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Relationship of the Number of Black Dots in the Nuclei of Argyrophilic Nucleolar Organizing Regions (AgNORs) Expressed Epithelial Cells with Nottingham Grading System in Invasive Breast Carcinoma of No Special Type (IBC-NST)

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ABSTRACT

Background
Invasive Breast Carcinoma of No Special Type (IBC-NST) is aggressive breast malignancy of women with average age of >40 years old. Tumor grading is one of prognostic factors with assessment using Nottingham grading system. Other prognostic factors include the proliferation index using special staining which requires relatively high costs and is not yet available in all health service centers in peripheral areas. Other proliferative markers, such as Argyrophilic nucleolar producing regions (AgNORs) have been shown to play an independent role in breast tumor prognosis. This study aims to analyze the relationship between the Nottingham grading system and AgNORs to be used as an indication in prognosis in patients with IBC-NST.

Methods
Descriptive analytical study was conducted on paraffin block specimens from 31 IBC-NST patients, each stained with Hematoxylin-eosin (H&E) and Argyrophilic nucleolar organize regions (AgNORs). Reassessment of the Nottingham grading system and the number of black dots expressing AgNORs in the nucleus of IBC-NST cells was performed. Spearman's test ($p<0.005$) was used to assess the relationship between the number of black dots expressing AgNORs in the nucleus and the Nottingham grading system in IBC-NST.

Results
The highest age group is ≤40-50 years old. Nottingham grading system grade 3 is the highest.The highest number of black dots was found in the Nottingham grading system grade 3 with the mean ± sd 937.13 ± 51.54, median (min-max) 932.00 (8.68-10.36).

Conclusion
Assessment of the number of black dots in the nuclei of epithelial cells expressing AgNORs associated with Nottingham grading system can be used as an indication of prognosis in patients with IBC-NST.

Keywords: AgNORs, black dots, Nottingham grading system, prognostic, proliferation.

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INTRODUCTION

Breast cancer is one of the leading causes of health problems in women worldwide. This disease ranks first in most frequently occurring in women. According to data from the global cancer observatory 2022, the incidence of breast cancer was 2,261,419 cases (11.7%) and the death rate was 684,996 (6.9%) in the world.[1,2] In Indonesia, the incidence of breast cancer was 65,858 cases (16.6%) followed by a death rate of around 22,430 (9.6%).[1]

The World Health Organization (WHO) explains that Invasive breast carcinoma (IBC) is a subtype of breast cancer. Invasive breast carcinoma (IBC) is a heterogeneous breast malignancy, with different morphological, molecular and clinical symptoms. The World Health Organization (WHO) classifies it as Invasive breast carcinoma, no special type (IBC-NST) if Infiltrating duct carcinoma NOS, Oncocytic carcinoma, Lipid-rich carcinoma, Glycogen-rich carcinoma, Sebaceous carcinoma are found.[2]

Increased risk of breast cancer cases, especially Invasive Breast Carcinoma of No Specific Type (IBC-NST), is greater in women aged >40 years old. This is related to hormonal exposure, especially estrogen and progesterone. Estrogen and progesterone are hormones that control the development of secondary sex characteristics, such as breasts and pregnancy. The production of estrogen and progesterone hormones decreases with age and decreases drastically before menopause. However, exposure to hormones over a longer period of time increases the risk of breast cancer.[3,4]

Invasive breast carcinoma, no special type (IBC-NST) has the highest incidence among breast cancer cases with a 10-years survival rate of 65-78%. Invasive breast carcinoma, no special type (IBC-NST) has several prognostic factors that play a major role. Among them, age, tumor grading, tumor staging, lymphovascular invasion (LVI), tumor infiltrating lymphocytes (TILs), and predictors of therapeutic response, such as ER, PR, and HER2. Ki-67 proliferation index and androgen receptor (AR). [2,5,6]

Tumor grading assessment in IBC-NST uses a standard scoring system recommended by WHO, namely the Nottingham grading system. In the Nottingham grading system, the characteristics evaluated are tubule formation as an expression of glandular differentiation, pleomorphic nuclear assessment and assessment of the number of mitoses. Assessment of tubule formation (score 3 1 = >75%, score 2 = 10-75%, score 3 = <10%), nuclear assessment (score 1= small, regular, uniform, similar to normal ductal epithelial cells, 2-3x red blood cells, score 2= moderate increase in size / variability, score 3= large nucleus, significant variation, often vesicular chromatin with prominent nucleoli) and the number of mitoses (score 1-3 according to the WHO scoring system).[2,7]

