with high IDC histopathological grading. Conversely, 19 low FASN levels patients predominantly belonged to the well differentiation group (p value = 0.003). The degree of correlation between levels of FASN and the grading of this histopathological was 0.702 (CI95%: 0.56-0.83).
Conclusions: The FASN level increases in accordance with the increase in histopathological grading of IDC. In addition, there is a significant relationship between the increase in FASN level and the increase in histopathological grading of IDC. The FASN level can be one of the promising biomarkers with fairly high sensitivity and specificity.
Keywords: breast cancer, FASN, histopathological grading, biomarker

INTRODUCTION

Breast cancer is the most prevalent cancer among women and ranks as a primary cause of cancer-related fatalities in women globally (1). Based on morphology and clinical implications, breast cancer is divided into four subtypes distinguished as Luminal (Luminal A and Luminal B), HER-2, and Basal-like (2). Luminal subtype breast cancer is the most frequently occurring type,

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accounting for nearly 70% of all subtypes (3). Stage is one of the prognosis factors in breast cancer. When compared to advanced breast cancer, early stage breast cancer has a better prognosis, with a 5-year survival rate of 90%. This rate will drastically decrease to 20% when there has been spread to distant organs (4).

FASN (Fatty Acid Synthetase) is a key enzyme involved in neoplastic lipogenesis. Excessive levels of FASN are common in many breast cancers, this enzyme is involved in metabolic oncogene processes that have an important role in tumor cell growth and survival (5).

FASN levels are associated with decreased survival in patients with luminal subtype breast cancer (6). Menendez J, et al, found an association between breast cancer metastasis and the expression of the FASN enzyme, a metabolic oncogene that is thought to provide a proliferative and survival advantage for cancer cells (7). In addition to the primary tumor, FASN can also be found in the blood, making it useful for detecting circulating tumor cells (CTCs) in the peripheral blood of cancer patients (8). Therefore, FASN levels may be used as a predictive and prognostic biomarker in breast cancer metastasis. The aim of this study was to determine the relationship between FASN levels and histopathologic grading in breast cancer in Makassar, South Sulawesi, Indonesia.

MATERIALS AND METHODS

This study is an analytic observational study using a retrospective cohort research design. This study will evaluate the relationship between Fatty Acid Synthetase levels and histopathological grading in breast cancer patients. This study will be conducted in March-May 2024 at Dr. Wahidin Sudirohusodo Hospital. Inclusion criteria included women with breast cancer both non-metastatic and de novo metastasis, histopathologically diagnosed as invasive mammary carcinoma, with immunohistochemical examination showing luminal and non-luminal subtype breast cancer, women with breast cancer who had a body mass index of 18.5 - 24.9 kg/m^2. Meanwhile, the exclusion criteria included women with recurrent breast cancer, breast cancer patients accompanied by other malignancies, breast cancer patients who had undergone chemotherapy and or radiotherapy, breast cancer patients suffering from systemic diseases such as diabetes mellitus, hypertension and dyslipidemia. A total of 62 samples were collected that met the inclusion and exclusion criteria.

The type of data in this study is primary and secondary data collected from medical records of breast cancer patients, including and age, ICD histopathological grading, histopathology, FASN level, HER-2, Ki-67 and breast cancer subtype. The data were obtained through examination of tissue specimen by immunohistochemistry at the Department of Anatomical Pathology of Dr. Wahidin Sudirohusodo Hospital. Histopathology slides were used to determine the subtype of breast cancer and FASN levels. The results were presented in tables and narratives, with continuous data presented as frequencies for each category. Data were also analyzed using Fisher Exact and Mann-Whitney to explore correlations between FASN levels and various clinical characteristics. Receiver Operating Characteristics (ROC) curve analysis was carried out to determine the FASN cut-off.

RESULTS

In this study there were 6 characteristics of the research sample, namely age, histopathological grading, FASN levels, HER 2, Ki-67, and imunohistokimia, described in the form of percentage frequency for data in the form of categories. The following is a description of the characteristics of the research sample.

The distribution and characteristics of the research subjects can be seen in *table 1*. Based on the age group, the subjects in this study were divided into three age groups with an average age of 53.02 ± 9.14.

