

Metabolic Profile and Negatively Association Between Insulin Resistance and Metastatic Incidence in Indonesian Primary Invasive Breast Cancer: A Cross-Sectional Study

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Introduction: Metastatic breast cancer was associated with high morbidity and mortality. Insulin resistance was hypothesized to be related to the incidence of advanced breast cancer. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and Triglyceride/Glucose Index (TyG Index) are two metrics used to measure the degree of insulin resistance. This study aims to assess the relationship between the incidence of metastatic breast cancer and insulin resistance as reflected by both metrics.

Material and Methods: This study is a cross-sectional study involving 150 primary invasive breast cancer patients recruited from two hospitals of different sectors from August 2019 to April 2020. Patients with double cancer and autoimmune disorder were excluded from this study. Data obtained from the patients include age, body mass index (BMI), type 2 diabetes mellitus (T2DM) status and treatment, and low-density lipoprotein (LDL) cholesterol. The electronic medical records (EMR) was consulted to find histopathology examination result, cancer staging, and any missing data. The association between HOMA-IR and TyG with metastatic incidence was analyzed using either the Mann-Whitney test (for non-normally distributed data) or the independent-sample *t*-test (for normally distributed data).

Results: The mean of the TyG index is 8.60, and the median of HOMA-IR is 1.22. We found no significant correlation between both variables and the incidence of metastases.

Conclusion: Insulin resistance was not associated with metastatic breast cancer.

Keywords: HOMA-IR, TyG index, breast cancer, metastases

Introduction

Female breast cancer has surpassed lung cancer as the most found cancer in the world, according to the GLOBOCAN 2020 study, contributing to 11.7% of all cancer cases.¹ It is the leading cause of cancer death in women. In Indonesia, breast cancer has been marked as the leading cancer diagnosis in women and the highest cause of cancer-related mortality in Indonesian women.

Based on data from GLOBOCAN 2020, breast cancer is the most common cancer in Indonesia (16.6%) and is the second highest contributor to all cancer-related mortality in Indonesia (9.6% of all cancer-related deaths).² Gondhowiardjo et al³ found that breast cancer is the second most common cancer according to data from the cancer registry of the Cipto Mangunkusumo Hospital, Indonesia's highest national central referral hospital. However, with the advancement of breast cancer therapeutics, survival rates of metastatic breast cancer have improved.⁴

Breast cancer has been associated with metabolic disturbances, of which insulin resistance is a highly noted aspect of this correlation.⁵ The pathophysiological basis of this relationship is still not fully understood. However, hyperinsulinemia has been thought of as the critical actor of this melodrama.⁶ Body mass index, an anthropometric indices associated

with insulin resistance, was observed to be positively correlated with the risk of breast cancer.^{7,8} In addition, Ariaans et al⁹ reported that breast cancer treatment might also contribute to the pathogenesis of insulin resistance. On the other hand, insulin resistance may negatively affect the prognosis of breast cancer.^{10,11} Thus, proper management of insulin resistance in breast cancer patients is crucial.

Several metrics have been proposed to measure the degree of insulin resistance. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) has been widely used in scientific research to determine the degree of insulin resistance in women with breast cancer. HOMA-IR is the most widely used metric to measure insulin resistance by incorporating fasting plasma glucose and insulin values.¹² An emerging metric is called the triglyceride/glucose index (TyG), which was found to be correlated with the risk and mortality of breast cancer.¹³ Existing evidence underlined the superiority of TyG in predicting metabolic syndrome and type 2 diabetes mellitus.^{14,15} A study conducted by Nam et al¹⁶ on Korean postmenopausal women reported a positive association between insulin resistance, assessed based on HOMA-IR, and the severity of breast cancer. Panigoro et al¹⁷ observed that the TyG index is related non-linearly to the risk of breast cancer.

This study aims to enrich the existing literature by assessing the burden of insulin resistance in patients with metastatic breast cancer, their interaction, and how both surrogate insulin resistance markers fared in predicting the dynamics of insulin resistance in metastatic breast cancer patients.

