Correlation between Plasma Soluble CD36 Levels with Body Mass Index of Breast Cancer Patients in the Indonesian Population

Andhika Rachman[1*], Cosphiadi Irawan[1], Aditia R.R.[2], Sukamto Koesnoe[3], Indra Wijaya[4]

[1]Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo General Hospital
[2]Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo General Hospital
[3]Division of Allergy and Immunology, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo General Hospital
[4]Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Universitas Padjajaran, Hasan Sadikin General Hospital

Abstract

The cluster of differentiation 36 (CD36) is a multiligand receptor protein that plays a role in lipid metabolism. Its biological functions involve lipid uptake, immune recognition, inflammation, molecular adhesion, and tumor metastasis. Soluble CD36 (sCD36) is the circulating form of CD36 in plasma. Research on the role of sCD36 in breast cancer is limited. This study aimed to investigate sCD36 concentration and evaluate the correlation between sCD36 concentration and BMI in breast cancer patients. This is a multi-center cross-sectional study done from June 2018 to February 2019 in Indonesia. Consecutive sampling was done for women with invasive breast cancer aged 18-70. Patients with locoregional recurrences, multiple comorbidities, diabetes, stroke, or liver impairment were excluded. Patients were grouped based on their BMI into normo-weight and overweight/obese. Plasma sCD36 was analyzed using Bioassay Laboratory™ ELISA. The correlation between plasma sCD36 and the patient's characteristics (metastasis status and molecular subtype) were then analyzed. A total of 76 patients were enrolled, 36 of whom were categorized into the overweight/obese group and 40 of them in the normo-weight. Plasma levels of sCD36 in breast cancer patients were higher than controls at 0.24±0.163 ng/mL and 0.46±0.175 ng/mL, respectively (p=0.006). However, no difference in plasma sCD36 levels was found between the overweight/obese group and the normo-weight breast cancer subjects (p>0.05). Plasma sCD36 increased significantly in breast cancer patients, but no significant difference was found based on body mass index. Further research is needed to determine the role of sCD36 in determining clinical outcomes and prognosis in breast cancer patients.

Keywords: *soluble CD36, body mass index, breast cancer, indonesia.*

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*Corresponding author: andhikarachman@gmail.com

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INTRODUCTION

Based on the Global Cancer Statistics (Sung, *et al*., 2021), breast cancer is reported to have the highest incidence, with around 2.2 billion cases worldwide, accounting for about 11.7% of all new cancer cases, closely followed by lung cancer at 11.4% and colorectal cancer at about 10%. In Indonesia, breast cancer ranks first in terms of incidence (Globocan-IARC, 2018), with approximately 65,858 new cases in both sexes, about 16.7% of all cancer cases reported in 2020. It also has one of the highest mortality rates among other cancers (Sung, *et al*., 2021). One of the known risk factors of breast cancer is obesity. Not only does obesity increase the risk of breast cancer, but some studies have also shown that obesity is linked to tumor progression and higher chances of metastasis due to higher circulating estrogen levels (Liang, *et al*., 2018).

The cluster of differentiation 36 (CD36) is a scavenger receptor belonging to the transmembrane glycoprotein that is widely expressed in several cells and tissues including thrombocytes, immune cells, adipocytes, myocytes, enterocytes, retinal cells, endothelial cells, and breast cells. CD36 is known to have a role in activating thrombocytes and increasing the inflammatory response of macrophages and monocytes, and also to induce bioactive lipid uptake via peroxisome proliferator activated receptor gamma (PPARγ) transcription pathway (Silverstein and Febbraio, 2009; Wang and Li, 2019).

Several studies have revealed the role of the CD36 molecules in breast cancer (Enciu, *et al*., 2018a). In the process of tumor adhesion, CD36 is involved in cellular interaction with collagen in the extracellular matrix (Uray, *et al*., 2004). High expression of the CD36 molecule plays important role in metastatic-promoting processes and relates to poor prognoses in type A luminal breast cancer (Pascual, *et al*., 2017). On the contrary, other studies showed that decreased expression of CD36 molecules is related to the aggressive characteristic of breast cancer (Wang and Li, 2019). In addition, one study revealed that decreased CD36 molecule expression in fibroblast stroma was related to the escalation in tumor size and histologic grade (DeFilippis, *et al*., 2012). Several micro-assay studies of total RNA also revealed a decrease in gene expression of invasive breast cancer cells, compared to the normal cells. Soluble CD36 (sCD36) is a free, non-cell bound, form of CD36 which is easily measurable by ELISA technique. Since CD36 presents in tissues, sampling of CD36 faces technical difficulties. Measurement of sCD36 has been done in studies and has been associated with atherosclerosis and metabolic syndrome including, obesity and type 2 diabetes. Therefore, sCD36 has been proposed as plasma markers for metabolic syndrome and inflammation (Perou, *et al*., 2000a; Radvanyi, *et al*., 2005; Richardson, *et al*., 2006; Sørlie, *et al*., 2001; Zhao, *et al*., 2004).