In addition to tumor grading assessment, Proliferation index assessment in breast cancer is one of the prognostic factors using special staining. As we know, Proliferation index is one of the parameters for evaluating the level of aggressiveness of malignancy which is useful in determining therapeutic, especially in chemotherapy. Proliferation index assessment using Ki-67 staining (single markers of proliferation). However, Ki-67 staining requires relatively high costs and is not available in all health service centers in peripheral areas. Previous studies also explained that there was no significant relationship between the Ki-67 proliferative index and the prognosis of breast cancer patients.[8]

Other proliferative markers, such as Argyrophilic nucleolar organizing regions (AgNORs), in recent times have often been used as independent prognostic factors in many types of tumors. In several previous studies, it was explained that the increase in the number of black dots AgNORs which are the result of silver dye binding with two argyrophilic proteins involved in rRNA transcription and processing in the nucleolus has been shown to be related to increased cell proliferation activity.[9,10]

Argyrophilic nucleolar organizing regions (AgNORs) are a group of argyrophilic proteins that have been selectively stained with silver and can be easily recognized as dark brown or black dots on a pale yellow background. This area is located in the DNA loop in the cell nucleolus on chromosomes 13-15, 21 and 22, containing genes responsible for ribosomal RNA transcription and end signal of

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mitotic activity, thus becoming a parameter of cell growth rate. AgNORs expression is related to the level of ribosome biosynthesis which is related to the length of the cell cycle in a proliferative state. The shorter the cell cycle, the higher the rRNA synthesis, so that the quantity of AgNORs expression in the nucleus becomes greater.[11-15]

Use of the Nottingham grading system is a component used in the assessment of prognosis in Invasive breast carcinoma of no special type (IBC-NST). The use of quantitative analysis of Argyrophilic nucleolar organizing regions (AgNORs) in IBC-NST is still rare. In this study, researchers wanted to find out whether there was a relationship between the number of black dots in the nuclei of epithelial cells expressing Argyrophilic nucleolar organizing regions (AgNORs) and the Nottingham grading system in Invasive breast carcinoma of no special type (IBC-NST), as an indication in the prognosis of patients with IBC-NST.

METHODS

Total of 31 cases of Invasive breast carcinoma of no special type (IBC-NST) tissue specimens embedded in paraffin blocks were collected in the Anatomical Pathology Laboratory of the Faculty of Medicine, Universitas Sumatera Utara. All cases have been confirmed pathologically. The clinical data for this study (in the form of patient age data) were obtained from secondary data in medical records and archives at the Department of Anatomical Pathology, Faculty of Medicine, Universitas Sumatera Utara. This study has been approved by the Health Research Implementation Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara.

Age range data of Invasive breast carcinoma of no special type (IBC-NST) patients obtained from secondary medical record data, recorded and grouped into age group ≤40-50 years old, age group 51-60 years ols, age group 61-70 years old and age group >70 years old.(16) The patient's age range data will then be entered into a frequency distribution table.

All paraffin blocks of specimens that have been collected, stored in the freezer and re-cut with 4-µm slices and attached to the object glass. The specimens are then dried and heated and stored in an incubator with a temperature of 38-40^{0}C. Each paraffin block is prepared as many as 2 slides and each is stained with Hematoxylin-eosin (H&E) and Argyrophilic nucleolar organizing regions (AgNORs).