Materials and Methods

Study Design, Setting, and Participants

The study is an analytic cross-sectional study conducted in the Hematology-Medical Oncology clinic and outpatient chemotherapy clinic of Cipto Mangunkusumo Hospital, Jakarta, Indonesia, and the medical oncology clinic of Siloam-MRCCC Hospital, Jakarta, Indonesia. Patients were recruited consecutively using the consecutive non-probability sampling approach from August 2019 to March 2020 until the minimum sample amount needed for the study had been fulfilled. The inclusion criteria for the sample are as follows: 1) older than 18 years old, 2) histopathologically diagnosed with primary invasive breast cancer with available hormone receptor data, and 3) has not undergone any chemotherapy regimen within the last three weeks. All patients with current autoimmune or infectious disorders are excluded from this study. In addition, pregnant patients and patients currently consuming anti-retroviral or long-term steroid medications are excluded from the data analysis. After the included patients signed the informed consent form, anthropometrical data were collected using calibrated equipment during their clinic visits. Then, the patient was asked to fast for 8 hours, and their blood was collected at the Clinical Pathology Laboratory of Cipto Mangunkusumo Hospital, Jakarta, Indonesia. The blood was analyzed to obtain each study sample's fasting glucose and plasma insulin levels.

Quantitative Variables, Data Measurement, and Possible Bias

Metastasized breast cancer was defined as histopathologically confirmed stage IV primary invasive breast cancer. We adapted the internal breast cancer diagnostic guideline from Cipto Mangunkusumo Hospital as the diagnostic criteria used in this study. Insulin resistance was defined as the degree of increased insulin production needed to produce a normal biological response.^{16,18} It was assessed using the HOMA-IR and TyG index, and the result was categorized based on the cut-off points obtained from the receiver operating characteristic (ROC) curve. Age and body mass index (BMI) were obtained from physical examination during the patient's clinic visit. History of type 2 diabetes mellitus (T2DM) treatment and low-density lipoprotein (LDL) cholesterol levels were also obtained during the examination. Age data were categorized into two groups using 60 years old as the cut-off point. BMI data were categorized per World Health Organization's obesity measurement guideline into obese I (BMI 25–29.9 kg/m²), obese II (BMI >30 kg/m²), and non-obese (BMI <25 kg/m²).¹⁹ History of T2DM and the medications used for the treatment were obtained from the patient during their clinic visit. Low-density lipoprotein cholesterol levels of each patient were obtained using the blood collected from the patients, and the result was categorized into two groups, with 130 mg/dL used as the cut-off point.

The possible bias that may arise from this study includes sampling and publication bias. To minimize sampling bias so that our study populations may capture patients from various backgrounds and the study population characteristic may be more similar to the general Indonesian population, we recruited samples from two large hospitals with differing

patient demographics. Patients recruited from Cipto Mangunkusumo Hospital came from all over Indonesia, mainly treating patients from the lower-to-middle socioeconomic class. On the other hand, Siloam MRCCC hospital is a private flagship hospital of one of Indonesia's largest private hospital groups, thereby representing patients from the middle-to-higher socioeconomic class in Jakarta, the most populous province in Indonesia. To prevent publication bias, we also reported the non-significant result obtained from our analysis in our study.

Study Size and Statistical Analysis

The minimum sample needed for this study was estimated using the sample size equation for categorical predictive multivariate analysis.²⁰ Based on this equation, at least 160 study subjects are needed. Additional data was collected retrospectively from the included patients' electronic medical records (EMR). The data collected from each patient's EMR were age, histopathology result and interpretation, and cancer staging. If data were not obtained properly during the clinical examinations, the EMR would be checked to obtain any possible missing data. Statistical analysis was done using SPSS software, with the bivariate analysis done between variables. Data will be described in the mean if the distribution is normal, while the median will be used if the distribution is not normal.

Results

A total of 155 study samples were obtained during the recruitment period. After being screened for eligibility, three samples were excluded due to double cancer, and two were excluded because they were diagnosed with an autoimmune disorder. Thus, 150 patients were included in the study (Figure 1).

