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Correlation between GATA3 and TP53 Expression as a Prognostic Predictor of Ovarian Carcinoma Subtypes.

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ABSTRACT

Background
Ovarian carcinoma is a cancer with high mortality in women, although comprehensive treatment with surgery and chemotherapy is at an advanced stage, survival rates are still low. GATA3 and p53 are predictors of some malignancies, but results vary in ovarian carcinoma.

Objective
To examine correlation between immunohistochemical expression of GATA3 and p53 in patients with ovarian carcinoma with various histopathological subtypes.

Methods
Cross sectional design is the method of this study conducted on slides of 28 ovarian carcinoma patients in several subtypes of hitopathology. Each slide was stained with hematoxylin and eosin (H&E) to assesses hitopathological subtypes and stained with GATA3 and p53 antibodies. Expression GATA3 was assessed using H-score and p53 quick score. A logistic regression assay ($p<0.005$) was used to assessed the association of GATA3 and TP53 immunohistochemical expression in several histopathological subtypes of ovarian carcinoma. Statistical analysis between GATA3 and p53 was performed using the eta correlation test is used because the data is nominal-ordinal.

Results
Among 28 specimens in patients with ovarian carcinoma, Cases was most prevalent in the age group >50-60 years old (age range 58 years old), history of nullipara parity, and most in the group of stage III ovarian malignancy. Positive immunohistochemical p53 expression is more prevalent in serous carcinoma. Postive GATA3 immunohistochemical expression is more prevalent in serous carcinoma.

Conclusion
There is no significant relationship. Immunohistochemical expression of GATA3 and TP53 in some histopathological subtypes of ovarian carcinoma. However, immunohistochemical expression of GATA3 high p53 positive tends to be found in high-grade serous carcinoma.

Keywodrs: GATA3, TP53, ovarian carcinoma subtypes

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INTRODUCTION

Ovarian cancer is the second most common malignancy after breast cancer. The Global Burden of Cancer (GLOBOCAN) in 2020 stated that ovarian cancer ranks 8th most cancers in women worldwide with 313,959 new cases and an ovarian cancer death rate of 207,252. The incidence of ovarian cancer in Indonesia in 2020 ranks 10th, with 14,896 new cases and 9,581 deaths from ovarian cancer. Most common cancer in women worldwide, the mortality rate is quite high, most patients present at stage III so the prognosis is poor. Ovarian carcinoma (more than 70%) is more often diagnosed at an advanced stage of stage III or IV based on stage FIGO because there are still few effective screening strategies at an early stage and the early symptoms of carcinoma are not specific. The various subtypes, they have different behavior and genetic.[1-4] This study aims to determine the relationship between immunohistochemical expression of GATA3 and P53 in several histopathological subtypes of ovarian carcinoma.

The most common histological picture of ovarian carcinoma is the high-grade serous carcinoma type. Other histological types of ovarian carcinoma are: low-grade serous carcinoma, mucinous adenocarcinoma, endometrioid adenocarcinoma, seromusinous carcinoma, clear cell adenocarcinoma, malignant Brenner tumor carcinosarcoma, and mixed cell adenocarcinoma. The morphology of the entity has a different etiology with the genetic characteristics, phenotype and behavior of the tumor and includes response to chemotherapy. [4-7]

Various markers have been used to predict behavior and prognosis in various subtypes of ovarian carcinoma, but the results research about the correlation between GATA3 and p53 on ovarian carcinoma, there is not much. Recent research Elarabey et al. Which did not find a significant relationship in previous studies regarding the relationship between GATA3 and p53 in high-grade serous ovarian carcinoma.[7]

GATA3 is a derivative of the GATA transcription factor located on chromosome 10p14 is one of the 6 transcription factors in the DNA sequence that functions to regulate the differentiation process during embryogenic development. In ovarian carcinoma, GATA3 acts as an oncogenic protein related to TP53 which functions to stimulate apaptosis. GAT3 expression is associated with a poor prognosis in ovarian carcinoma.[10]