Some measurement methods of CD36 expression molecules include gene expression measurement through micro-assay total RNA analysis (Perou, *et al*., 2000b; Radvanyi, *et al*., 2005; Richardson, *et al*., 2006; Sørlie, *et al*., 2001; Zhao, *et al*., 2004), gene expression through quantitative polymerase chain reaction (Q-PCR) examination (DeFilippis, *et al*., 2012; Pascual, *et al*., 2017), and plasma examination through ELISA techniques already done in subjects with non-alcoholic fatty liver disease (Handberg, *et al*., 2012; Heebøll, *et al*., 2017), diabetes mellitus (Handberg, *et al*., 2006; Jiang, *et al*., 2017; Shiju, *et al*., 2015), insulin resistance (Handberg, *et al*., 2012), coronary arterial disease (Krzystolik, *et al*., 2015), atherosclerotic carotis (Handberg, *et al*., 2012; Jiang, *et al*., 2017), chronic kidney disease (Chmielewski, *et al*., 2010), and ischemic stroke (Woo, *et al*., 2016). However, concentration measurement of CD36 within the

Table 1. Baseline characteristics of study subjects.

Characteristics	Overweight/obese subjects (N=36)	Normo-weight subjects (n=40)
Metastatic status, N (%)		
Metastatic	16 (44.4)	17 (42.5)
Non-metastatic	20 (55.6)	23 (57.5)
Cancer stadium		
IA	1 (2.8)	1(2.5)
IIA	4 (11.1)	6 (15)
IIB	3 (8.3)	5 (12.5)
IIIA	4 (11.1)	4 (10)
IIIB	8 (22.2)	6 (15)
IIIC	0 (0)	1 (2.5)
IV	16 (44.4)	17 (42.5)
Molecular subtype cancer, n (%)		
Luminal	27 (75)	32 (80)
Her-2 over-expression	6 (16.7)	6 (15)
Triple negative breast cancer (TNBC)	3 (8.3)	2 (5)
Histopathologic type, n (%)		
Invasive ductal carcinoma	33 (91.7)	35 (87.5)
Invasive lobular carcinoma	3 (8.3)	4 (10)
Invasive mucinous carcinoma	0 (0)	1 (2.5)
Histopathology grade, n (%)		
I	1 (2.8)	4 (10)
II	19 (52.8)	25 (62.5)
III	14 (38.9)	7 (17.5)
Unknown grade	2 (5.6)	4 (10)
Lympho-vascular invasion (LVI), n (%)		
Positive	7 (19.4)	8 (20)
Negative	29 (80.6)	32 (80)
Tumor size, n (%)		
T1 (≤2 cm)	5 (13.9)	7 (17.5)
T2 (2,1–5 cm)	18 (50)	20 (50)
T3 – T4 (>5 cm)	13 (36.1)	13 (32.5)
Lymph node involvement, n (%)		
N0	9 (25)	14 (35)
N1	15 (41.7)	17 (42.5)
N2	8 (22.2)	6 (15)
N3	4 (11.1)	3 (7.5)

plasma of breast cells using ELISA technique was not yet revealed in previous studies. This research aimed to compare whether there is a difference in plasma CD36 levels between obese/overweight and normo-weight breast cancer patients.

METHODS

This is a cross-sectional study, done in two major cancer centers in the capital Jakarta, Indonesia: Cipto Mangunkusumo Hospital and MRCCC Siloam Jakarta from June 2018 to February 2019. By means of consecutive sampling, 76 breast cancer patients aged 18-70 years old with all molecular subtypes were enrolled. Patients with locoregional recurrences, multiple comorbidities, diabetes, stroke, coronary artery disease, chronic kidney disease, and patients with impaired liver function were excluded. All subjects were given information for consent and were asked to provide written consent.