Table 1 - Sample characteristic

Variable	N	%
Age (years)	53.02 ± 9.14	
< 40	6	9.7
40-60	42	67.7
> 60	14	22.6
IDC histopathological grading		
Well differentiation	3	4.8
Moderate differentiation	36	58.1
Poor differentiation	23	37.1
FASN levels	1.21 ± 0.62	
Low (< 0.99)	27	43.6
High (> 0.99)	35	56.4
HER 2		
Positive	35	56.5
Negative	27	43.5
Ki-67		
Low	34	54.8
High	28	45.2
Immunohistochemistry		
Luminal A	20	32.2
Luminal B	8	13
Overexpression HER 2	24	38.7
TNBC	10	16.1

IDC: Invasive Ductal Carcinoma; FASN : Fatty Acid Synthetase; HER 2: Human Epidermal Growth Factor Receptor 2; TNBC: Triple Negative Breast Cancer

Subjects with age groups < 40 years were 6 subjects (9.7%), age groups 40-60 years were 42 subjects (67.7%) while subjects with age groups > 60 years were 14 subjects (22.6%). In terms of histopathological grading, the number of samples with well differentiation histopathological grading was 3 subjects (4.8%), moderate differentiation grading was 36 subjects (58.1%) and histopathological with poor differentiation was 23 subjects (37.1%).

Based on FASN level calculations, the range was 1.21 ± 0.62 and was divided into two groups. FASN levels below 0.99, with 27 subjects (43.55%), and FASN levels above 0.99, with 35 subjects (56.45%). Based on HER2 assessment, 35 subjects (56.5%) were HER2-positive and 27 subjects (43.5%) were HER2-negative. Based on Ki-67 values, 34 subjects (54.8%) had low Ki-67, while 28 subjects (45.2%) had high Ki-67. The most common immunohistochemistry type was HER2 overexpression, with 24 subjects (38.7%) testing positive. This was followed by luminal A, with 20 subjects (32.2%) testing positive. Triple-negative breast cancer (TNBC) accounted for 10 patients (16.1%), while luminal B accounted for 8 patients (13%).

Relationship between FASN Levels and Histopathological Grading

In this study, the relationship between FASN levels and histopathological grading was tested using linear regression (*fig. 1*). Based on *table 2*, it was found that the majority of research subjects who had high FASN levels were patients with IDC histopathological grading of poor differentiation (high grade) with a total of 18 subjects (29.3%) followed by moderate differentiation with a total of 17 subjects (27.4%). As for the low FASN levels, it was dominated by moderate IDC histopathological grading with a total sample of 19 subjects (30.6%), for the low FASN levels in poor differentiated IDC histopathological grading itself only ranged from 5 subjects (8%).

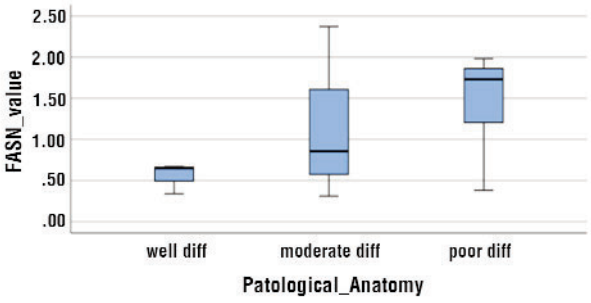

Figure 1 - Relationship between FASN levels and histopathological grading based on linear regression test.

Statistical Analysis

Based on the statistical test conducted, the p value is 0.003, so it can be concluded that there is a significant relationship between FASN levels and IDC histopathological grading in breast cancer patients. In the linear regression test conducted, a positive regression coefficient was also obtained so it can be concluded that the higher the FASN levels, the higher the histopathological grading obtained.

In this study, statistical tests based on Receiver Operating Characteristic (ROC) curves were also conducted to assess the sensitivity and specificity of FASN levels on histopathological grading of breast cancer patients. Based on *fig. 2*, it can be seen that the Area Under Curve (AUC) of FASN levels to histopathological grading is 0.702 (95% CI: 0.56-0.83). This value indicates that the FASN levels has a fairly high sensitivity and specificity in determining the histopathological grading of IDC.

