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Correlation between CD44 and Human Epidermal Growth Factor Receptor 2 Expression with Distant Metastasis on Women Non-Luminal Breast Cancer

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ABSTRACT

Background: HER2 shows a link in the regulation of CD44+/CD24 expression. CD44 overexpression is associated with cancer cell progression and metastasis. The study aims to evaluate whether to determine the relationship between CD44 and HER2 expression and distant metastasis in breast cancer.

Methods: This study was cross-sectional with breast cancer patients. We performed clinicopathology data collection, which involved age and grading. Then, we performed immunohistochemistry panel examination of ER, PR, Her2, and Ki-67. Immunohistochemical examination to assess CD44 and HER2 expression used Mouse anti-CD44 monoclonal antibody and Rabbit Anti-Human c-erbB-2 oncoprotein monoclonal antibody. Staining intensity and percentage of positive nuclei were recorded after manually segmenting the tumor from the stroma.

Results: There were 60 subjects in this study. CD44 overexpression was positively associated with HER2 overexpression (p=0.011). The results of the odds ratio calculation show that subjects with the HER2 subtype are 4.6 times more likely to experience CD44 overexpression than those with the triple-negative subtype. Overexpression of CD44 was positively associated with the occurrence of distant metastases in breast cancer (p=0.007). The results of the odds ratio calculation show that subjects with CD44 overexpression are six times more likely to experience distant metastases than subjects with low CD44 expression. Statistically, there was no significant difference between CD44 expression and HER2 expression on the incidence of distant metastasis in breast cancer.

Conclusion: These results suggest that CD44 overexpression is associated with the occurrence of distant metastases in breast cancer.

Keywords: breast cancer; Metastases; immunohistochemistry, CD44, HER2.
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INTRODUCTION

Breast cancer (BC) is still a global health problem today, especially in women, where the incidence is the second highest after lung cancer.[1,2] According to Globocan data, it is estimated that there are around 18.1 million new cases of cancer overall.[3] Research conducted in the last decade has highlighted many metastatic factors in BC, some of which are associated with the CD44 gene. The CD44 protein is a transmembrane glycoprotein receptor that binds to extracellular glycosaminoglycans, hyaluronan, as the main ligand. This binding triggers intracellular signal transduction, which affects cellular adhesion, migration, and invasion, which are the main factors in cancer progression, in this case, metastasis.[4] In BC, CD44 expression is closely related to overexpression of human epidermal growth factor receptor 2 (HER2) and in the basal-like subtype of BC.[5]

Based on the gene expression profile, BC is grouped into four intrinsic subtypes: Luminal A, Luminal B, HER2 overexpression and triple-negative BC (TNBC), each with different clinicopathological features.[6-8] Overexpression of the HER2 protein activates the tyrosine kinase signaling pathway, which triggers cell survival, tumor growth and metastasis. HER2 shows a link in regulating CD44+/CD24- expression (a marker for BC stem cells). Cell culture experiments indicate that CD44 binding to hyaluronic acid can trigger HER2 dimerization, resulting in phosphorylation, which triggers cell survival, tumor growth and metastasis.[9] Recent studies show that CD44 overexpression increases tumor-initiating cells in several cancers associated with cancer stem cell biomarkers.[10] This gene is involved in the process of tumorigenesis and metastasis in colon, bladder, stomach and breast cancer.[11]

Several studies show that CD44 overexpression is associated with cancer cell progression and metastasis.[12-14] In

contrast, other studies state that BC with CD44 overexpression has a good prognosis, such as Luminal A and basal subtypes.[5] Furthermore, since CD44 is associated with markers of stem cell cancer and resistance to trastuzumab, it is hoped that CD44 can be used as a prognostic indicator of tumor progression related to metastasis. It is even expected that it can be developed to support the treatment of BC as a targeted therapy.[4,7] This study aims to see the correlation between CD44 and HER2 expression in tissue and the incidence of distant metastases in BC patients.