The patients' characteristics were obtained from the medical records, including molecular subtype of cancer (estrogen receptor and progesterone receptor status, and Ki-67 data) and cancer stadium.

Patients who agreed to participate in this research then had their weight and height measured; and 2 cc of venous blood drawn. The blood was then centrifuged at 3000 RPM for 15 minutes. Plasma sCD36 was analyzed using Bioassay Technology Laboratory™ solid phase Enzyme-linked immunosorbent assay (ELISA) and measured in ng/mL. The assay was performed according to the manufacturer's protocol, which includes the preparation of reagents, samples, and standards, followed by incubating the reagents and standards. Afterwards, samples were added to the wells, and incubated at room temperature. Antibody was added, and subsequently, after washing after each step, Streptavidin solution, substrate reagent, and stop solution were added. Afterwards, the mean absorbance for each sample, standard, and control were calculated and plotted into the standard curve to obtain the sCD36 values. Patients were grouped based on their body mass index into two categories, normo-weight (BMI≤23) and overweight/obese (BMI>23) based on the Asian criteria. The mean difference in sCD36 levels between breast cancer patients of normo-weight and those of overweight or obese

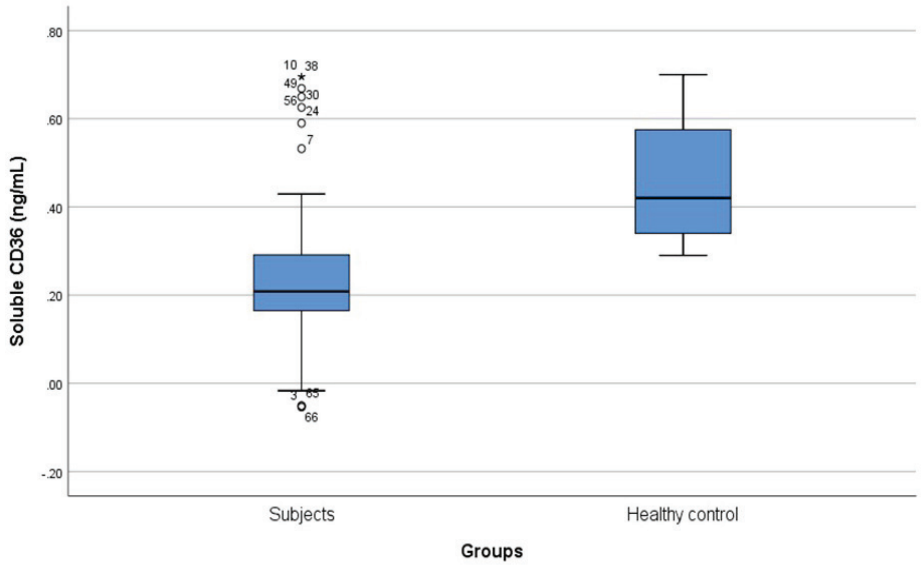

Figure 1. The difference of CD36 concentration in healthy subjects, breast cancer subjects.

Table 2. Mean comparison of sCD36 level based on characteristics between overweight/obese subjects and normo-weight subjects.

Characteristics	Overweight/obese (N=36) sCD36 concentration (ng/mL), mean ±SD/ median [IQR]	Normo-weight (N=40) sCD36 concentration (ng/mL), mean ±SD/ median [IQR]	Sig. (*p*)
All cases	0.195 [0.08]	0.237 [0.18]	0.259
Metastasis status			
Metastatic	0.199 [0.16]	0.249±0.181	0.958
Non-metastatic	0.193 [0.06]	0.247±0.164	0.144
Molecular subtype cancer			
Luminal	0.182 [0.07]	0.251±0.160	0.063
Her-2 over-expression	0.316±0.280	0.163 [0.23]	0.470
Triple negative breast cancer (TNBC)	0.221 [-]	0.173 [-]	1.00
Lympho-vascular invasion (LVI)			
Positive	0.194±0.016	0.226±0.179	0.648
Negative	0.1911 [0.11]	0.254±0.170	0.276
Tumor size, n (%)			
T1 (≤2 cm)	0.195 [0.28]	0.399±0.220	0.291
T2 (2,1–5 cm)	0.205 [0.08]	0.221±0.119	0.977
T3–T4 (>5 cm)	0.186±0.114	0.208±0.175	0.702
Lymph node involvement, n (%)			
N0	0.209 [0.18]	0.280±0.191	0.186
N1	0.182 [0.05]	0.200 [0.12]	0.584
N2	0.193 [0.16]	0.239±0.155	0.519
N3	0.215 [0.32]	0.197±0.094	0.289

breast cancer patients was analyzed using SPSS Software version 26. Student's T-test was used to compare means in those with normal data distribution. For nonparametric data, the Mann-Whitney test was used. The threshold for significance level in this study was $p<0.05$.