The specimen preparation to be stained with Hematoxylin-Eosin was previously deparaffinized with xylene and rehydrated with alcohol (96%, 80% and 50%). Furthermore, it was stained with Hematoxylin, then fixed with 1% acid alcohol solution and washed with running water. Continued with alcohol dehydration (80%, 90% and absolute), then stained with eosin, then fixed with alcohol (96% and absolute, each 2 times), dried and inserted into xylene solution, the glass object was covered with deck glass and EZ-mount xylene base. Furthermore, the specimen was evaluated by researchers and two Anatomical Pathology Specialists to determine Invasive breast carcinoma of no special type (IBC-NST) and histopathological grading assessment using the Nottingham grading system for each sample slide using a light microscope with 4 times magnification for gland formation and 40x for nuclear pleomorphism and the number of mitoses. Evaluation of breast cancer scores is semi-quantitative. The calculation of all three parameters describes the degree of aggressiveness of the tumor. The minimum score is 3 (1+1+1) and the maximum score is 9 (3+3+3). Patients with a score of 8 or 9 are assigned grade 3. Grade 2 is assigned with a score of 6 or 7, while grade 1 is assigned with a score of 3, 4 or 5.[2]

The specimen preparation to be stained with Argyrophilic nucleolar organizing regions (AgNORs) was previously deparaffinized with xylene 3 times (3 minutes each). Then 2 solutions were prepared for staining, namely Solution A (25% silver nitrate solution) and Solution B (2% gelatin solution in 1% formic acid). Furthermore, two parts of solution A were mixed with one part of solution B to make a working solution. Then rehydrate the preparation using 100% ethanol, 95% ethanol, and 70% ethanol for two minutes, two minutes, one minute and finally with water for one minute. Then immerse the preparation in sodium citrate buffer (pH 6.0), continued with incubation in an autoclave at a temperature of

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120^0C (pressure 1.1-1.2 bar) for 20 minutes, cool and immerse the preparation into the prepared silver staining solution at a temperature of 37^0C for 1 minute. Afterwards, stop the staining reaction by washing the slide using aqua bidestilata to remove non-specific silver precipitates. Dehydrate the slide using ethanol with gradually increasing concentrations (50%, 70%, 95%). Clean the slide with xylene and cover the slide with a coverslip. Furthermore, the specimen was evaluated by the researcher and two Anatomical Pathology Specialists by observing the number of black dots per cell using a light microscope with a magnification of 1000x (with the help of immersion oil). The quantitative parameter of AgNORs is pAgNOR, which is by counting 100 cells that have more than 5 black dots per cell. The measurement results are the total number of black dots per sample. The average number of black dots in breast cancer cells is ≥5 dots per cell in 100 malignant cells, while for normal cells there are only 1-2 dots per cell. The number of black dots of each grade will be added up and the average value will be determined.

The collected data will be analyzed using the SPSS statistical program. Data analysis will be performed using the Spearman Test. The p-value <0.05 was stated to be statistically significant.

RESULT

Characteristics of the Study Sample by Age

We have grouped the age ranges of IBC-NST patient samples in this study (Table 1). It was noted that the youngest sample age group with invasive breast carcinoma of no specific type (IBC-NST) was 25 years old, the oldest was 67 years old and the average age of patients was 50.1 years old.The highest age group sample was in the age range ≤40-50 years old (17 samples, 54.8%), followed by 51-60 years old in second place (9 samples, 29.0%), 3rd was 61-70 years old (5 samples, 16.1%) and samples with age >70 years old were not found.

Table 1. Characteristics of the study sample by age.

Variable (n=31)	Frequency (f)	Percent (%)
Age		
≤40-50 years old	17	54.8
51-60 years old	9	29.0
61-70 years old	5	16.1
>70 years old	0	0.0

Characteristics of Research Samples Based on Nottingham Grading System.

In this study, researchers re-evaluated the histopathological grading assessment of IBC-NST specimen samples stained with hematoxylin-eosin (H&E) staining with the Nottingham grading system (table 2). It was found that the highest histopathological grading was grade 3 for 15 samples (48.4%), the second highest histopathological grading was grade 2 for 14 samples (45.2%) and histopathological grading was grade 1 for 2 samples (6.5%).

Table 2. Characteristics of research samples based on grading.

