ORIGINAL ARTICLE

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CD 105 as prognostic factors in advanced stage breast cancer patients

Dedy Hermansyah,[1*] Zafiral Azdi Albar,[2] Denni Joko Purwanto,[3] Lenny Sari,[4] Rizky Ifandriani Putri[5]

ABSTRACT

Background: Breast cancer is the most common cancer found in women worldwide. In 2012, more than 50% of breast cancer patients in Cipto Mangunkusumo Hospital were advanced breast cancer patients. Stage 3 breast cancer patients have five years' survival rate by 72%, while who's in stage 4 only by 22% even after receiving adequate treatment. It is said that only CD105, which specifically describes the intratumoral angiogenesis occurrences.

Methods: A retrospective cohort analytic data from patient medical records Dharmais Cancer Hospital from 2011-2014 were studied. A simple random sampling and obtained a total of 32 patients. Statistical analysis was performed using univariate and multivariate analysis SPSS version 17.0 and medcalc.

Results: The expression between CD105 with the survival rate is: crude HR 1.724 (95% CI 0.693 to 4.288) p=0.241. The median survival of the CD105 positive group is higher than the negative group. The relationship between CD105 groups Luminal A, therapy, and metastasis, the group with negative CD105 expression had a higher survival rate. There was a significant relationship between CD105 and clinicopathologic of breast cancer patients from age and CD105 expression (p=0.034). 71.8% of patients with HER2 negative, has a negative CD105 as well, and 60% of subjects with HER2-positive, suggesting that CD105 expression was also positive.

Conclusion: CD105 can not be used as a prognostic factor in patients with advanced stage breast cancer, high CD105 patients have a lower survival compared with low or negative CD105 patients, and CD105 expression correlated with age and PR.

Keywords: advanced stage breast cancer, CD105, prognostic factors, survival rate of breast cancer, angiogenesis marker

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[1]Surgery Subspecialty Study Program, Specialisation in Surgical Oncology
[2,3]Indonesia University
[4,5]Anatomic Pathology Department, Indonesian University

[*]Correspondence to: Dedy Hermansyah, Surgery Subspecialty Study Program, Specialisation in Surgical Oncology
escape744@gmail.com

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INTRODUCTION

Breast cancer is the most common cancer found in women worldwide. There were nearly 1.7 million new cases discovered in 2012, representing 12% of all cancer cases that exist, and 25% of all cancers in women.[1,2] In Indonesia, breast cancer is the greatest prevalence cancer after cervical cancer. According to Profil Kesehatan Indonesia 2008, breast cancer was first ranked cancer at the hospital in 2004 - 2007.[3,4] In Cipto Mangunkusumo Hospital, it is known that the number of patients with advanced breast cancer is increasing in many years. In 2008 there were 49.70% unknown advanced breast cancer patients of all cases of breast cancer in the hospital, then increased to 55.30% in 2009, declined slightly to 50.44% in 2010, but that number increased to 58% in 2011 and 2012.

Most patients with advanced breast cancer have a low survival rate despite getting adequate treatment. In patients with stage 3 breast cancer, five years survival by 72% while in stage 4 only by 22%. According to the American Cancer Society, the average survival rate of patients with stage 3 breast cancer is 84%, while stage 4 is only 19%. A study by Shenkier T, et. al. said that patients with stage 3B breast cancer with chemotherapy only have an overall survival of 60% .5 According to Mandal A, data in the UK suggests that 85% of women with breast cancer will live up to 5 years after diagnosis, and more than 75% of them survive up to 10 years. Based on data from the National Cancer Database in the year 2001 - 2002, obtained five years survival stage 3A breast cancer patients by 67%, 41% 3B, 3C 49%, and stage 4 by 15%. In addition, research by Rau KM, et. al. said that the recurrence rate for breast cancer is still in 20-30% despite having provided a diverse adjuvant therapy

There are a lot of angiogenesis marker has been shown to depict events in human neoangiogenesis, namely: CD31, CD34, VEGF and Von Willebrand Factor (vWF). However, these markers have not been able to describe specifically neoangiogenesis induced by cancer cells alone (intratumoral).

From various studies, it has been found that serum levels of CD105 associated with the incidence of metastasis, and high levels of CD105 are associated with changing in cells surface morphology, increasing migration, chemotaxis, and invasion towards the brain.[6,7] In addition, research

by Tabata et. al., Yao et. al., Tanaka et. al., are shown that there is a correlation between the anti-CD105 monoclonal antibody and increased survival rate of breast cancer patients. However, in studies by Page DL, et. al. and Lindmark G, et. al. are said that there is no relationship of serum levels of CD105 with survival rate.