RESULTS

Seventy-six patients met the inclusion and exclusion criteria, provided written consent, and were enrolled in this study. About 47% of the subjects were classified as overweight or obese while 53% of those were normo-weight. Of all the subjects, approximately 43% of the subjects had metastatic breast cancer with luminal molecular subtype being the most prevalent (77%). The rest of the characteristics of the subjects are described in Table 1.

We found that breast cancer subjects' plasma concentration of sCD36 is significantly different from healthy controls at 0.24±0.163 ng/mL vs. 0.46±0.175 ng/mL, respectively ($p=0.006$). Figure 1 represents an illustration of the difference is sCD36 between breast cancer patients and healthy controls.

We also found that there is no difference in median plasma CD36 concentration in metastatic breast cancer compared to non-metastatic breast cancer, 0.21 [0.16] ng/mL vs 0.21 [0.11] ng/mL as illustrated in Figure 2. We further compared the mean differences of sCD36 between the overweight/ obese group and the normo-weight group

(Table 2). Our analysis showed that there were no differences in sCD36 levels in metastatic status, molecular subtypes, LVI, tumor size, and lymph node involvement.

DISCUSSION

Based on a report by the International Agency for Research on Cancer in 2020, there were about 2,261,419 cases of breast cancer worldwide. About 24% of said cases are in the Asia-Pacific region (WHO, 2022). Indonesia contributes to approximately 12% of the breast cancer population in the Asia-Pasific, following China (46%) and Japan (14%). In 2020, there was estimated 65,858 new cases of breast cancer in Indonesia (Sung, *et al*., 2021).

Studies have shown that there is a strong correlation between obesity and breast cancer. Obesity is associated with a higher risk of developing breast cancer, particularly in postmenopausal women, and with worse disease outcomes for women of all ages. Some theories hypothesized molecular mechanistic insights that may underlie the effects of obesity to increase local and circulating proinflammatory cytokines, promote tumor angiogenesis and stimulate the most malignant cancer stem cell population to drive cancer growth, invasion, and metastasis (Picon-Ruiz, *et al*., 2017). Adipose tissue in obese patients expresses hypoxia-inducible factor-1 (HIF-1), which increases vascular endothelial growth factor (VEGF), increases leptin, and suppresses adiponectin, causing the decrease of adiponectin: leptin ratio, which causes the infiltration of pro-inflammatory cells and the formation of crown-like structures (CLS). Destruction of adipocyte cells releases free fatty acids (FFA), which will bind to toll-like receptor 4 (TLR-4) present in macrophages (Fuster, *et al*., 2016; Picon-Ruiz, *et al*., 2017). This will cause an activation of nuclear factor kappa B (NF-kB) and upregulate pro-inflammatory cytokines including tumor necrosis factor-a (TNF-a), interleukin-6 (IL-6), IL-8, chemokine (C-C motive) ligand 5 (CCL5) and CCL 2). These cytokines will cause lipolysis, further