The mean age was 50 and they were premenopausal. The most common breast cancer molecular subtype among the sample is luminal type B, followed by luminal type A. Most patients were diagnosed with metastatic breast cancer. Among the included sample, 70% received hormonal therapy and 26% were still under active chemotherapy. The mean BMI was 23.9 kg/m², with most subjects categorized as non-obese. T2DM was found in 10% of the sample and had LDL cholesterol levels higher than 130 mg/dL. The median value of fasting plasma insulin is 5.6 µIU/mL. Since only the distribution of TyG is normal, we described the TyG using the mean and HOMA-IR using the median. The mean of TyG is 8.60, while the median value of HOMA-IR is 1.22, as can be seen in Table 1.

Bivariate analysis of HOMA-IR and TyG with the incidence of metastases test found no significant correlation between both variables. The difference in both indexes between metastases groupings was not significant (Table 2).

Subgroup analysis was done on postmenopausal subjects. From the analysis, we found no significant correlation between any confounding variables in the postmenopausal subjects, as can be observed in Table 3.

Discussion

This study aimed to elucidate the elusive relationship between metabolic syndrome values and primary invasive breast cancer. From this study, we observed that insulin resistance, as reflected by the HOMA-IR and TyG score, does not correlate with the incidence of metastases in breast cancer, which can be seen in Table 2. However, we noted how BMI,

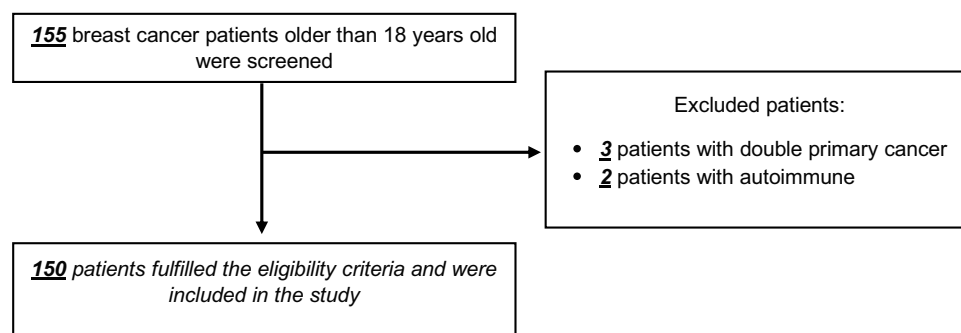


Figure 1 Sample recruitment flow diagram.

Table 1 Study Sample Characteristics

Variable	Description (N=150)
Age, n (%)	
< 60 years old	117 (78)
≥ 60 years old	33 (22)
Molecular subtype, n (%)	
Luminal A	38 (25.4)
Luminal B	93 (62)
Her2 OverExp	9 (6)
Triple negative	10 (6.6)
Hormonal therapy, n (%)	
None	43 (29)
Tamoxifen	62 (41)
Aromatase inhibitor	45 (30)
Last chemotherapy, n (%)	
< 1 month	40 (26.7)
≥ 1 month	110 (73.3)
Metastasis, n (%)	
Not metastasized	79 (52.6)
Metastasized	71 (47.4)
BMI, mean kg/m² (SD)	23.9 (3.77)
BMI grouping, n (%)	
Not Obese (< 25 kg/m ²)	101 (67.4)
Obese I (25–29.9 kg/m ²)	40 (26.6)
Obese 2 (> 30 kg/m ²)	9 (6)
T2DM, n (%)	
No	134 (89.4)
Yes	16 (10.6)
LDL cholesterol, n (%)	
< 130 mg/dL	94 (62.7)
≥ 130 mg/dL	56 (37.3)
Fasting Blood Glucose, median mg/dL (min-max)	87 (54–339)
Fasting Insulin, median (μIU/mL) (min-max)	5.6 (0.7–29.6)
HOMA-IR, median (min-max)	1.22 (0.11–12.92)
TyG, mean (SD)	8.60 (0.60)

Abbreviations: BMI, body mass index; Her2 OverExp, human epidermal growth factor receptor 2 over expression; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL, low density lipoprotein; TyG Index, Triglyceride/Glucose Index; T2DM, type 2 diabetes mellitus.

