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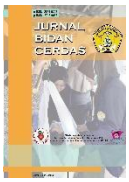

Serum Progranulin Levels as Markers of Mammary Tumors in Women

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ABSTRACT

Introduction: Carcinoma mammae is a malignant tumor that develops from breast cells and has the potential to invade the surrounding tissue (invasive) or metastasize to other parts of the body. While it is more frequently diagnosed in women, there are cases where it is also found in males. **Purpose**: This study aims to identify variations in serum progranulin levels as distinguishing factors between benign mammary tumors and mammary carcinoma. **Method**: The research adopts a quantitative approach with a cross-sectional design to ascertain the significance of serum progranulin levels in patients with mammary tumors. The study includes the entire accessible population diagnosed with mammary tumors by clinicians in the Surgical Oncology Department of Dr. Wahidin Sudirohusodo Teaching Hospital in Makassar, with a sample size of 78 individuals. Normality is assessed using the Kruskal-Wallis test, and differences are examined through the Mann-Whitney test. **Result**: A substantial difference exists in serum progranulin levels among breast carcinoma patients with benign mammary tumors and the control group (P<0.001). The mean difference in benign tumors is 121.08±56.84, whereas in breast carcinoma, it is 239.54±34.79. **Conclusion**: Serum progranulin levels can be employed as a potential alternative for diagnostic support in the early detection of both benign mammary tumors and mammary carcinoma

INTRODUCTION

Carcinoma mammae is a growing malignant tumor from cells breasts and can spread to network surrounding (invasive) or spread to part body (metastasis), most often found in women, but in some cases are also found in men (Smith et al., 2014). Data from the International Agency for Research on Cancer (IARC) in 2012, shows The incidence of mammary carcinoma is 40 per 100,000 women. System Hospital Information (SIRS) 2010, mammary carcinoma as many as 12,014 cases (28.7%) were the highest type of carcinoma in the patient take care stay nortake care road throughout

House sick in Indonesia. Carcinoma is reason death number seven in Indonesia with percentage of 5.7%. whole reason death (Kemenkes, 2018).

Hinder mental growth and development (Anindita, Marnolia, Putra, Haikal, & Tambunan, 2018). 2014 is estimated as many as 715,000 cases new mammae carcinoma in developed countries and 577,000 cases in less developed countries until currently growing, 2012 in Europe more of 131,000 women die because of mamma's carcinoma. Year 2012 worldwide forecast about 522,000 women die due to carcinoma mammae with level 2 death varies around the world. The metastatic ability of mammary carcinoma greatly affects the prognosis and survival life patient because that detection early detection and prevention of metastatic processes objective main from management of mammae carcinoma (American Cancer Society, 2013-2014).

at this time there is a number of method used _ For monitoring patient with early-stage and advanced- stage mammary carcinoma . the test are the Cancer Antigen 15-3 (CA 15-3) Test, Cancer Antigen 27-29 (CA27-29) and Carcinoembryonic Antigen (CEA). Hou et al's research shows that in patients with metastatic mammary carcinoma the sensitivity and specificity of CA 27-29 was 85.7%, CA 15-3 82.8% and CEA 62.8%. this show that CA 27-29 more sensitive and specific compared to CEA, but similar with CA 15-3 for detection of metastatic mammary carcinoma and monitoring. Detection rate low in stage early in mammary carcinoma causes lack of use routine CA 15-3 for screening and for recurrence of mammary carcinoma, though moment this CA 15-3 was used For monitor effectiveness maintenance patients with metastatic mammary carcinoma other than imaging and symptoms clinical (Tkaczuk et al., 2011).