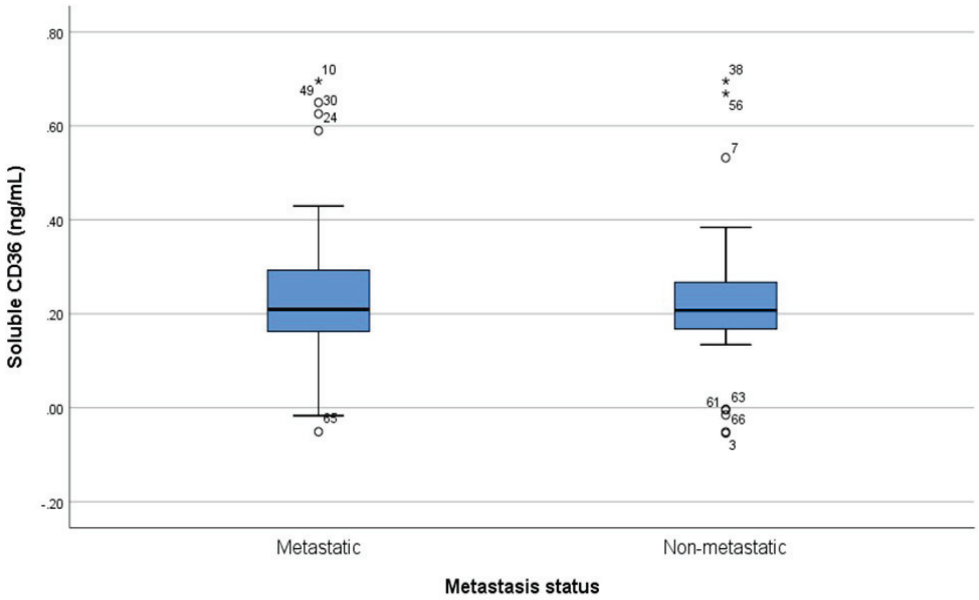

Figure 2. Profile concentration of plasma CD36 in metastatic breast cancer and non-metastatic breast cancer. Data presented in Median (min-max).

increasing the levels of FFA, causing a chronic inflammation cycle which will eventually lead to increased expression of aromatase and estrogen synthesis, increasing the total bioavailable estrogen. This cycle is linked to increased cancer stem cells (CSCs) (Himoto, *et al*., 2013; Nattenmüller, *et al*., 2018). IL-6, IL-8, CCL2, CCL5, and VEGF are linked to the prognosis of breast cancer patients. The more of these cytokines present, combined with the stage of the disease, the worse the outcome. These cytokines are also linked to the promotion of tumor invasion and metastasis (Enciu, *et al*., 2018b; Feng, *et al*., 2019; Xu, *et al*., 2019). About 35% of the IL-6 are from adipose tissues. IL-8 is known to promote angiogenesis, tumor development, metastasis, and resistance to chemotherapy. CCL2 and CCL5 promote tumor growth by mediating the signaling between ancer cells and its microenvironment and facilitating the cancer motility and metastasis. TNF-a and IL-1 also promote cancer cell growth and migration (Kaviani, *et al*., 2013).

Adipose tissue in obese patients will also causes pro-inflammatory cytokine secretion via the shift to the M1 macrophage subtype. Obesity is also known to cause an increased level of insulin and insulin-like growth factor (IGF-1). Leptin and IGF-1 cause hyperactivation of the HER2 pathway, decreasing the sensitivity towards targeted therapy and increasing disease relapse. Hyperinsulinemia decreases the amount of hormone-binding globulin and increases estrogen bioavailability. This is made worse by heightened levels of TNF-a and IL-6, which cause a decrease in glucose transport while further stimulating insulin secretion and increasing the levels of IGF-1 (Balistreri, *et al*., 2010; Kolb, *et al*., 2016).

Recent research has shown the scavenger receptor CD36 to be linked with serum lipids and to some of the metabolic complications of obesity, such as insulin resistance, inflammation, atherosclerosis, and thrombosis (Love-Gregory and Abumrad, 2011). CD36 was originally identified as a type B scavenger receptor family member and an 88-kDa glycosylated membrane protein. It can bind multiple ligands, including thrombospondin, fatty acids, anionic phospholipids, and oxidized low-density lipoprotein (ox-LDL) (Liang, *et al*., 2018). CD36 is found in all types of cells, such as macrophages, dendritic cells, microglia, the epithelial pigment of the retina, erythroid precursors, hepatocytes, adipocytes, myocytes, specialized epithelial cells including breast cells, renal cells, and gut cells (Silverstein and Febbraio, 2009; Wang and Li, 2019).

In breast tissues, this molecule is produced in adipocyte, endothelium, and fibroblast, and plays a role in cell adhesion with collagen tissue within the extracellular matrix (DeFilippis, *et al*., 2012; Uray, *et al*., 2004). CD36 acts as a receptor for type I collagen and trombospondin (Perou, *et al*., 2000a; Yu, *et al*., 2015). CD36 is able to translocate fatty acid and initiates monosaturated fatty acid uptake from exogenous adipocyte to the tumor cells (Zhao, *et al*., 2017). CD36 has been found to be upregulated in tumor tissues but downregulated in microvessels and stroma. Recent studies have reported that CD36 expression is also involved in tumorigenesis, but the results are controversial. A study reports that CD36 expression is defective in invasive breast cancers (Liang, *et al*., 2018), which suggests that loss of CD36 may facilitate tumor progression and metastasis. In another study, CD36 expression is suppressed by estradiol in hormone-dependent MCF-7 and T47D breast cancer cell lines (Liang, *et al*., 2018). However, the exact role of CD36 in tumorigenesis, particularly in breast cancer, needs more investigation.