METHODS

This study was cross-sectional with breast cancer patients who received chemotherapy at Wahidin Sudirohusodo Hospital Makassar from January until May 2023. The inclusion criteria were women with locally advanced breast cancer, invasive ductal carcinoma, and received a Cyclophosphamide-Doxorubicin-5FU (CAF) regimen.

We performed clinicopathology data collection, which involved age and grading. Then, we performed immunohistochemistry panel examination of ER, PR, Her2, and Ki-67. Data were collected, managed, analyzed, and presented in table and narration form, and then we compared it with the results of other studies.

Immunohistochemical examination

Immunohistochemical examination to assess CD44 and HER2 expression used Mouse monoclonal antibody anti-CD44 (HCAM) [156-3C11], USA and Rabbit Anti-Human c-erbB-2 oncoprotein monoclonal antibody (Leica biosystem, Singapore).[15] Next, it was observed through a light microscope with 400x magnification. Staining intensity and percentage of positive nuclei were recorded after manually segmenting the tumor from the stroma.

Statistical Analysis

Data was analyzed using SPSS version 22.0 (IBM Corp.; Armonk, NY, USA), version 26. Samples were analyzed using Chi-Square and Wilcoxon test. All procedures for this study were approved by the Health Research Ethics Committee of the Medical Faculty of Hasanuddin University, Universitas Hasanuddin Hospital, dan Dr. Wahidin Sudirohusodo Hospital, number: 267 / UN.4.6.4.5.31 / PP.36 / 2019

RESULTS

During the study period, 60 research participants were enrolled. Based on the characteristics of the participants, the youngest was 32 years, and the oldest was 69 years. In BC with de novo metastasis, the location of the most metastases was the lungs 22 cases (73.3%), followed by bones and brain, each with 3 cases (10%), then liver in 2 cases (6.7%) (Table 1).

According to the histopathological grade, the most cases obtained were grade 2 (medium) with 34 cases (56.6%) followed by grade 3 (high) with 22 cases (36.7%) and grade 1 (low) with 4 cases (6, 7%). Of the 30 BC samples with de novo metastasis, 22 were HER2 subtype (73.3%), and eight were triple negative (26.7%). Meanwhile, for BC samples without metastasis, 18 samples were obtained with the HER2 subtype (60.0%) and 12 samples with the triple-negative subtype (40.0%). Based on CD44 expression, 45 samples (75.0%) showed high expression, and 15 samples (25.0%) showed low expression.

In BC as a whole, both those with de novo metastases and those without metastases, a statistically significant relationship was found between HER2 expression and CD44, which are reflected in their p-value ($p<0.05$). In the table above, the odd ratio value is 4.636, which means there is a 4.6-fold tendency for CD44 overexpression in BC patients with the HER2 subtype compared to those with the triple-negative subtype (Table 2).

The results above show a significant relationship between CD44 expression and metastasis. This can be seen in the p-value of 0.007 ($p<0.05$). In the table above, an odd ratio value of 6,000 is obtained, meaning there is a 6-fold tendency for metastasis to occur in BC patients who experience CD44 overexpression (Table 3).

The statistical test results in the table above show no significant difference between CD44 and HER2 expression on the incidence of distant metastases. This can be seen from the p-value = 0.073 in the HER2 subtype and the p-value = 0.197 in the triple negative subtype, both of which show a p-value> 0.05.

DISCUSSION

Bivariate analysis between HER2 and CD44 expression using the Chi-square test showed a significant relationship with a significance value of $p=0.011$ ($p<0.05$). If we refer to the odds ratio (OR) value, subjects with HER2 overexpression have a 4.6 times tendency to experience CD44 overexpression. These results are supported by research by Lu et al. (2011), which showed a significant relationship between CD44+/CD24- expression and molecular subtype where CD44 overexpression was found in the HER2 subtype.