This is a question for researchers, whether CD105 can be used as angiogenesis marker that replaces existing three markers, and whether CD105 can be used as a prognostic factor in advanced stage breast cancer. Therefore, researchers interested in conducting research on the role of angiogenesis in patients with advanced-stage breast cancer that using CD105 as a marker.

METHODS

This is a retrospective cohort study, using data gathered retrospectively obtained from the medical records for survival analysis and prognostic factor. This study used patient data in Anatomic Pathology Department Dharmais Cancer Hospital from 2011 to 2014.

The population is advanced stage breast cancer (IIIB-IV) cases who had been diagnosed at the Department of Anatomic Pathology of Dharmais Cancer Hospital in the period 2011-2014. A number of cases acquired during 3 years are 100 patients, then simple random were executed to obtained 32 patients as samples.

Table 1 **Relationship between confounding variables and Survival Rate of advanced stage breast cancer patients**

Variable		Status		HR (IK 95%)	P
		Live	Death		
Age	< 45 yo	10 (55,6)	8 (44,4)	0,612 (0,240-1,565)	0,306
	≥ 45 y o	20 (64,5)	11 (35,5)		
Stadium	III B	21 (70,0)	9 (30,0)	1,187 (0,744-4,547)	0,205
	IV	9 (47,4)	10 (52,6)		
Grade	1	9 (81,8)	2 (18,2)	Reff	
	2	12 (54,5)	10 (45,5)	2,931 (0,638-13,463)	0,167
	3	9 (56,2)	7 (43,8)	2,439 (0,505-11,783)	0,267
Metastase	No	21 (70,0)	9 (30,0)	1,839 (0,744-4,547)	0,187
	Yes	9 (47,4)	10 (52,6)		
Luminal A	Yes	21 (63,6)	12 (36,4)	1,989 (0,768-5,154)	0,157
	No	9 (56,2)	7 (43,8)		
Mastectomy	Yes	24 (61,5)	15 (38,5)	2,010 (0,624-6,474)	0,242
	No	6 (60,0)	4 (40,0)		
Therapy	Hormonal	18 (75,0)	6 (25,0)	3,240 (1,147-9,148)	0,026
	Chemotherapy	12 (48,0)	13 (52,0)		

Histopathological prognostic parameters for each tumor assessed by independent pathologists. Networks that have been used as paraffin block sliced 3 millimicrons and placed on a slide overnight. Then sample slide was heated on a hotplate for 60 minutes at 60°C temperature. After that, the slides are arranged on a tool Ventana XT and start to begin the process for 3 hours. CD105 antibody / Endoglin / TGF Receptor 1/3 of SpringBio USA dropped as much 7ml when the process is already running 2 hours. Once completed, the slide is washed with soapy water then do serial dehydration with alcohol concentration increased from 70%, 100%, 100%, 100% and clearing with xylol 2 X. At the final stage, the slide is closed. Negative controls were made for each case by skipping the step of administering the primary antibody.

Positivity of tumor cell nucleus that stained positive assessed from a minimum of 500 tumor cells by using computer applications Image J. The choice of location of tumors assessed from the tumor with strongest immunohistochemical expression. Part of tumors was evaluated for MVD at 20X magnification. MVD is expressed as the number of blood vessels per field. Average of four visual fields is recorded as MVD for each tumor.

Data was analyzed using univariate and multivariate analysis. Survival analysis has done by creating Kaplan-Meier graph. The significance of these risk factors was analyzed using Cox Regression test. Data analyzed using computer SPSS program version 17.0 and medcalc.

RESULTS

General Characteristics

Demographic data subject of this study can be seen in table 1. Thirty people aged ≥ 45 years and the remaining 19 persons aged <45 years. Based on this age group, as many as 11 people who died (57.9%) were from group ≥ 45 years and 8 others (42.1%) were from group <45 years. Based on the clinicopathologic characteristics, there are 30 subjects in stage 3B, while the remaining 19 people on stage 4. Of 19 subjects who died, 10 (52.6%) were patients with stage 4 cancer.

There are 30 subjects without metastases, with 21 people living and 9 people died. In this study, the majority of subjects are in grade 2 and of the whole subject who died, 10 (52.6%) are in grade 2. There are two types of therapy were obtained by the subject of this study, namely hormonal and chemotherapy. A total of 6 people (31.6%) that died, got hormonal therapy while the remaining 13 (68.4%) received chemotherapy.