The tumor suppressor gene P53 is an important biological molecule in the human body as a guardian of genome integrity, and to ensure cell homeostasis runs properly. TP53 is encoded by the p53 gene located on the short arm of chromosome 17p13.1 and composed by 393 amino acids.The biological function of p53 protein is as a multitarget gene transcription factor, cell cycle regulation, cell aging, apoptosis, DNA synthesis, repair of DNA damage caused by genotoxic material, angiogenesis and oxidative stress. This protein plays an important role in preventing tumors by stopping the cell cycle or programming cell death in response to DNA damage. Due to damage and disruption of p53 function, uncontrolled cell division occurs, resulting in ovarian carcinoma. [80]

In ovarian carcinoma, GATA3 acts as an oncogenic protein related to TP53, which functions to stimulate apoptosis. If GATA3 is strongly expressed in ovarian carcinoma, it will interfere with the work of TP53, resulting in resistance to apoptosis. If GATA3 is strongly expressed in ovarian carcinoma, it will interfere with the work of TP53 so that resistance to apaptosis occurs.[10]

METHODS

This research is an analytical study with a cross sectional approach. The research was conducted at the Department of PA FK USU from December 2022 to November 2023. The samples in this study were paraffin blocks and slides from operating tissue diagnosed histopathologically as ovarian carcinoma that met the inclusion (Age, stage, subtype slide review ovarian carcinoma) and exclusion criteria at the Anatomic Pathology Unit of RSUP Haji Adam Malik Medan 2019-2021 as a research sample.

Immunohistochemical expression of GATA3 (monoclonal antibody, primary mouse clone L50-823) identified by the presence of stained brownish granules in the nucleus of tumor cells using Olympus CX23 microscope with 20x magnification. This expression is determined by assessing the colored area and categorized into: 0=≤5% cells, +1=<6-25% cells, +2=26-60% cells, +3=61-100% cells; and the intensity of the stained is grouped into: 0=negative, +1=weak, +2=medium, +3=strong. Then, the H-score formula will be used which is calculated using the following equation: H-score=Pi (i+1), where i is the intensity of the tumor stained (0 to 3+), and Pi is the percentage of tumor cells stained for each intensity. The cut-off value is set as 150%,

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which is the H-score. Cases that have a value of 0% are considered negative GATA3 expressions; when less than 150% is considered a GATA3 low expression and when the value equals or exceeds 150% is considered a GATA3 high expression.[79] Therefore, the assessment of GATA3 expression in this study can be categorized into: <150%=low expression, ≥150%=high expression.[79]

Immunohistochemical expression of p53 antibody (DO-7): sc-47698 (monoclonal antibody) The degree of expression of p53 staining is seen from the percentage of colored cell groups and the intensity of staining. The percentage is obtained from the results of positive cell summation in the entire field of view of tumor preparations examined using a light microscope. Currently, there is no standard scoring system, but based on various references, the scoring system commonly used is a score of 0 if there are no colored cells or there are no immunoreactive cells; score 1 if positive cells amount to <10%; score 2 if positive cells are between 10-50%; and score 3 if positive cells are >50%. The next scoring result is interpreted as follows: negative=when the score is 0 or 1, positive=when the score is 2 or 3.[80]

RESULT

Based on clinical data on medical records/anatomical pathology archives, in this study the distribution of ovarian carcinoma samples found the youngest age in this study was 18 years old and the oldest was 76 years old, and the most group was found at the age of >50-60 years old as many as 12 cases (42.9%). The history of parity was more prevalent in the number of nulipara groups as many as 14 cases (50.0%), multiparous as many as 14 cases (50.0%). The most stages obtained in this study in stage III were 14 cases (50.0%), followed by stage I as many as 8 cases (28.6%), stage II as many as 4 cases (14.3%), and the least was stage IV as many as 2 cases (7.1%).

Table 1. Table of frequency distribution characteristics of ovarian carcinoma patients by age group, parity history, clinical stage and histopathological subtype of ovarian carcinoma.