Olsson et al.[5] in a study of 187 breast cancers, found a significant relationship

Table 1. Characteristics of participants

Variable		n	(%)
Age (years)	< 40	13	21,7
	40 - 49	27	45.0
	50 - 59	14	23.3
	≥ 60	6	10.0
Metastasis location	Lung	22	73,3
	Liver	2	6,7
	Bone	3	10,0
	Brain	3	10,0
Stage	I	4	6,7
	II	34	56,6
	III	22	36,7
Subtype	HER2	40	66,7
	TNBC	20	33,3
CD44 expression	Low	15	25,0
	High	45	75,0

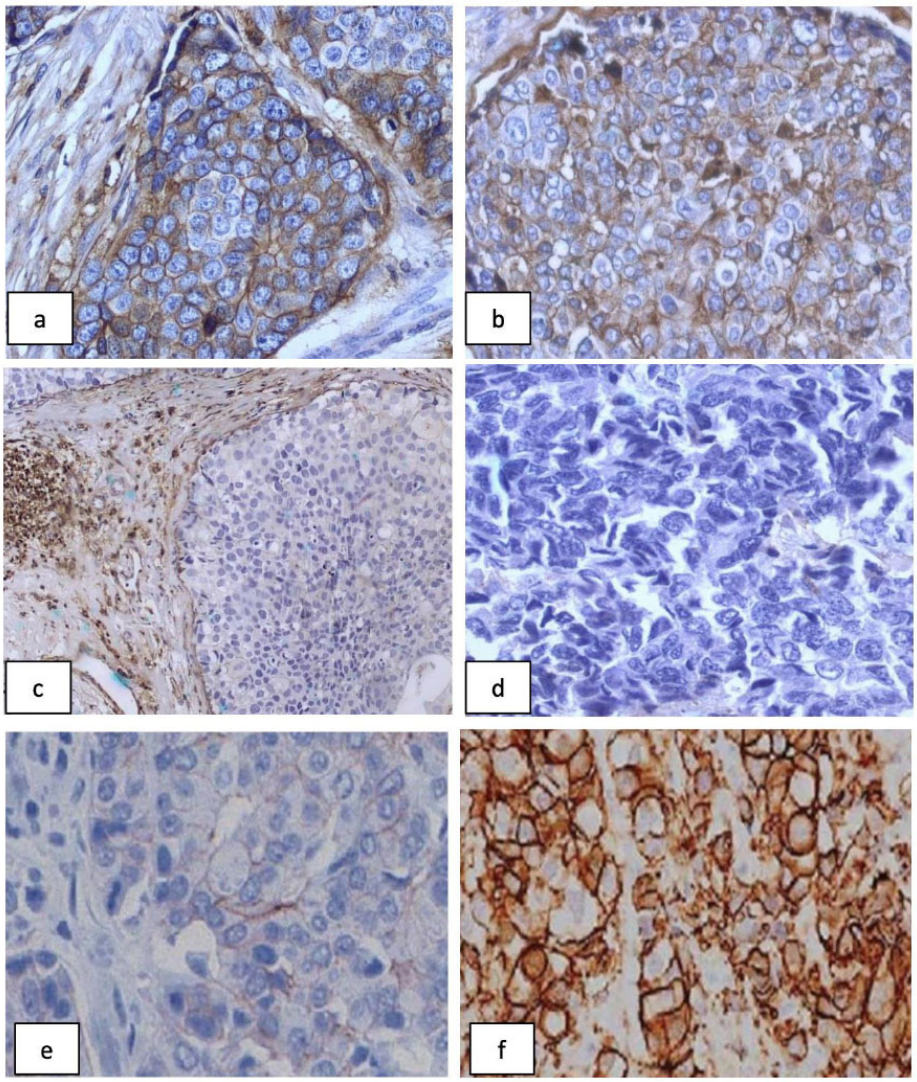

Figure 1. Immunohistochemistry of high CD44 expression, magnification 100x (a) and 200x (b); low CD44 expression (c and d); HER2 expression negative, magnification 400x (e); HER2 overexpression, 400x magnification (f).