CD36 is also present in a soluble protein form, sCD36. It has been suggested that sCD36 is composed of a specific subset of microparticles derived from tha exposed extracellular domain of the transmembrane CD36 that is shed by proteases in the plasma (Wang and Li, 2019). There have been

conflicting reports concerning the role of sCD36. Some have found that sCD36 is upregulated in patients with type 2 diabetes (Handberg, *et al*., 2006). It has also been shown to correlate with markers of cardiovascular diseases, fatty liver (Himoto, *et al*., 2013), and insulin resistance (Handberg, *et al*., 2011). Some studies also found a correlation between sCD36 levels and obesity (Heebøll, *et al*., 2017; Himoto, *et al*., 2013).

In our study, there is lower levels of sCD36 in breast cancer cells compared to healthy control (Figure 1). This is in accordance with other studies that studied CD36 levels in breast cancer tissue by DeFilippis, *et al.* (DeFilippis, *et al*., 2012). Lower levels of tissue CD36 expression in breast cancer subjects may be due to receptor loss within the breast cancer stroma and desmoplastic changes that can induce differential disturbances within the adipocytes (Uray, *et al*., 2004). Several studies have found the correlation between the level of CD36 and tumor metastatic potency (Uray, *et al*., 2004; Yu, *et al*., 2015). Several micro-assay studies of total RNA also revealed the decrease in gene expression of CD36 in invasive breast cancer cells, compared to the normal cells (Perou, *et al*., 2000a; Sørlie, *et al*., 2001; Zhao, *et al*., 2004). However, in our study, there was no difference in the plasma concentration of CD36 between metastatic breast cancer and non-metastatic breast cancer (Figure 2). This suggests that there is a difference between sCD36 and tissue. Several studies have found that CD36 accelerates tumor growth (Liang, *et al.*, 2018; Wang and Li, 2019). However, there was no significant difference in sCD36 levels between tumor size, and lympho-vascular invasion in study. This differs from a study by Defilippis, *et al*., who found a decrease in tissue CD36 expression in third-grade tumors compared to first-grade tumors, as well as a decrease in tissue CD36 expression with every 1 cm increase in tumor size (DeFilippis, *et al*., 2012). Another study by Perou, *et al.,* showed a lower expression level of CD36 in breast cancer-invading lymph nodes, compared with primary tumor cells (Perou, *et al*., 2000a).

Our study has some limitations, including the small sample size and the cross-sectional method. The measurement technique of CD36 concentration within plasma ELISA did not isolate monocytes, thrombocytes, and circulating endothelial carcinoma cells specifically that might cause contamination. A study examining plasma CD36 concentration using the ELISA technique has not been previously reported.

CONCLUSION

Recent studies have shown that CD36 is highly expressed and enhances the progression of solid malignancies, including in breast cancer, though some results of studies are controversial. CD36 overexpression is hypothesized to be associated with the upregulation of survivin, a protein linked to apoptosis resistance, metastasis, bypass of cell cycle checkpoints, and resistance to therapy. We discovered that plasma-soluble CD36 levels significantly increased in breast cancer patients, but there was no significant difference based on body mass index. Further research is needed to determine this biomarker's role in determining clinical characteristics of breast cancer patients.

REFERENCES

Balistreri, C.R., Caruso, C., and Candore, G., 2010, The role of adipose tissue and adipokines in obesity-related inflammatory diseases, *Mediators Inflamm*, **2010**, 802078.

Chmielewski, M., Bragfors-Helin, A.-C., Stenvinkel, P., Lindholm, B., and Anderstam, B., 2010, Serum soluble CD36, assessed by a novel monoclonal antibody-based sandwich ELISA, predicts cardiovascular mortality in dialysis patients, *Clinica Chimica Acta*, **411**(23-24),

2079–2082.