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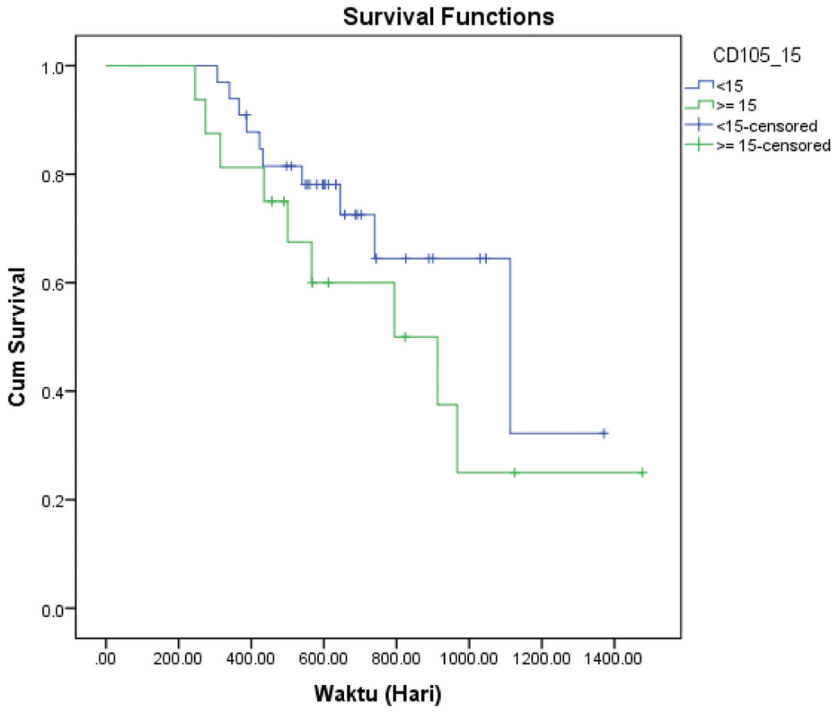

Figure 1 Kaplan-Meier curves that Describing Patient Survival Rate Related to CD105 Expression

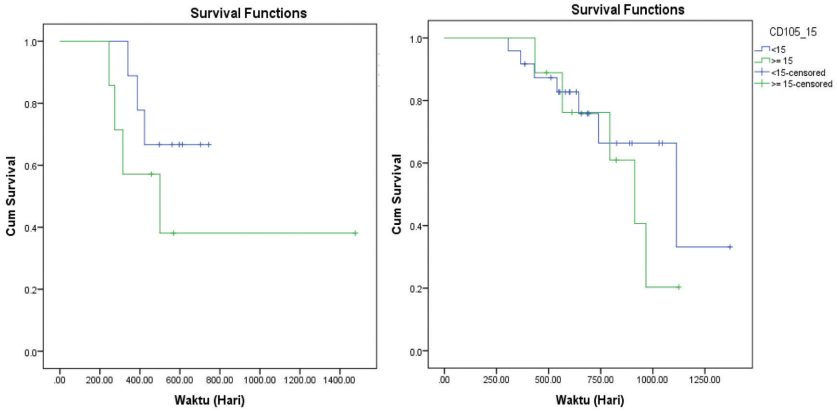

Figure 2 Kaplan-Meier curves that Describing Survival Rate Patients Associated with CD105 expression based on Luminal A group (up: non-Luminal A, down: Luminal A)

Table 2 Relationship between CD105 and Advanced Stage Cancer Patients Survival Rate in Dharmais Hospital

	Status			
Variable CD 105	**Live**	**Death**	**HR (IK 95%)**	**p**
Negative (< 15)	23 (69,7)	10 (30,3)	1,724	0,241
Positive (≥ 15)	7 (43,8)	9 (56,2)	(0,693-4,288)	

Other Characteristics

In bivariate analysis, no significant correlation between the expression of CD105 and crude survival rate with HR 1.724 (95% CI 0.693 to 4.288) p = 0.241.

From table 2, looks no statistical significance. Where the analysis of survival by Kaplan-Meier showed no significant differences between positive groups of CD105 expression and CD105 negative groups in patients with advanced stage breast cancer (log-rank p=0.236), but analysis of median survival for mortality incidence of CD105 positive expression groups are in 1113 days, while for negative CD105 groups are 794 days. Here we see that the CD105 positive had better median survival than CD105 negative with a median difference as much as 319 days. Kaplan-Meier curves that showed the survival rate of mortality based on CD105 expression can be seen in Figure 1.

After looking at the relationship between CD105 expression and mortality observed the relationship between confounding factors with an increased hazard ratio (table 1).