Variable	f	%
Age (Mean±sd; median; min-max)	(45.86±14.5; 50.5; 18-76)	
Age		
≤20 years old	2	7.1
>20-30 years old	4	14.3
>30-40 years old	2	7.1
>40-50 years old	6	21.4
>50-60 years old	12	42.9
>60 years old	2	7.1
Paritas		
Nulipara	14	50.0
Primipara	0	0,0
Multipara	14	50.0
Stadium		
Stadium I	8	28.6
Stadium II	4	14.3
Stadium III	14	50.0
Stadium IV	2	7.1
Histopathology Subtypes		
Serous carcinoma	12	42.9
Mucinous carcinoma	5	17.9
Endometrioid carcinoma	6	21.4
Clear cell carcinoma	5	17.9
GATA3 Expression		
Low Expression	23	82.1
High Expression	5	17.9
Expression P53		
Negative	6	21.4
Positive	22	78.6

Table 2. Table of Eta Correlation Test on p53 expression against several carcinoma of ovary subtypes.

Variable	Expression p53		Total	value	p*
	Negative f (%)	Positive f (%)	f (%)		
Subtype					
Serous carcinoma	0 (0.0)	12 (42.9)	12 (42.9)		
Mucinous carcinoma	2 (7.1)	3 (10.7)	5 (17.9)	0.508	>0.05
Endometrioid carcinoma	3 (10.7)	3 (10.7)	6 (21.4)		
Clear cell carcinoma	1 (3.6)	4 (14.3)	5 (17.9)		
Total	6 (21.4)	22 (78.6)	28 (100.0)		

*)The Eta correlation test is used because of nominal-ordinal data. The test results found no significant correlation between P53 expression and the histopathological subtype of ovarian carcinoma.

P53 expression in several histological subtypes of ovarian carcinoma found negative p53 expression as many as 6 cases (21.4%) and positive p53 expression as many as 22 cases (78.6%). To calculate the significance of p53 expression against several subtypes of carcinoma of ovary used the Eta test, the results of the calculation, namely: 1). Have a relationship if Fcalculate>Ftable. 2). Have no significant relationship when Fcalculate<Ftabel. Conclusion of the analysis: There was no significant association between P53 expression and histopathological subtypes of ovarian carcinoma (F_{count}<Ftable; 2.78<3.01).

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Table 3. Table of Etap Correlation Test on GATA3 expression against several subtypes of carcinoma of ovary.

Variable	GATA3 Expression		Total	value	p*
	Low Expression f (%)	High Expression f (%)	f (%)		
Subtype					
Serous carcinoma	9 (32.1)	3 (10.7)	12 (42.9)		
Mucinous carcinoma	5 (17.9)	0 (0.0)	5 (17.9)	0.233	>0.05
Endometrioid carcinoma	5 (17.9)	1 (3.6)	6 (21.4)		
Clear cell carcinoma	4 (14.3)	1 (3.6)	5 (17.9)		
Total	23 (82.1)	5 (17.9)	28 (100.0)		

*) The Eta correlation test is used because of nominal-ordinal data. The test results found no significant correlation between GATA3 expression and the histopathological subtype of ovarian carcinoma.

GATA3 expression in several histological subtypes of ovarian carcinoma found 23 cases (82.1%) and 5 cases of high expression GATA3 (17.9%). The results of the above calculations are: 1). Have a relationship if Fcalculate>Ftable. 2). Have no significant relationship if Fcalculate<Ftabel Conclusion of the analysis: There was no significant relationship between GATA3 expression and the histopathological subtype of ovarian carcinoma (Fcalculate<Ftable; 0.46<3.01).

Table 4. GATA3 Expression Logistic Regression Test Table, P53 Expression with Ovarian Carcinoma Histopathology Subtype.

Variable	Expression		Say	p
Subtype				0.010
Serous carcinoma	GATA3	Low	0.990	
	p53	High Negative Positive	-	
Mucinous carcinoma	GATA3	Low	0.993	
	p53	High Negative Positive	0.992	
Endometrioid carcinoma	GATA3	Low	0.992	
	p53	High Negative Positive	0.992	
Clear cell carcinoma	GATA3	Low	0.994	
	p53	High Negative Positive	-	

After analysis with logistic regression tests, it was found that there was no statistically significant relationship between GATA3 and each subtype of ovarian carcinoma histopathology did not show a significant relationship, nor did the correlation between P53 and each subtype of ovarian carcinoma histopathology show no significant relationship.