Progranulin, also known as GP88, acrogranin, or precursor epithelin granulin, is the largest member of the cysteine-rich polypeptide growth modulator family, consisting of 6 kDa epithelins or granulins. Progranulin plays a role in tumorigenesis, including the stimulation of proliferation, angiogenesis, migration, invasion, cell survival, and Matrix Metalloprotease activity. Tkaczuk et al.'s research (USA, 2011) suggests that serial testing of serum progranulin levels (GP88) may have significant value as a biomarker for detection, monitoring, and follow-up in the management of mammary carcinoma (Tkaczuk et al., 2011). Breast cancer, the most frequently occurring cancer in women, represents a significant public health concern, with potentially fatal consequences. It is estimated that there are 1,384,155 new cases worldwide, resulting in nearly 459,000 associated deaths (Olawoye, Adeagbo, & Bolaji, 2018; Winters, Martin, Murphy, & Shokar, 2017). The identification of modifiable factors can contribute to the development of prevention strategies aimed at reducing the incidence of breast cancer (Kamińska, Ciszewski, Łopacka-Szatan, Miotła, & Starosławska, 2015). This study aims to identify variations in serum progranulin levels as distinguishing factors between benign mammary tumors and mammary carcinoma.

METHOD

This cross-sectional study aims to determine the role of serum progranulin levels in breast cancer patients. The population in this study comprises all breast tumor patients examined at the Surgical Polyclinic of Dr. Wahidin Sudirohusodo Teaching Hospital in Makassar and other affiliated hospitals. The research sample includes the entire accessible population of breast tumor patients diagnosed by clinicians in the Surgery Department of Dr. Wahidin Sudirohusodo Teaching Hospital in Makassar and other

affiliated hospitals who meet the inclusion criteria. The analysis involves using the Kruskal-Wallis test to determine the normality distribution of the data and the Mann-Whitney test to identify differences in serum progranulin levels among breast cancer patients.

RESULT

The results of this study can be seen in the following tables.

Table 1. Sample Distribution Based on Serum Progranulin Levels, Histopathology and Staging

Variable	n	Serum Progranulin Level (ng/ml)	
		10-700	>700
		n(%)	n(%)
Group Control *	38	38 (100)	-
Benign Mammary Tumor	40	40 (100)	-
Carcinoma Mammae			
Early Stage**	35	35 (100)	-
Advanced Stage ***	37	26 (70.30)	11 (29.7)

Based on table 1, there were 150 research subjects consisting of 38 control group samples from a study conducted by Wahyunie et al in 2015 (100%), 40 samples with benign mammary tumors and 75 samples with carcinoma mammary divided into 35 samples of early stage mammary carcinoma 5 samples came from Wahyunie et al's study (14.3%), and 37 samples of advanced stage mammary carcinoma 27 samples came from Wahyunie et al's study (72.9%). All of these subjects were women who met the research sample criteria with a minimum age of 20 years and a maximum of 51 years. Serum progranulin levels were divided into 3 groups, namely <10 ng/mL, 10-700 ng/mL and >700 ng/mL. Benign mammary tumors with a total sample of 40 (100%), were found to be in the range of 10-700 ng/mL and based on the stage of carcinoma mammary found in 35 samples (100%) at an early stage serum progranulin levels in the range of 10-700 ng/mL. Advanced stage 26 samples (70.3%) progranulin levels 10-700 ng/ml, 11 samples (29.7%) with serum progranulin levels >700 ng/mL (Table 1).

Table 2. Comparison of Serum Progranulin Levels in Tumor Patients Mammae and Group Control

Variable		n	Median (Min-Max)	Mean±sd	*p* *
Group patient	Control	38	126.28 (9.74-266.06)	121.08±56.84	<0.001
	Stage Benign Tumor	40	243.90 (138.90-307.10)	239.54±34.79	
	Early Stage	35	321.00 (147.99-649.80)	333.51±122.86	
	Advanced Stage	37	444.29 (151.67-1237.70)	551.61±365.83	

*Kruskal-Wallis test. Mann-Whitney post-hoc test: control vs benign tumor p<0.001; control vs early stage p<0.001; control vs advanced stage p<0.001; benign tumor vs early stage p<0.001; benign tumor vs advanced stage p<0.001; early stage vs advanced stage p=0.02.

Serum Progranulin levels in the group of patients with breast carcinoma were found to be higher than those with benign mammary tumors, similarly those with benign mammary tumors had higher serum progranulin levels compared to the control group, and the Kruskal-Wallis test showed a significant difference between the four groups ($p < 0.001$) (Table 2).