Variables that have p <0.25 in the bivariate analysis are included in multivariate analysis. Variables that included in the multivariate analysis was the stage, grade, metastasis, luminal A, mastectomy, and therapy. In a multivariate analysis by Cox Proportional Hazard Regression Model, showed that Fully adjusted hazard ratio between advanced breast cancer patients and positive CD105 expression patients that died after addition of confounding variables, i.e. therapy and metastasis. Changing of adjusted hazard ratio for positive CD105 expression on each additional confounding variables can be seen in Table 3.

Table 3 shown that changing of HR for CD105 expression after added variables gradually. Variables that had value > 10% are confounding variables, that is therapeutic and metastasis.

From table 4 can be seen groups of luminal A and non-luminal A, the CD105 expression is not statistically significant in influencing the survival rate. Breast cancer patients that included in Luminal A group with positive CD105 expression at risk of dying 1,475 times compared to the negative group. While in non-Luminal A group, patients with positive CD105 was 2,306 times at risk of dying than those with negative CD105 expression.

When explored further into the analysis of survival in Kaplan-Meier curves, in Luminal A group, patients with negative CD105 expression has mean survival 153.42 days longer than positive CD105 expression. Similarly, the non-Luminal A group, negative CD105 has mean survival 158.47 days longer than positive CD105 expression. (Figure 2)

When viewed from therapeutic modality, CD105 expression was not statistically significant in influencing the survival rate. However, breast cancer patients who get hormonal therapy with

Table 3 **Crude HR and Adjusted HR with 95% CI for CD105 expression on mortality in confounding variables with Gradual Addition**

CD105 Positive expression (≥ 15)	HR (IK 95%)	HR Change
Crude HR	1,724(0,693-4,288)	
Adjusted HR		
+ Therapy	1,508 (0,602-3,780)	12,5%
+ Luminal A	1,416 (0,561-3,574)	6,10 %
+ Metastase	1,029 (0,369-2,874)	27,33%
+ Grade	1,038 (0,359-2,892)	0,87%
+ Mastectomy	1,078 (0,378-3,099)	3,85%
+ Stadium	1,094 (0,366-3,270)	1,48%

Table 4 **Relationship between CD105 with Survival Rate by category of Luminal A**

	Status			
Variable	**Live**	**Death**	**HR (IK 95%)**	**P**
Luminal A (n=33)				
CD 105 Negative (< 15)	17 (70,8)	7 (29,2)	1,475	0,510
CD 105 Positive (≥ 15)	4 (44,4)	5 (55,6)	(0,465-4,683)	
Non-Luminal A (n=16)				
CD 105 Negative (< 15)	6 (66,7)	3 (42,9)	2,306	0,276
CD 105 Positive (≥ 15)	3 (33,3)	4 (57,1)	(0,513-10,356)	

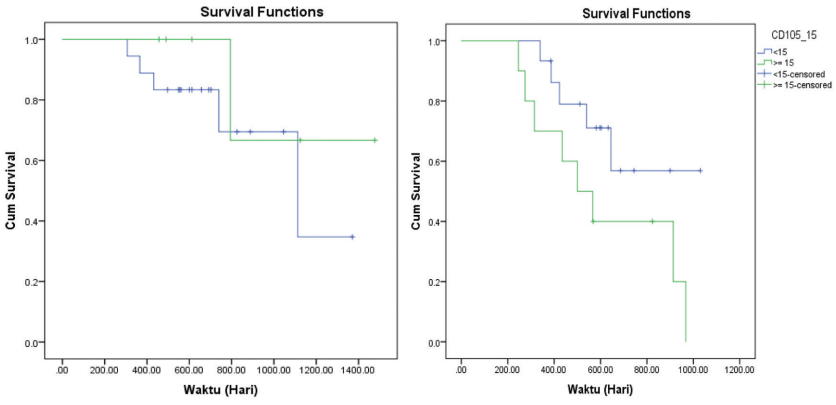

Figure 3 Kaplan-Meier curves that Describing Survival Rate Patients Associated with CD105 expression based on therapy group (up: Chemotherapy, down: Hormonal)

positive CD105 expression were 0.391 times riskier of dying compared with negative CD105 expression. While in chemotherapy group, patients with positive CD105 was 2,519 times riskier of dying than negative CD105 expression (Table 7).