Table 2. Correlation between CD44 expression and HER2 in non-luminal BC

Subtype	CD44		p-value	OR (95% CI)
	Overexpression n (%)	Low expression n (%)		
HER2	34 (75,6)	6 (40,0)	0,011	4,636 (1,346 – 15,968)
TNBC	11 (24,4)	9 (60,0)		

Note: *p= Chi-Square Test; CI = Confidence Interval.*

between CD44s expression and HER2 overexpression, where in the HER2 subtype, there was a high median CD44s isoform expression. Different results were shown by Xu et al.[4], where of the 120 BC samples studied, it was found that CD44 overexpression was more commonly found in negative HER2 status (48 samples). Meanwhile, 72 samples with HER2 overexpression showed low CD44 expression. However, prognostic analysis showed that CD44 mRNA overexpression in the HER2 subtype was significantly higher (p=0.007) than in the basal subtype (p=0.035). These two subtypes have an impact on shorter progression-free survival (PFS), which shows that CD44 can trigger tumor progression.

As is known, the CD44 molecule is a co-receptor with several other signal receptors, such as HER2. These two molecules bond via disulfide chains on the cell surface. Hyaluronan (HA)-CD44 interaction in BC cells can activate Grb2 and p185Her2. Furthermore, intra-cytoplasmic CD44 will bind to N-WASP, triggering cell growth and invasion through Ras and SOS.[16] Many studies show that tumors with HER2 overexpression cause poor prognoses, such as breast and ovarian cancer. It is because overexpression of this proto-oncogene is associated with poor tumor differentiation.[17]

The bivariate analysis results showed a significant relationship between CD44 expression and metastasis. This can be seen in the value p=0.007 (p<0.05). Based on the odds ratio (OR) value of 6.00 with a confidence interval (95% CI=1.346–15.968, it can be interpreted that BC subjects with CD44 overexpression have a 6-fold tendency to experience distant metastases.

These results are supported by in vivo studies which suggest that CD44 overexpression triggers invasion and metastasis of breast cancer cells to the liver via CD44–HA/NF-κB/cortactin signaling in addition to the PI3K/E2F1/surviving pathway.[16,18-20] Other studies also show that CD44 variant isoforms (CD44v3, v6, and v7-8) are positively associated with breast tumor development and poor prognosis.[21,22] However, different results were obtained from the study of Tse et al.[23], where loss of CD44 expression increased the risk of distant BC metastasis.

CD44 activates several signaling pathways, including Rho GTPase, Ras-MAPK pathway, and PI3K/AKT. Without intrinsic kinase activity, CD44 can trigger signals through adaptation with intracellular kinases and adapter proteins, binding the CD44 cytoplasmic domain to the actin cytoskeleton. CD44 can trigger signals through interactions with growth factors, enzymes, and cytokines. This signal transduction occurs through several mechanisms, such as HA-CD44 binding, activating kinases (Tiam1, p115, Rac1, c-Src and FAK, and Rho and Rac), then triggering cell migration.[16]

Bourguignon[24] showed that Rho-kinase plays an important role in the CD44v-ankyrin and RhoA interaction required for cell migration. Meanwhile, the interaction