Significant differences between the control group, benign mammary tumors, early and late stage mammary carcinoma. Serum Progranulin levels increased significantly according to the increased stage of mammary tumors.

Post-hoc test using the Mann-Whitney test on serum progranulin levels of mammary tumors found significant differences between the control group and benign mammary tumors ($p<0.001$), the control group and early stage mammary carcinoma ($p<0.001$), the control group and advanced mammary carcinoma advanced ($p<0.001$), benign mammary tumors and early stage mammary carcinoma ($p<0.001$), benign mammary tumors and advanced mammary carcinoma ($p<0.001$) and between early and late stage mammary carcinoma ($p=0.02$).

Receiver Operating Characteristic (ROC) analysis was performed to produce a curve of the tug-of-war between sensitivity and specificity at various intersection points using serum progranulin levels in the control group and benign mammary tumors, showing an AUC value of 98.2% which statistically has very high diagnostic power. Good. The ROC curve was studied to determine the cut off point of serum Progranulin with the most optimal level of accuracy. The serum Progranulin cut-off point value obtained was 183.1 (Figure 1).

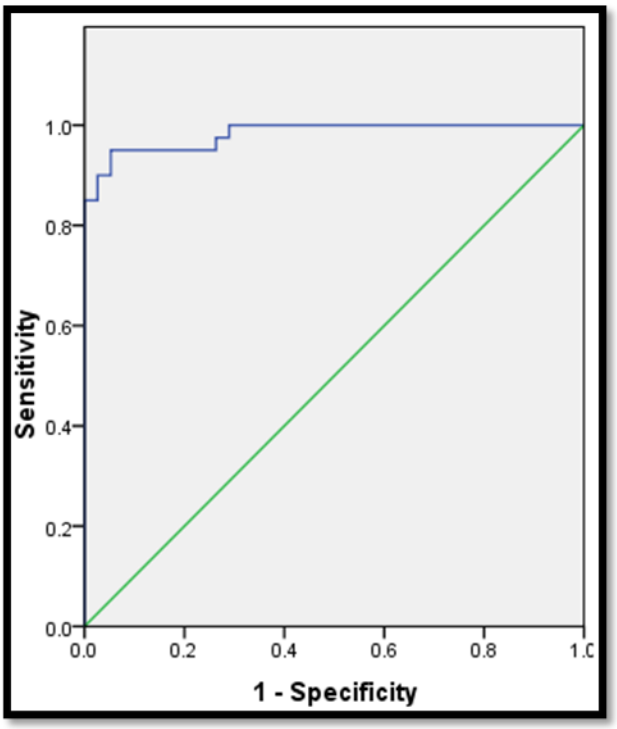

Figure 1. ROC curve of serum progranulin in the control and benign mammary tumor groups

DISCUSSION

Study done during January to February 2016 at RSUP Dr. Wahidin Sudirohusodo Makassar, RSPTN-UH and Ibnu Sina Makassar Hospital. Study This is study advanced from Wahyunie S, Uleng B, Ibrahim AS, Ilhamjaya P, William H, in 2015 with use data from study such and then added with results research conducted _ moment this . Amount whole sample ie 150 samples consisting from group control 38 samples from research data (Wahyunie S, Uleng B, Ibrahim AS, Ilhamjaya P, William H, 2015), benign tumor group a total of 40 samples obtained from study moment this , a group of early- stage mammary carcinoma a total of 35 samples (5 samples from research data before and 30 samples from study moment this), as well group advanced stage of mammary carcinoma with total of 37 samples (27 samples from research data before and 10 samples from study moment this). Population sample study in the group of benign mammary tumors with range aged 18-40 years and 35-51 years. For population sample mammary carcinoma group. as big lump breasted at age young is benign and happening enhancement risk suffer from carcinoma mammae will increase along with increase age.