DeFilippis, R.A., Chang, H., Dumont, N., Rabban, J.T., Chen, Y.-Y., Fontenay, G.V., *et al.*, 2012, CD36 repression activates a multicellular stromal program shared by high mammographic density and tumor tissues, *Cancer Discov*, **2**(9), 826–839.

Enciu, A.-M., Radu, E., Popescu, I.D., Hinescu, M.E., and Ceafalan, L.C., 2018a, Targeting CD36 as biomarker for metastasis prognostic: How far from translation into clinical practice?, *Biomed Res Int 2018*, **2018**, 7801202.

Enciu, A.-M., Radu, E., Popescu, I.D., Hinescu, M.E., and Ceafalan, L.C., 2018b, Targeting CD36 as biomarker for metastasis prognostic: How far from translation into clinical practice?, *Biomed Res Int 2018*, 2018, 7801202.

Feng, W.W., Wilkins, O., Bang, S., Ung, M., Li, J., An, J., *et al.*, 2019, CD36-mediated metabolic rewiring of breast cancer cells promotes resistance to HER2-targeted therapies, *Cell Rep*, **29**(11), 3405–3420.

Fuster, J.J., Ouchi, N., Gokce, N., and Walsh, K., 2016, Obesity-induced changes in adipose tissue microenvironment and their impact on cardiovascular disease, *Circ Res*, **118**(11), 1786–1807.

Globocan-IARC, 2018, Indonesian incidence, mortality, and prevalence by cancer site in 2018, Global Cancer Observatory: Cancer Today.

Handberg, A., Højlund, K., Gastaldelli, A., Flyvbjerg, A., Dekker, J.M., Petrie, J., *et al.*, 2012, Plasma sCD36 is associated with markers of atherosclerosis, insulin resistance and fatty liver in a nondiabetic healthy population, *J Intern Med*, **271**(3), 294–304.

Handberg, A., Levin, K., Højlund, K., and Beck-Nielsen, H., 2006, Identification of the oxidized low-density lipoprotein scavenger receptor CD36 in plasma, *Circulation*, **114**(11), 1169–1176.

Heebøll, S., Poulsen, M.K., Ornstrup, M.J., Kjær, T.N., Pedersen, S.B., Nielsen, S., *et al.*, 2017, Circulating sCD36 levels in patients with non-alcoholic fatty liver disease and controls, *Int J Obes*, **41**, 262–267.

Himoto, T., Tani, J., Miyoshi, H., Morishita, A., Yoneyama, H., Kurokohchi, K., *et al.*, 2013, Investigation of the factors associated with circulating soluble CD36 levels in patients with HCV-related chronic liver disease, *Diabetol Metab Syndr*, **5**, 51.

Jiang, X., Zhao, X., Chen, R., Jiang, Q., Zhou, B., 2017, Plasma soluble CD36, carotid intima-media thickness and cognitive function in patients with type 2 diabetes, *Archives of Medical Science*, **13**(5), 1031–1039.

Kaviani, A., Neishaboury, M., Mohammadzadeh, N., Ansari-damavandi, M., and Jamei, K., 2013, Effects of obesity on presentation of breast cancer, lymph node metastasis and patient survival: A retrospective review, *Asian Pacific J Cancer Prev*, **14**(4), 2225–2229.

Kolb, R., Sutterwala, F.S., and Zhang, W., 2016, Obesity and cancer: inflammation bridges the two, *Curr Opin Pharmacol*, **29**, 77–89.

Krzystolik, A., Dziedziejko, V., Safranow, K., Kurzawski, G., Rać, M., Sagasz-Tysiewicz, D., *et al.*, 2015, Is plasma soluble CD36 associated with cardiovascular risk factors in early onset coronary artery disease patients?, *Scand J Clin Lab Invest*, **75**(5), 398–406.

Liang, Y., Han, H., Liu, L., Duan, Y., Yang, X., Ma, C., *et al.*, 2018, CD36 plays a critical role in proliferation, migration and tamoxifen-inhibited growth of ER-positive breast cancer cells, *Oncogenesis*, **7**, 98.

Love-Gregory, L., and Abumrad, N.A., 2011, CD36 genetics and the metabolic complications of obesity, *Curr Opin Clin Nutr Metab Care*, **14**(6), 527–534.