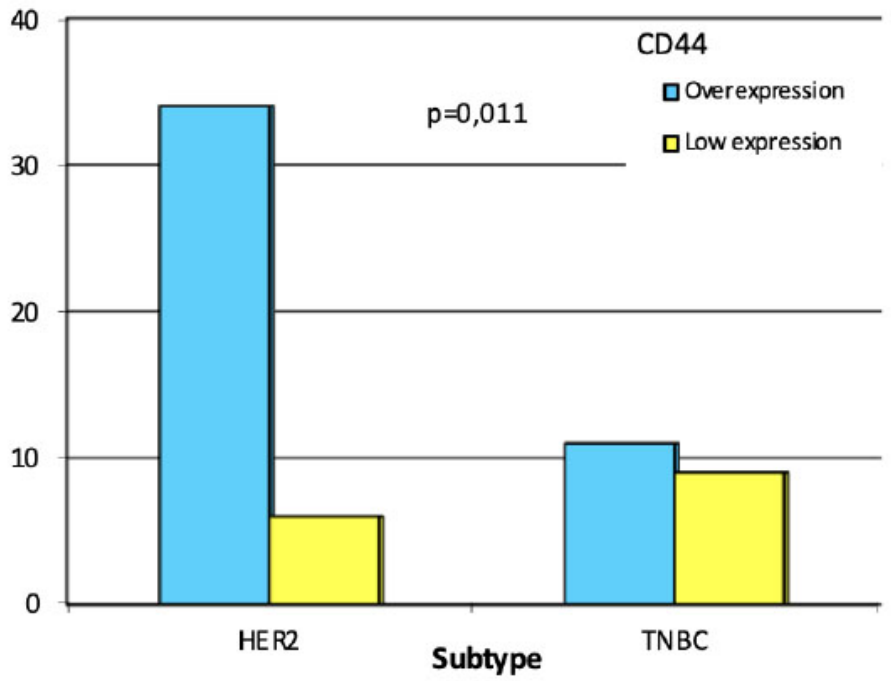

Figure 2. The relationship between CD44 expression and HER2 in non-luminal BC.

Table 3. Correlation of CD44 expression with distant metastasis in non-luminal BC

CD44 expression	Metastasis		p-value	OR (95% CI)
	Metastasis n (%)	No metastasis n (%)		
Overexpression	27 (90.0)	18 (60.0)	0,007	6,000 (1,482 – 24,299)
Low expression	3 (10.0)	12 (40.0)		

Note: *p= Chi-Square Tests; CI = Confidence Interval.*

of CD44 with actin filaments via the Ezrin/Radixin/Moesin (ERM) protein will trigger actin cytoskeleton remodeling and cell invasion, activation of PI3K and inhibition of the Merlin protein by Pak2. Merlin protein will inhibit CD44 and ERM binding, resulting in deregulation of cytoskeleton remodeling and cellular invasion. CD44 can also activate MMP-9, which causes collagen degradation and invasion.[25]

Other studies show that changes (switching) of CD44 are related to the epithelial-mesenchymal transition (EMT) process, which triggers recurrence and metastasis. In in vitro and in vivo studies in mice, it can be seen that the change in the variant isoform (CD44v) to the standard isoform (CD44s) is regulated by epithelial splicing regulatory protein 1 (ESRP1). Furthermore, the CD44s isoform activates the Akt signal, the key trigger for the EMT process. So, it was concluded that alternative splicing of CD44 contributes to the EMT process and BC progression and that gene regulation at this stage is necessary for regulating normal and pathological processes.[26,27]

Overall, there were 40 participants of the HER2 subtype. Meanwhile, the triple-negative subtype consisted of 20 participants. Analysis of the relationship between CD44 and HER2 expression on the incidence of distant metastasis through stratification tests did not show significant differences in the two subtypes. The HER2 subtype's p-value was obtained = 0.073 (p> 0.05). Meanwhile, for the triple negative subtype, the p-value = 0.197 (p> 0.05). Although no statistically significant relationship was found clinically, it was found that 95.5% (21/22) of BC subjects with HER2 subtype and 75% (6/8) of subjects with triple-negative subtype who experienced distant metastases showed CD44 overexpression.

Olsson et al.[5] and Inoue and Fry[28] showed a relationship between CD44 isoforms and intrinsic subtypes. Overexpression of variant isoforms (v2–v10 and v3–v10) is associated with good prognosis because it shows a positive expression of hormone receptors (ER, PR) and a low proliferation rate, which is generally found in luminal A subtype. Meanwhile, the overexpression of CD44s is more associated with poor prognosis because it is associated with HER2 overexpression and also the basal subtype, both of which often experience distant metastases. It was also found that BC with CD44 overexpression showed strong expression of ALDH1 as a marker for cancer stem cells (CSC). Regarding BC stem cells, research conducted by Rabinovich et al.[29] also concluded that there was a significant relationship between the CD44+/CD24- phenotype and the molecular subtype (p=0.02), especially the HER2 subtype, which is known to have a poor prognosis. However, this is still a matter of debate because several studies have found that CD44+/CD24- is more associated with the basal subtype.[5,30-32] On the other hand, Lu et al.[33] revealed that CD44+/CD24– cells act as progenitor cells in transit unrelated to specific molecular subtypes or clinicopathological parameters of invasive ductal BC.