This in accordance with data from the American Cancer Society and research by Azamris that risk suffer from carcinoma mammae will increase along with increase age someone, age the most suffering from mammary carcinoma namely 45-55 years (American Cancer Society, 2016; Sukmayenti & Sari, 2019). Generally sample own Serum progranulin levels between 10-700 ng/ml, both normal and benign and mamma's carcinoma. Distribution sample shows spread rate The progranulin abnormal after the normality test was carried out . In table 5 can seen that serum progranulin level >700 ng/ml only found in patients with advanced breast cancer, while in the group control, benign mammary tumor and early stage mammary carcinoma No obtained serum progranulin level >700 ng/ml. this in accordance with research conducted by Wahyunie S, Uleng B, Ibrahim AS, Ilhamjaya P, William H, (2015) that Serum progranulin levels are increased in a manner significantly in patients with carcinoma mamma compared with group control and increase in a manner significant in advanced mammary carcinoma compared to the early stages Jian, Konopka, & Liu, (2013) concluded progranulin acts as factor growth, increase the proliferation cell and is very important for rapid development-from epithelial, endothelial and mammary carcinoma cells , as well as research conducted by (Tangkeangsirisin & Serrero, 2004) concluded that progranulin acts stimulate proliferation, angiogenesis and metastasis of mamma carcinoma cells as well as continuity life cell (Ong & Bateman, 2003; Tangkeangsirisin & Serrero, 2004; Jian et al., 2013). Comparison Serum progranulin levels in mammary tumor patients and groups control own p- value <0.001. In groups, control had a median of 126.28 ng/ml, benign tumour 249.9 ng/ml, early stage 321.00 ng/ml, advanced stage 444.29 ng/ml, ke four group This own median rate different.

Furthermore, the function of cancer stem cells is influenced by the microenvironment. This challenging subset of cells has been associated with malignant properties (McTiernan, 2003). Serum progranulin levels were found increase in a manner significantly in patients with breast carcinoma compared to benign mammary tumors and groups control. Research conducted (Leerkes et al., 2002) detected the presence of the PGRN gene with more incidents more in mammary tumors (37,980 samples) compared normal epithelium (21,437 sample) with ratio 17:1. Based on post hoc test results found difference meaning between each group. This in accordance with research conducted by

Wahyunie S, Uleng B, Ibrahim AS, Ilhamjaya P, William H, (2015), serum progranulin levels increased in a manner significantly in patients with carcinoma mamma compared with group control, and increase in a manner significant in advanced mammary carcinoma compared to the early stages. This result in accordance with research conducted by Tkaczuk et al., (2011) which shows there is difference meaning serum progranulin levels between normal people and patients with mammary carcinoma. Study pathogic with use paraffin on tumor tissue showed enhancement Progranulin expression in 80% of breast cancer while in normal tissue and benign tumors No show Progranulin expression (Lu & Serrero, 2001). Progranulin in normal tissue plays a role in healing wound and inflammation, but Progranulin is also a factor growth role in such tumorigenesis stimulate proliferation, trigger activity MMP matrix (It show that progranulin has mark as a biomarker for detect , monitor and act progress to mamma's carcinoma) (Tkaczuk et al., 2011; Ong & Bateman, 2003). Progranulin is involved in activation track signaling mitogen-activated protein kinase (MAP Kinase Erk ½), phosphatidylinositol 3-kinase (PI-3 Kinase), and focal adhesion kinase (FAK) (Tkaczuk et al., 2011). In several developed countries, the 5-year relative survival rate for breast cancer patients is above 80% due to early prevention (Sun et al., 2017; Momenimovahed & Salehiniya, 2019).

Another limitation is that this study has uneven sample distribution for each group of mammary carcinoma, and the selection of the control group is based solely on medical history and physical examination. Future research will examine the relationship between progranulin levels and age and families suffering from breast cancer (Galimberti et al., 2018; Martens et al., 2012).

CONCLUSIONS AND SUGGESTIONS

Serum progranulin levels can used as inspection support possible alternative used in help detection early benign mammary tumor and mammary carcinoma. Serum progranulin levels can used as inspection support alternative together with inspection supporting/ other markers for differentiate between early and advanced mammary carcinoma. Required study more carry on For compare serum progranulin and progranulin levels in the sample network and see expression on a variety of stage group. Required study more carry on for determine values diagnostic of mammary carcinoma based on histopathological grading.

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