Table 2 Correlation Between HOMA-IR and TyG with Metastasis Incidence

Variable	Metastasized (n= 71)	Not Metastasized (n=79)	P
HOMA-IR, median (Min-max)	1.26 (0.11–12.92)	1.18 (0.34–6.94)	1.00 ^a
TyG, mean (SD)	8.70 (0.62)	8.52 (0.57)	0.74 ^b

Notes: ^aAnalyzed using Mann–Whitney U-test. ^bAnalyzed using independent sample t-test.

Abbreviations: HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; TyG Index, Triglyceride/Glucose Index.

Table 3 Subgroup Analysis in Postmenopausal Subjects

Variable	Metastasized	Not Metastasized	P
T2DM, n (%)			
No	11 (42.3)	15 (57.7)	0.98
Yes	3 (42.8)	4 (57.2)	
BMI grouping, n (%)			
Not Obese (< 25 kg/m ²)	10 (41.6)	14 (58.4)	0.19
Obese 1 (25–29.9 kg/m ²)	2 (28.6)	5 (71.4)	
Obese 2 (≥ 30 kg/m ²)	2 (100)	0 (0)	
HOMA-IR, median (min-max)	1.63 (0.54–12.92)	1.26 (0.64–5.23)	0.43
TyG, mean (SD)	8.70 (0.62)	8.53 (0.58)	0.08

Abbreviations: BMI, body mass index; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; TyG Index, Triglyceride/Glucose Index; T2DM, type 2 diabetes mellitus.

diabetes status, HDL, triglyceride, total cholesterol, and type of hormonal therapy might affect HOMA-IR and TyG index values in primary invasive breast cancer patients.

Nam et al¹⁶ reported the exact opposite finding, stating that increased HOMA-IR value is significantly associated with cancer severity. At the same time, Panigoro et al¹⁷ reported TyG index value was higher in patients with breast cancer. The Women's Health Initiative study mentioned that increased cancer-specific mortality corresponds with increased cancer-specific mortality.¹² Ferguson et al²¹ reported that hyperinsulinemia promotes metastasis via insulin receptor (IR) activation. Metabolic syndrome was observed to be associated with primary invasive breast cancer via decreasing levels of adiponectin, a peptide involved in fatty acid oxidation and glucose utilization.^{22,23} Furthermore, resistance to chemotherapy in breast cancer patients was related to change in glucose metabolism and administration of diabetes drugs was found to resensitize breast cancer to chemotherapy.^{22,24} Kundaktepe et al²⁵ mentioned that the HOMA-IR value of breast cancer patients is significantly higher compared to the average population, and it was cited that the value was significantly higher in stage IV B breast cancer patients compared to other staging levels. In this study, since the result did not reach statistical significance, we cannot find the area under the curve (AUC) of both scorings' receiver operating curve (ROC).

Theoretically, the hyperglycemic status may affect breast cancer's metastasis and outcome by increasing circulating insulin levels, and hyperinsulinemia was found to increase cancer cell survival.^{11,26} This difference may be due to the different socioeconomic and biodemographic characteristics of each study's population, as Tahapary et al²⁷ found that the value of HOMA-IR and TyG index may vary between populations. As an example of comparison, this study sample population is dominated by samples younger than 60 years old and diagnosed with luminal B subtype, distinctively different from Nam et al¹⁶ which were composed of older samples with luminal A subtype as the majority of diagnosis. A similar example was illustrated by Ferroni et al²⁸ in which most of the sample was diagnosed with stage II breast cancer, unlike the sample from our study, which mainly comprised patients with stage IV breast cancer.

The blood glucose level status in breast cancer patients was found to be directly impacted by HOMA-IR value, age, and the interaction between both variables.²⁹ In breast cancer patients, heightened blood glucose levels will impinge on the cancer progressivity and staging via different pathways.^{30–32} Regarding aromatase inhibitors, administration of the drug was identified to impact visceral adiposity and glucose metabolism due to its mechanism of action.^{33,34} Metabolic disturbance due to obesity impairs insulin sensitivity, and most obese people were ascertained to have at least one afflicted metabolism and insulin sensitivity parameters.³⁵ The mechanism by which obesity disturbs metabolic status was hypothesized due to adipocyte dysfunction, resulting in decreased adiponectin/leptin ratio.^{36,37} Plasminogen activator inhibitor-1 was also noted to be associated with carcinogenesis in obese patients.³⁸ Since HOMA-IR is calculated by taking into account blood glucose level, diabetes will undoubtedly affect both scorings since diabetes was diagnosed by looking at the blood glucose level.