Based on the analysis of survival in Kaplan-Meier curves, patients with hormonal therapy had mean survival 427.33 days longer than patients with chemotherapy. (Figure 3)

Viewed from no metastasis group, CD105 expression was not statistically significant in influencing survival rate. However, breast cancer patients who undergo metastasis with positive CD105 expression were riskier of dying 1,841 times compared with negative CD105 expression. From group without metastasis, patients with positive CD105 were 1,530 times riskier of dying than negative CD105 expression. (Table 8)

When explored further into the analysis of survival in Kaplan-Meier curves, from group of metastasis, patients with negative CD105 expression had mean survival of 547 days longer than positive CD105 expression. Similarly, the group without metastasis with negative CD105 have mean survival 68.03 days longer than positive CD105 expression. (Figure 4)

Researchers analyzed the relationship between CD105 expression and clinicopathological in advanced stage cancer patients. In Table 10, can be seen that in age group <45 years there were 10 people with negative CD105 and 8 people with positive CD105, whereas in the age group 45 years and above, there are 23 people with negative CD105 and 8 people with positive CD105. Relationship between age and CD105 expression was considered statistically significant (p = 0.034). In stage 3B or 4, there were more subjects with CD105 negative than positive (69% and 63.3%). In the relation with the expression of ER and PR, more than 50% subjects had a negative CD105 expression in both positive or negative ER and PR expression. However, Relationship between CD105 expression and PR expression was statistically significant (p = 0.042).

A total of 71.8% patients with HER2 negative, has negative CD105 as well, and 60% of subjects with HER2-positive, has also positive CD105 expression. In relation to KI67 expression, both in positive and negative KI67 expression, more subjects with negative CD105. Similarly with metastasis, but after calculation, obtained RR = 1.2. In grading, grade 1,2, and 3 has more subject with negative CD105. In variables therapy, as well as luminal A, obtained more subjects with negative CD105.

DISCUSSION

Characteristics of Research Subjects

From demographic data, more patients aged ≥ 45 years old compared to those <45 years old. This is similar to the research Aryandono T, where the average age of breast cancer patients in Yogyakarta is 49 years old.[8] In a study by Hisham, et. al. who took the subjects of Malaysian women also obtained the highest incidence at ages 40-49 years old.[9] In addition, research by Ferlay D, et. al. obtained incidence of breast cancer in the Asia-Pacific region increased at

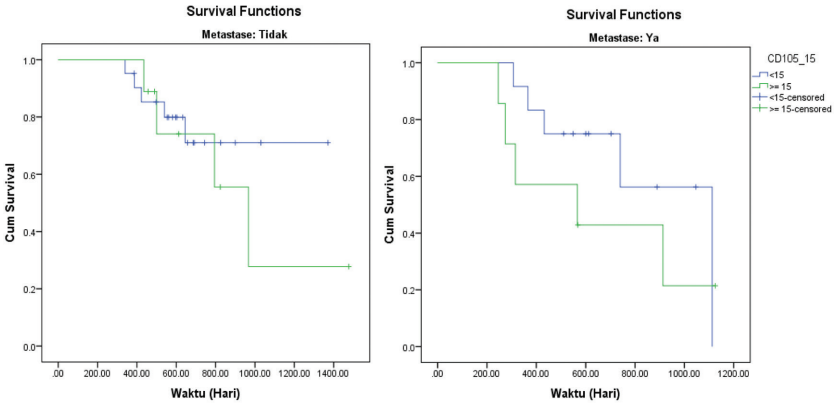

Figure 4 Kaplan-Meier curves that Describing Survival Rate Patients Associated with CD105 expression based on Metastasis (up: non-metastatic, down: metastasis)

Table 5 Median Survival of CD105 Expression in Luminal A and non-Luminal A Group

Variable	Median Survival
Luminal A	
Negative (< 15)	777,19
Positive (≥ 15)	623,77
Non-Luminal A	
Negative (< 15)	1010,21
Positive (≥ 15)	851,74

Table 6 Relationship between CD105 and Survival Rate Based on Therapy Group

	Status			
Variable	Live	Death	HR (IK 95%)	P
Hormonal (n= 24)				
CD 105 Negative (< 15)	13 (72,2)	5 (27,8)	0,391 (0,045-3,439)	0,398
CD 105 Positive (≥ 15)	5 (83,3)	1 (16,7)		
Kemoterapi (n=25)				
CD 105 Negative (< 15)	10 (66,7)	5 (33,3)	2,519 (0,813-7,805)	0,109
CD 105 Positive (≥ 15)	2 (20,0)	8 (80,0)		

Table 7 Median Survival in therapy group based on CD105 Expression

Variable	Median Survival
Hormonal (n= 24)	
Negative (< 15)	1138,43
Positive (≥ 15)	
Chemoterapy (n=25)	
Negative (< 15)	711,10
Positive (≥ 15)	

the age of 45-50 years old.[1] However, this incidence is slightly different compared to the incidence of breast cancer in European women who are in the older age range that is 60-70 years old.[10] In the age group ≥45 years old, the mortality rate is higher than age group <45 years old. According to a study by Ferlay J, et. al., survival rate was worse in patients with older age.[1] Survival rate was also associated with comorbidities that may exist in older patients.[1,11]

Based on the clinicopathologic characteristics, there were 30 subjects with stage 3B, while the remaining 19 were at stage 4. Of the 19 subjects who died, 52.6% are patients with stage 4.