Variable (n=31)	Frequency (f)	Percent (%)
Nottingham grading system		
Grade 1	2	6.5
Grade 2	14	45.2
Grade 3	15	48.4

The Number of Black Dots Analysis Based on Nottingham Grading System

In this study, specimen samples stained with Argyrophilic nucleolar organizing regions (AgNORs) were observed and the black dots in the nucleus of 100 Invasive breast carcinoma of no special type (IBC-NST) cells were counted, which had the criteria of ≥5 black dots per cell. The number of black dots from each histopathology grading was then added up and the average value was taken. It is known that the number of black dots in grade 1 has a mean ± sd 584.50 ±12.02, median (min-max) 584.50 (5.76-5.93). In grade 2, the mean ± sd 676.79 ±16.97, median (min-max) 679.50 (6.48-7.10). At level 3, the mean ± sd 937.13 ±51.54, median (min-max) 932.00 (8.68–10.36) (Table 3).

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Table 3. Descriptive analysis of the number of black dots based on Nottingham grading system.

Variable	Nottingham Grading System	n	Mean ± sd	Median (Min-Max)
Number of black dots	Grade 1	2	584.50 ±12.02	584.50 (5.76 – 5.93)
	Grade 2	14	676.79 ± 16.97	679.50 (6.48 – 7.10)
	Grade 3	15	937.13 ± 51.54	932.00 (8.68 – 10.36)

Correlation of The Number of Black Dots Expressed Argyrophilic Nucleolar Organizing Regions (Agnors) And Nottingham Grading System.

The number of black dots will then be tested for its correlation level with the histopathology grading of the Nottingham grading system using the Spearman correlation test (Table 4). From this test, a p value of 0.000 (p<0.05) was obtained. With these test results, there is a significant relationship between the Nottingham grading system and the number of black dots expressed by Argyrophilic nucleolar organize regions (AgNORs). The correlation is very strong (r=0.81-1.00) with a positive direction, meaning that the higher the degree of the Nottingham grading system, the higher the number of black dots. Likewise, the lower the degree of the Nottingham grading system, the lower the number of black dots.

Table 4. Test the correlation of the number of black dots expressed Argyrophilic nucleolar organize regions (AgNORs) and Nottingham grading system.

Variable	Number of black dots		
	n	r	p*
Nottingham grading system	31	0.892	0.000

*)Spearman correlation test

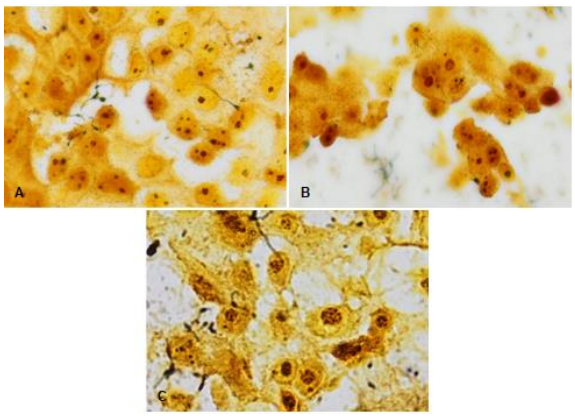

Figure 1. Picture of display the number of black dots at: A. Nottingham grading system grade 1, black dots median (min-max) 584.50 (5.76-5.93). B. Nottingham grading system grade 2, black dots median (min-max) 679.50 (6.48-7.10). C. Nottingham grading system grade 3, black dots median (min-max) 932.00 (8.68-10.36).

DISCUSSION

Breast cancer is a malignant disease in women, where data from the global cancer observatory shows the incidence of breast cancer is the highest case in women in the world, which is 2,261,419 cases (11.7%) and in Indonesia as many as 65,858 cases (16.6%).[1.3] In this study, the average age of the sample with the largest age group was obtained ≤40-50 years old (54.8%). The cases in this study may have occurred by hormonal exposure factors, particularly estrogen and progesterone. The hormones estrogen and progesterone are hormones that control the development of secondary sex characteristics. The production of the hormones estrogen and progesterone decreases with age and decreases dramatically before menopause. However, exposure to hormones for a longer time increases the risk of breast cancer. The results of this study are in line with other theories and research, such as in research by Idris A et al., (2020)[17] which states that age factors affect the high cases of breast cancer and hormonal roles.

Genetic factors can affect IBC-NST cases in patients aged <50 years old. This was once expressed by Pharoah et al and Zavala et al in their research, stating that the increased risk of breast cancer in women with a family history of breast cancer occurs at age <50 years oldand a family history of breast cancer diagnosed at age <50 years old.[18,19] In this study, the highest sample was found in the age group ≤40-50 years old with a percentage of 54.8%. This is very interesting because to explore the history of the disease in the family, but the researchers did not find data related to the family history of breast cancer from the sample.