Nam et al¹⁶ ascertained that age was positively correlated with cancer progressivity. A higher incidence of lymph node metastasis (LMN) in older patients was thought to be contributed by increased coatamer protein complex subunit beta-2 (COPB2) gene expression, which was found to be increased along with age.³⁹ Diabetes and high blood glucose level were linked to a higher risk of metastasis in breast cancer patients, which was thought to be implicated by the role of angiotensinogen and Akt1 pathway.^{30,40} In addition, treatment of diabetes with incretin and metformin decreased the risk of metastases in breast cancer patients with T2DM.⁴¹

A high level of LDL was recorded to affect breast cancer progression by increasing reactive oxygen species (ROS) formation due to xanthine oxidase activity and promoting cholesterol uptake by the cancer cells via the activation of the LDL receptor.^{42–44} Furthermore, total cholesterol and triglyceride levels were also documented to raise the risk of metastasis, possibly mediated by the binding of LDL cholesterol with its receptor.^{45,46} Nonetheless, breast cancer patients undergoing chemotherapy were observed to have higher levels of total cholesterol, LDL, and triglyceride, which could explain why we did not report a significant correlation with the incidence of metastases.⁴⁷ Chemotherapy was found to affect several metabolic parameters, including fasting blood glucose,^{48,49} HbA1c,⁴⁸ triglyceride,⁵⁰ and LDL.⁴⁹ Metastases and advanced staging were also highlighted to be more prevalent in obese breast cancers. This phenomenon was considered due to higher circulating leptin levels in obese patients.^{51,52} Nevertheless, Osman et al⁵³ mentioned that obesity did not significantly affect the incidence of metastasis, in line with the finding in our study. On the other hand, Buch et al³³ reported that adjuvant chemotherapy and hormonal therapy increased the weight of breast cancer patients, implying that obesity happened as a consequence of drug therapies in breast cancer patients instead. The underlying contrivance causing increased body weight in breast cancer patients receiving adjuvant chemotherapy lies in the decreased basal metabolic rate and physical activity levels, thereby increasing adipokine expression and circulating lipid levels and, ultimately, inducing sarcopenic obesity.^{48,54}

We also found from subgroup analysis that there was no correlation between any of the confounding variables in the postmenopausal study subjects. Another study noted a significant correlation between cancer progression and obesity in postmenopausal women.^{16,55} We used 60 years of age as the cut-off to define menopause per the NCCN guideline. Thus, this may contribute to the different findings of our study when compared with other published studies. The pathogenesis basis of the convergence between menopausal status and obesity in advancing cancer progression lies in heightened neovascularization rate and earlier switching of the tumor to the vascular phenotype.⁵⁵ Genetics were also found to play a significant role in the interaction between insulin resistance and breast cancer in postmenopausal women.⁵⁶

The main limitation of this study is its cross-sectional design and the number of patients who met the subject selection criteria during this period was insufficient. As a result, no direct causality may be concluded from the finding obtained from our study. Hence, we suggest conducting a longitudinal study with a larger sample size for future research. Other limitations of this study include the lax exclusion criteria and limited operational definition of menopause used in this study. The study subjects we enrolled in this study were recruited from Indonesia's highest national governmental central referral hospital and one of the largest cancer-focused private hospitals in Jakarta. Thus, we argue that the sample we used in this study represents primary invasive breast cancer patients in Indonesia.

Conclusion

There was no significant correlation between the incidence of metastases in breast cancer patients and insulin resistance parameters.

Ethics Approval and Informed Consent

The Ethics Committee of The Faculty of Medicine, Universitas Indonesia granted ethical approval for this study (ethical approval number: KET-372/UN2.F1/ETIK/PPM.00.02/2023). This study was carried out in accordance with the Helsinki Declaration. All subjects who took part in the study provided written informed consent.

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All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declared no conflicts of interest in this work.

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