In the study by Aryandono T, showed that in a higher stage, the greater number of metastases, the mortality rate will increase (p = 0.001).[8] Soerjomataram I, et. al. also showed that patients with higher stage, the survival rate is down by 40% compared to the lower stage when diagnosed early, while the survival rate in patients with metastatic just 0.72 when compared to patients without metastasis.[11] Arriagada R, et. al. Suggests that the relationship between metastasis and mortality, there were RR increased from 1.4 times to 4.6 times depending on number of metastasis.[12]

In PA grading, most of the subjects are in grade 2 and the higher the grade, the more the percentage of subjects who died than the number living on each grade. The similarity with research by Soerjomataram I, et. al. that there is a linear relationship between increasing in grade with numbers of mortality.[11] Research by Arriagada R, et. al also supports the findings of this study with the results of increased RR in patients with higher grade (RR = 1.6 to 2.0 for grade 2 and grade 3).[13]

In terms of therapy obtained by patients, as many as 13 people who died (68.4%) received chemotherapy and 6 (31.6%) received hormonal therapy. This is possible because of chemotherapy tend to be given to end-stage cancer. In addition, hormonal therapy was used in cancer patients with positive hormonal receptor expression. Anaise D explained that the 5-years survival rate in patients with hormone receptor positive was 97% while the negative ones only 54%.[12] Description about longer live of patients with Luminal A, can also be indirectly associated with positivity of hormonal receptor in group luminal A.

CD105 as a Prognostic Factor

In a variety of malignancies, including breast cancer, angiogenesis showed to correlate with the high rate of metastasis. CD105 is cell membrane glycoprotein that is expressed on activated proliferative of endothelial cells, and have been correlated with prognosis in patients with breast cancer.[5]

Table 8 Relationship between CD105 and Survival Rate Based on Metastasis

Variable	Status		HR (IK 95%)	P
	Live	Death		
Metastasis (n=19)				
CD 105 Negative (< 15)	7 (58,3)	5 (41,7)	1,841 (0,524-6,468)	0,341
CD 105 Positive (≥ 15)	2 (28,6)	5 (71,4)		
Non Metastasis (n=30)				
CD 105 Negative (< 15)	16 (76,2)	5 (23,8)	1,530 (0,401-5,834)	0,533
CD 105 Positive (≥ 15)	5 (55,6)	4 (44,4)		

Table 9 Median Survival in Metastatic group based on CD105 Expression

Variable	Median Survival
Metastasis (n=19)	
Negative (< 15)	1113.00
Positive (≥ 15)	566.00
Non Metastasis (n=30)	
Negative (< 15)	1116.36
Positive (≥ 15)	948.33

This study found that the subject of research with positive CD105 has a mortality rate of 56.2% as compared to subjects with negative CD105 (30.3%), but apparently, this data is not statistically significant (p = 0241). However, it can be seen the value of hazard ratio for 1724, which means subjects with positive CD105 1.7x greater risk of experiencing mortality compared with subjects with negative CD105.

Viewed on a Kaplan-Meier curve, it was found that the survival rate of patients with positive CD105 was 319 days lower than patient with CD105 negative, but this data was not statistically significant (log rank = 0.236). This is possible because of the time (435 days) in which there is contact between the survival curves of subjects with positive and negative CD105 that can reduce significantly. However, after day 435, seen constantly that subjects with negative CD105 had better survival rate than subjects with positive CD105. In research by Dales. JP, et.al. states that the number of new blood vessels more than 15 pieces in positive CD105, significantly correlated to the survival rate of breast cancer patients (p = 0.001).[14] This study result that not statistically significant can also be affected by sample size that too small where these