The results of research by Chen et al.[34] involving 132 BC samples showed that of the 29 samples with HER2 overexpression, 24 samples (82.8%) showed CD44 overexpression. Meanwhile, for samples without HER2 overexpression, there were 59.2% (61/103) samples with CD44 overexpression. These results show a significant difference (p=0.015). There was a significant difference between disease-free survival (DFS) and overall survival (OS) regarding CD44 expression. Median DFS for CD44 overexpression was 46.89 months, while for low CD44 expression, it was 53.54 months (95% CI: 49.80–56.88 months, p=0.037). Meanwhile, the median OS in the CD44 overexpression sample was 51.85 months, while in the low CD44 expression sample, it was 57.61 months (95% CI: 55.54–59.68 months, p=0.032).

The limitation of this study is that the study is retrospective with the possibility of bias. Many study subjects were excluded because they had yet to undergo

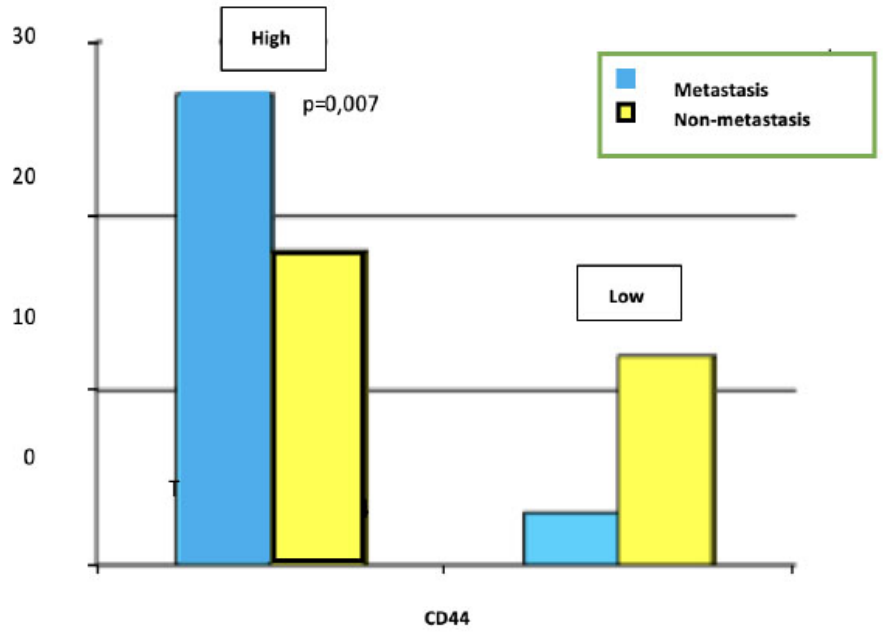

Figure 3. Relationship between CD44 expression and the incidence of distant metastasis.

Table 4. Correlation of CD44 and HER2 expression with distant metastasis in non-luminal BC

Subtype	CD44	Metastasis		p-value
		Metastasis n (%)	No metastasis n (%)	
HER2	High	21 (95,5)	13 (72,2)	0,073[a]
	Low	1 (4,5)	5 (27,8)	
TNBC	High	6 (75,0)	5 (41,7)	0,197[b]
	Low	2 (25,0)	7 (58,3)	

Note: [a,b] *p*=Fisher's Exact Test; CI = Confidence Interval.

immunohistochemical examination, tissue samples were not representative of the study, and they lost control.

CONCLUSION

There is a positive relationship between CD44 overexpression and HER2 overexpression, and subjects with the HER2 subtype are 4.6 times more likely to have CD44 overexpression than those with the triple-negative subtype. Overexpression of CD44 is positively associated with the occurrence of distant metastases in breast cancer. Subjects with CD44 overexpression tend to experience distant metastases 6 times more than subjects with low CD44 expression. CD44 expression is a prognostic factor for the incidence of distant metastasis in non-luminal breast cancer.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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AUTHOR CONTRIBUTION

DS: Conceptualization, Data curation, Formal analysis, Project administration, Funding acquisition, Investigation, Methodology, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing.

WH: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing.

SAS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing.

NS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Resources, Software, Validation, Visualization, Writing – review & editing.

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