Nattenmüller, C.J., Kriegsmann, M., Sookthai, D., Fortner, R.T., Steffen, A., Walter, B., *et al.*, 2018, Obesity as risk factor for subtypes of breast cancer: Results from a prospective cohort study, *BMC Cancer*, **18**, 616.

Pascual, G., Avgustinova, A., Mejetta, S., Martín, M., Castellanos, A., Attolini, C.S.-O., *et al.*, 2017, Targeting metastasis-initiating cells through the fatty acid receptor CD36, *Nature*, **541**, 41–45.

Perou, C.M., Sørlie, T., Eisen, M.B., van de Rijn, M., Jeffrey, S.S., Rees, C.A., *et al.*, 2000a, Molecular portraits of human breast tumours, *Nature*, **406**, 747–752.

Perou, C.M., Sørlie, T., Eisen, M.B., van de Rijn, M., Jeffrey, S.S., Rees, C.A., *et al.*, 2000b, Molecular portraits of human breast tumours, *Nature*, **406**, 747–752.

Picon-Ruiz, M., Morata-Tarifa, C., Valle-Goffin, J.J., Friedman, E.R., and Slingerland, J.M., 2017, Obesity and adverse breast cancer risk and outcome: Mechanistic insights and strategies for intervention.,*CA Cancer J Clin*, **67**(5), 378–397.

Radvanyi, L., Singh-Sandhu, D., Gallichan, S., Lovitt, C., Pedyczak, A., Mallo, G., *et al.*, 2005, The gene associated with trichorhinophalangeal syndrome in humans is overexpressed in breast cancer, Proceedings, *National Academy of Sciences*, **102**(31), 11005–11010.

Richardson, A.L., Wang, Z.C., De Nicolo, A., Lu, X., Brown, M., Miron, A., *et al.*, 2006, X chromosomal abnormalities in basal-like human breast cancer, *Cancer Cell*, **9**(2), 121–132.

Shiju, T.M., Mohan, V., Balasubramanyam, M., and Viswanathan, P., 2015, Soluble CD36 in plasma and urine: A plausible prognostic marker for diabetic nephropathy, *J Diabetes Complications*, **29**(3), 400–406.

Silverstein, R.L., and Febbraio, M., 2009, CD36, a scavenger receptor involved in immunity, metabolism, angiogenesis, and behavior, *Sci Signal*, **2**(72).

Sørlie, T., Perou, C.M., Tibshirani, R., Aas, T., Geisler, S., Johnsen, H., *et al.*, 2001, Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications, *Proceedings, National Academy of Sciences*, **98**(19), 10869–10874.

Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., and Bray, F., 2021, Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, *CA Cancer J Clin*, **71**(3), 209-249.

Uray, I.P., Liang, Y., and Hyder, S.M., 2004, Estradiol down-regulates CD36 expression in human breast cancer cells, *Cancer Lett*, **207**(1), 101–107.

Wang, J., and Li, Y., 2019, CD36 tango in cancer: Signaling pathways and functions, *Theranostics*, **9**(17), 4893–4908.

WHO, 2022, WHO Fact Sheet, International Agency for Research on Cancer.

Woo, M.-S., Yang, J., Beltran, C., and Cho, S., 2016, Cell Surface CD36 Protein in monocyte/macrophage contributes to phagocytosis during the resolution phase of ischemic stroke in mice, *Journal of Biological Chemistry*, **291**(45), 23654–23661.

Xu, W.H., Qu, Y.Y., Wang, J., Wang, H.K., Wan, F.N., Zhang, H.L., *et al.*, 2019, Elevated CD36 expression correlates with increased visceral adipose tissue and predicts poor prognosis in ccRCC patients, *J Cancer*, **10**(19), 4522–4531.

Yu, X., Guo, C., Fisher, P.B., Subjeck, J.R., and Wang, X.-Y., 2015, Scavenger receptors: emerging roles in cancer biology and immunology, *Advances in Cancer Research*, **128**, 309–364.

Zhao, H., Langerød, A., Ji, Y., Nowels, K.W., Nesland, J.M., Tibshirani, R., *et al.*, 2004, Different gene expression patterns in invasive lobular and ductal carcinomas of the breast, *Mol Biol Cell*, **15**(6), 2523–2536.

Zhao, J., Zhi, Z., Wang, C., Xing, H., Song, G., Yu, X., *et al.*, 2017, Exogenous lipids promote the growth of breast cancer cells via CD36, *Oncol Rep*, **38**(4), 2105–2115.