DISCUSSION

Ovarian carcinoma is a malignancy of gynecological origin which is the cause of most deaths in women in the world in this study based on age obtained the average age of carcinoma samples with the largest age group is ≥50 years old (49.2%). This is in line with Luviano et al and Momenimovahed et al stating that the incidence of ovarian cancer varies in different age groups and races. Patients with ovarian carcinoma have a wide age range and are mostly found in women over 40 years old (perimenopausal age) and postmenopause, and the risk increases with increasing age and length of ovulation.[23,27]

Ovarian carcinoma is a group of tumors that have various sutypes with various differences in morphology, molecular biology/ genomics, pathogenesis, and cell behavior. In this study, the most common type of serous carcinoma was obtained as many as 12 samples (42.9%). This is in line with the research of Peres et al and Waruwu research where obtained high grade serous carcinoma type is the most common type, and mucinous carcinoma type is the least found in Waruwu research, while in Peres et al. [46,47] One factor that causes this difference is the geographical difference in which Peres et al. conducting research in America, as well as based on literature it is said that serous types are found in America and Europe.[7]

Certain tumors in some ovarian carcinomas are deprived of GATA3, which is associated with a poor prognosis. In ovarian carcinoma, GATA3 acts as an oncogenic protein related to TP53, which serves to stimulate apoptosis. If GATA3 is strongly expressed in ovarian carcinoma, it will interfere with the work of TP53 so that resistance to apoptosis will occur.22 This study illustrates no significant association between GATA3 and TP53 in serous ovary carcinoma. This study is in line with El-Arabey et al, it shows GATA3

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rarely mutates in OC and these mutations trigger tumor growth.[73,79,81]

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CONCLUSION

After a study of 28 ovarian carcinoma samples aimed to see the relationship between GATA3 expression and TP53 expression in several subtypes of ovarian carcinoma. In patients with ovarian carcinoma at the Anatomic Pathology Unit of RSUP H. Adam Malik Medan, it can be concluded as follows: The frequency distribution of ovarian carcinoma characteristics is most common in the age group >50-60 years old (age range 58 years old), history of nulliparity parity, and most in the group of stage III ovarian malignancy. Positive immunohistochemical p53 expression is more prevalent in serous carcinoma. Positive GATA3 immunohistochemical expression is more prevalent in serous carcinoma. Immunohisto-chemical expression of GATA3 and TP53 in several histopathological subtypes of ovarian carcinoma was not significantly associated. however, high immunohistochemical express-ion of high p53 positive GATA3 tends to be found in high-grade serous carcinoma.

Table 5. GATA3 immunohistochemical expression and P53 immunohisto chemical expression with Ovarian Carcinoma

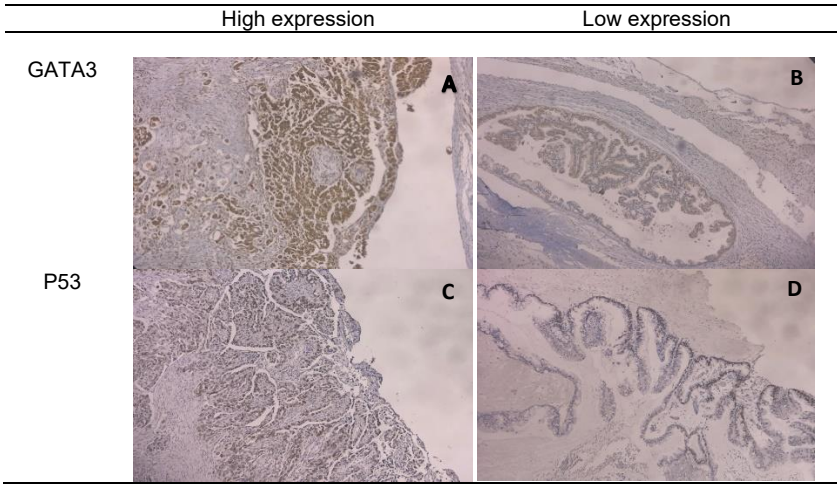

Figure A. Serous carcinoma, high immunoexpression of GATA3 (10 times). B. Serous carcinoma, low immunoexpression of GATA3 (4 times). C. Serous carcinoma, postive immunoexpression of P53 (10 times). B. Serous carcinoma, negative immunoexpression of P53 (4 times).

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