Table 10 Relationship between Expression of CD105 and clinicopathologic

Variable		CD105		P
		Negative (< 15)	Positive (≥ 15)	
Age	< 45 yo	10 (55,6)	8 (44,4)	0,034
	≥ 45 yo	23 (74,2)	8 (25,8)	
Stadium	III-B	21 (70,0)	9 (30,0)	0,475
	IV	12 (63,2)	7 (36,8)	
Estrogen Receptor (ER)	Positive	26 (70,3)	11 (29,7)	0,052
	Negative	7 (58,3)	5 (41,7)	
Progesterone Receptor (PR)	Positive	25 (69,4)	11 (30,6)	0,042
	Negative	8 (61,5)	5 (50,0)	
Her-2	Negative	28 (71,8)	11 (28,2)	0,320
	Positive	5 (50,0)	5 (50,0)	
KI 67	≤ 10%	3 (75,0)	1 (25,0)	0,796
	>10%	30 (66,7)	15 (33,3)	
Metastasis	No	21 (70,0)	9 (30,0)	0,472
	Yes	12 (63,2)	7 (36,8)	
Grade	1	8 (72,7)	3 (27,3)	Reff
	2	15 (68,2)	7 (31,8)	0,349
	3	10 (62,5)	6 (37,5)	0,379
Therapy	Hormonal	18 (75,0)	6 (25,0)	0,037
	Chemotherapy	15 (60,0)	10 (40,0)	
Luminal A	Yes	24 (72,7)	9 (27,3)	0,085
	No	9 (56,2)	7 (43,8)	

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study samples were 49 patients while in a study by Dales. JP, et. al. are 929 samples.[15,16] Moreover, prognosis of CD105 that not statistically significant on this research is understandable because it is based on research by Rau KM, et. al. and Martinez LM, et. al. that stated CD105 correlated more strongly as a prognostic factor in patients with early stage breast cancer compared to patients who had been on advanced stage.[17,18,19,20]

In addition, positive CD105 is also associated with the incidence of metastasis, especially bone metastasis in early stage breast cancer.[15,21] In this study, seen a tendency (RR = 1.2) even though the research subjects are patients with advanced breast cancer.

Confounding Factors Affecting Relationship between CD105 and Survival Rate

In this research, there are confounding factors that were statistically significant in the relationship between CD105 and survival rate, the choice of therapy and metastasis. From the data of patient characteristics, can be seen that difference in treatment choice affected the mortality number. In addition, a study by Ferlay J, et.al. and Youlden DR stated that the mortality rate has a relation with the absence of hormonal receptors. This is associated with hormonal therapy options that can be selected if the hormonal receptors of cancer cells were positive.[1,3,11,12,22,23] As for metastasis, we can refer to Aryandono T research that suggests the higher the stage, the greater number of metastases, the mortality rate will increase (p = 0.001).[8] Soerjomataram I, et. al. also stated that patients with higher stage, the survival rate is going down by 40% compared to lower stage when diagnosed early, while the survival rate in patients with metastatic just 0.72 when compared to patients without metastasis.[11]

The relationship between CD105 with Survival Rate by category of Luminal A

Researchers are also trying to compare the survival rate of patients by Luminal A group. It can be seen that CD105 expression is not statistically significant in influencing the survival rate. However, breast cancer patients in Luminal A group with positive CD105 expression were at risk of dying compared to 1,475 times in Luminal A breast cancer patients with negative CD105 expression. While in the non-Luminal A, patients with positive CD105 was at risk of dying 2,306 times than negative CD105 expression.

It can be associated with Luminal A that has positive hormonal receptor expression levels with negative Ki67 level. As has been discussed in research by Ferlay J, et. al. and Youlden DR that stated the mortality rate has positive relationship with the absence of hormonal receptors, we can conclude indirectly why non-luminal A patients with positive CD105 had higher hazard ratio when compared with luminal A group with positive CD105.[1,3]

The relationship between CD105 with Survival Rate Based on Therapy group

Based on group therapy modalities whether CD105 expression was statistically significant in influencing survival rate, and the result was not statistically significant. However, when viewed from the Kaplan-Meier curve, patients with hormonal therapy had mean survival 427.33 days longer than patients with chemotherapy.

This may be caused by the tendency of chemotherapy in end stage cancer with a high grade. Additionally, Anaise D explained that the 5-years survival rate in patients with hormone receptor positive was 97% while the negative ones only by 54%.[12] In the study by Gavin, et. al. said that using hormonal therapy tamoxifen can decrease angiogenesis, besides, in research by Ramadan, et. al. stated that hormonal therapy may also reduce levels of VEGF 65 as much as 82%.