Table 2 - Relationship between FASN levels and histopathologycal garding

Variable		FASN Levels		Total	R	p-value
		Low	High			
Histopathological grading	Well differentiation	3 4,8%	0 0%	3	0.41	0.003
	Moderare differentiation	19 30.6%	17 27.4%	36		
	Poor differentiation	5 8%	18 29.3%	23		
	Total	27	35	62		

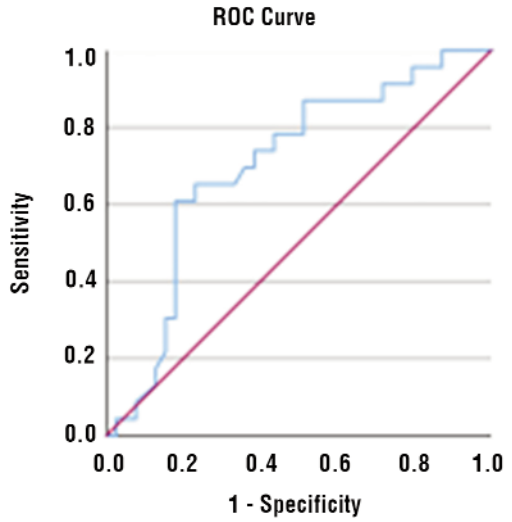

Figure 2 - ROC test of FASN levels to histopathological grading

DISCUSSION

Cancer accounts for approximately 13% of all deaths worldwide (9), with breast cancer being the most common type of cancer and the leading cause of female cancer-related deaths (10). Currently, metastasis and drug resistance are two major challenges in breast cancer management that are often associated with the metabolic activity of fatty acids. Fatty acid synthetase (FASN) is an enzyme involved in endogenous fatty acid synthesis. In tumor cells and pre-cancerous tissues, this endogenous fatty acid synthesis can serve as a source of fatty acids that can significantly trigger tumor cell proliferation (11). In several studies it has been presented that overexpression of FASN is associated with the development of several types of cancer cells such as breast, prostate, colon, ovarian, pancreatic cancer and others.

In this study, the ROC (Receiver Operating Characteristic) measurement was carried out to assess the level of sensitivity and specificity of the FASN level for histopathology grading of breast cancer patients, which obtained quite high sensitivity and specificity results.

From the results of this study, the value of FASN is up-regulated in accordance with the increase in histopathological grading, this is in accordance with studies on the role of FASN in tumor cell growth and development. FASN is a major enzyme in the fatty acid synthesis pathway that has two multifunctional polypeptide chains. FASN catalyzes basic compounds such as acetyl-CoA and malonyl-CoA to form saturated fatty acids. In tumor cells, the level of FASN will be maintained in low levels and controlled by hormonal and nutritional regulatory signals (12). In cancer cells that continue to proliferate, fatty acids will be synthesized de novo to provide adequate amounts of lipids that will be used in cell membrane biosynthesis to produce energy through β-oxidation. This de novo synthesis of fatty acids will trigger up-regulation and activation of the FASN enzyme (5,13).

In addition, increased expression of FASN may also inhibit apoptosis of cancer cells and potentially cause worsening in patients especially with metastatic lesions (10). Based on the increased overexpression of FASN enzyme found in many cancers, FASN inhibitors are currently one of the potential targets as biomarkers of cancer diagnostics and therapy (14,15).

CONCLUSIONS

In this study, it can be concluded that the FASN levels increases in accordance with the increase in IDC histopathological grading. In addition, there was a significant relationship between the increase in FASN levels and the increase in IDC histopathological grading. In this study, it is known that FASN levels can be one of the promising biomarkers in assessing histopathological grading with high sensitivity and specificity.

Author's Contributions

All authors contributed significantly to the study design, data collection, analysis, and manuscript writing. S, SAS, and SRL contributed to the study design and data collection. SAS, SRL, ES and NS guided the manuscript writing. S, H, and AJN were responsible for data analysis. All authors read and approved the final version of the manuscript.

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Conflict of Interest

Each authors declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrange-

ment etc.) that might pose a conflict of interest in connection with the submitted article.

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Ethical Approval

This research was approved by the Ethics Committee of Biomedical Research on Humans, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia. Based on recommendation letter Number: 109/UN4.6.4.5.31/PP36/2025 with protocol number: UH25010051. The study protocol ensured compliance with standard ethical declarations.

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