Determination of the degree of malignancy of breast cancer, especially invasive breast carcinoma of no special type (IBC-NST) aims to evaluate the aggressiveness of breast cancer. WHO has recommended the use of the Nottingham Grading System in the evaluation of breast cancer aggressiveness as a universal measuring tool.[20] This study used

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the Nottingham Grading System in assessing the degree of malignancy and was associated with the assessment of proliferation levels with the use of silver dye in the nuclei area. The results of this study, showed grade 3 with the most samples (48.4%), followed by grade 2 (45.2%) and grade 1 (6.5%). The results of this study are in line with research by Prabhu et al (2021) which shows that the most samples are grade 3 Nottingham grading system with a percentage of 64%, followed by grade 2 (20%) and grade 3 (16%).(21) This condition is caused by various factors, including the level of awareness of patients in conducting early detection checks to be the cause of the shift in the distribution of grading levels, this was also stated by Pradhan et al., (2017).[22]

Furthermore, this study also assessed the relationship between the number of black dots in the nuclei of Argyrophilic nucleolar organizing regions (AgNORs) expressed epithelial cells and Nottingham grading system in invasive breast carcinoma of no special type (IBC-NST). From the analysis of the number of black dots in each Nottingham grading system grade, the number of black dots in grade 1 was obtained with a mean ± sd 584.50 ±12.02, median (min-max) 584.50 (5.76 – 5.93). In grade 2 grades with mean ± sd 676.79 ±16.97, median (min-max) 679.50 (6.48 – 7.10). In grade 3 with a mean ± sd 937.13 ±51.54, the median (min-max) 932.00 (8.68 – 10.36). These results are in line with previous studies conducted by Darkwah et al, (2021)[11] and Idris A et al, (2022)[17].

Black dots are the result of binding of silver dye with two argyrophilic proteins that play a role in rRNA transcription and processing and are known as AgNORs. AgNORs expression is related to the level of ribosome biosynthesis which is related to the length of the cell cycle in a state of proliferation. The shorter the cell cycle, the higher the rRNA synthesis, so that the quantity of AgNORs expression in the nucleus becomes greater.[35,51] Research related to AgNORs and breast carcinoma has also been conducted by darkwah et al which explains that AgNORs are good proliferation markers and provide a picture of black dots ≥5 dots per cell in 100 breast cancer cells, while for normal cells there are only 1-2 black dots per breast cancer cell.

From the results of statistical analysis by conducting a spearman correlation test, the result is p-value = 0.000 (p<0.05) and it can be concluded that there is a significant relationship between the Nottingham grading system and the number of black dots expressed by Argyrophilic nucleolar organizing regions (AgNORs). Where the amount of correlation value is very strong (r = 0.81-1.00) with a positive direction, meaning that the higher the degree of Nottingham grading system, the higher the number of black dots. This condition is because the expression of AgNORs is related to the level of ribosome biosynthesis related to the length of the cell cycle in a state of proliferation. The shorter the cell cycle, the higher the rRNA synthesis, so the quantity of AgNORs expression in the nucleus becomes more. The results of this study are in line with several previous studies, namely research conducted by Darkwah et al, (2021)[11], Idris A et al, (2022)[17], Ganz et al, (2022)[23].

CONCLUSION

The most age group was aged ≤40-50 years old, the most grade was grade *grade* 3 (*Nottingham grading system*), The number of black dots expressed AgNORs in Nottingham grading system grade 1 with mean ± sd 584.50 ±12.02, median 584.50 (5.76-5.93), grade 2 with mean ± sd 676.79±16.97, median 679.50 (6.48-7.10) and grade 3 with mean ± sd 937.13±51.54, median (min-max) 932.00 (8.68-10.36). There is a statistically significant relationship between number of black dots in expressed epithelial cell nuclei Argyrophilic nucleolar organizing regions (AgNORs) and Nottingham grading system with p-value <0.05. Assessment of the number of black dots in the nuclei of epithelial cells expressing AgNORs associated with Nottingham grading system can be used as an indication of prognosis in patients with IBC-NST.

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