In a study by Beresford MJ Research, stated that chemotherapy in patients with positive CD105 has a lower survival rate than in patients with negative CD105. This is related to the fragility of new blood vessels are formed during the process of neoangiogenesis that relatively fragile when compared to normal blood vessels and causes the distribution of chemotherapy was not optimal. Moreover, the research by Adamson noted that chemotherapy causes injury to endothelial cells.

The relationship between CD105 with Survival Rate Based on Metastasis

Based on the presence or absence of metastasis, the expression of CD105 was also not statistically significant to the survival rate. However, both patients with metastatic or not, the group with positive CD105 had mean survival rate that is shorter than negative CD105 expression. This is similar to a research by Vo MN, et. al. which states that the expression of CD105 is a marker predictive of the survival rate that is low and hormonal therapy success rate that is small for breast cancer with metastasis.[24]

Relationship between Expression of CD105 and Clinicopathologic

The relationship between the CD105 expression with clinicopathologic, can be seen from the range of patients number, there is an inverse relationship between the CD105 expression with age where there are more patients with negative CD105 in

both age groups, as well as the expression of the receptor hormonal either PR or ER where as many as 78.7% of patients with negative CD105 have a positive expression of ER and only 24.2% of patients with negative CD105 expression which also has a negative PR. While the expression of HER2, there was a positive relationship where 84.4% of patients with negative CD105 has a negative HER2 gene expression as well. In conjunction with KI67 expression, both in the expression of positive and negative KI67, there were more subjects with negative CD105. From all this data, which has statistically significance result is the relationship between CD105 with age and PR.

Results in this study is quite similar to the research by Rau KM, et. al. that stated there is an inverse relationship between the expression of hormonal receptors and CD105 expression and there is a positive correlation between the expression of CD105 with HER2 expression and KI67.[16] Similar statements are also listed on the research by Esquer FG, et. al. stated that CD105 expression had inverse correlation with estrogen receptor expression and progesterone.[16,20] Significance of the relationship between CD105 with PR in this study may be due to the relationship of both of them with the mortality rate of breast cancer patients. Meanwhile, the research by Roura S, et. al. stated that there was no correlation between age and the expression of CD105 (young subjects mean age 24 years old and older subjects mean 77 years old).[23] The significance of the relationship between CD105 with age may be caused by age ranges are quite different from previous studies. Discrepancy from theory that CD105 expression is supposed to have a positive relationship to KI67 expression can be described by statement by Park D, et. al. that the cutoff of > 10% is optimal for making KI67 as a single prognostic factor in primary tumor cells, whereas the optimal cutoff for tumor cell metastasis Is > 15%.[25]

In relation with tumor grade, this study found that in all grade obtained that more patients with negative expression of CD105 than the positive group. In a study by Miyata Y, et. al. states that CD105 is a marker that is highly related with the stage and grade of cancer. This difference is probably due to the results of a number of research subjects were less when compared with 122 subjects who stated in the study by Miyata Y, et. al.

When viewed from the selection of therapeutic modality, there are 18 people (75%) patients with hormonal therapy who have a negative CD105, whereas, from the expression on the modalities of chemotherapy, there was no significant difference between the positive and negative expression of CD105. While in relation to the classification based on Luminal A and non-Luminal A, there were 24 people (72.7%) patients were included Luminal A group with negative CD105 expression. As we know, the selection of hormonal therapy is done when the hormonal receptor expression of tumors was positive. While the category that includes Luminal A are patients with positive hormonal receptor expression. In the study by Rau KM, et. al. mentioned that there is inverse relationship between the expression of hormonal receptors with expression of CD105 and there is a positive correlation between the expression of CD105 with HER2 expression and KI67.[16] Esquer FG, et. al. stated that CD105 expression had inverse correlation with estrogen receptor expression and progesterone.[16,20] Therefore the findings in this study were similar to previous studies. Regarding the significant relationship between modality therapy with CD105 expression may also be associated with statements regarding this hormonal receptors.

RESEARCH LIMITATIONS

The author realizes that this study does have some limitations, among others, are:

1. Data were retrospectively made the author can not control the subject well
2. A large amount of data that can not be used in this study
3. Limited observation time that is available

CONCLUSION

It can be concluded that in this study, CD105 can not be used as a prognostic factor in patients with advanced stage breast cancer, high or positive CD105 has lower survival compared with low or negative CD105, and expression of CD105 correlated with age and PR.

SUGGESTION

This study found nominally significant differences in mortality subject with positive CD105 compared to negative CD105, so did the Kaplan-Meier curves although the two are not statistically significant. This is probably because the study was not able to do the control of the subject and how much data is excluded. Therefore, the authors suggest further research is continued in the form of a prospective study in order to better control the research subjects.

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