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The Correlation of Immunohistochemical Expression of Matrix Metalloproteinase-9 with Tumor Budding Index and Histopathological Grading in Endometrial Carcinoma

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ABSTRACT

Background
Malignancies of the uterine corpus are the sixth most common malignancy in women, where endometrial carcinoma accounts for the largest number of these cases. Tumor budding has been described as a sign of cancer cell motility and as an early step in the metastatic process. One of the most important aspects of the metastatic process is the correlation between tumor budding and the epithelial-mesenchymal transition (EMT), which is characterized by an increase in matrix metalloproteinases. One of MMPs is matrix metalloproteinase-9 (MMP-9) which plays a role in degrading the extracellular matrix and basement membrane, which is a prerequisite for the process of invasion and metastasis.

Methods
This is an analytic study with a cross-sectional approach on 38 surgical samples diagnosed as endometrial carcinoma and then performed with MMP-9 immunohistochemical staining. The statistical analysis was performed to analyze the correlation of immunohistochemical expression of MMP-9 with tumor budding index and histopathological grading in endometrial carcinoma.

Results
Based on statistical analysis for 38 samples of endometrial carcinoma patients, there was a significant correlation between the immunohistochemical expression of MMP-9 with tumor budding index (p-value: 0.021) and histopathological grading (p-value: 0.005).

Conclusion
There was a significant correlation between the immunohistochemical expression of MMP-9 with tumor budding index and histopathological grading in endometrial carcinoma, where the immunohistochemical expression of MMP-9 increased at high tumor budding index and histopathological grading as well.

Keywords: endometrial carcinoma, histopathological grading, tumor budding, matrix metalloproteinases-9.

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INTRODUCTION

Malignancy of the uterine corpus is the sixth most common malignancy in women, with 417,000 new cases and 97,000 deaths according to the statistical data of the Global Burden of Cancer Study (GLOBOCAN) in 2020.[1] Endometrial carcinoma accounts for the largest number of these cases, which is around 90%, whereas less than 10% are sarcomas.[2,3] According to the International Agency for Research on Cancer, the incidence of endometrial carcinoma will increase rapidly compared to 2018, and is expected to increase by more than 50% worldwide in 2040.[4]

Based on the data of several studies, the incidence and mortality of endometrial carcinoma are different around the world. The incidence rate of endometrial carcinoma is generally higher in high-income countries compared to low- and middle-income countries.[5,6] On the other hand, deaths caused by endometrial carcinoma are found to be highest among women with low socioeconomic status.[5]

Research in Indonesia found that the prevalence of endometrial carcinoma at Cipto Mangunkusumo Hospital Jakarta reached 7.2 cases per year. From these data, endometrial carcinoma is rarely found in the age group below 40 years. Research at Adam Malik Haji Center General Hospital Medan in 2012-2015, the number of patients with endometrial carcinoma was as many as 48 people, in which the most patients were > 55 years old (45.8%), followed by patients aged 45-55 years (31.3%) and the least were patients aged <45 years (22.9%).[7]

Endometrial carcinoma is generally associated with a good prognosis, especially since low-grade endometriod carcinoma is the most common subtype and usually has a low clinical presentation and stage. However, the mortality rate of women with endometrial carcinoma is found to be more than 20% and is expected to increase in the coming decades. Stage, age, histopathological grading, deep of myometrial invasion, lymphovascular invasion, and biomolecular type determine the prognosis of endometrial carcinoma.[8,9]

Tumor budding is defined as single cells or cell groups consisting of <5, cells located at the margins of the invasive tumor front. During local cancer growth, some of these cell clusters break away from the main tumor body and invade the surrounding stroma. This phenomenon is considered the histological basis for the formation of metastases and subsequent tumor invasion.[10] One of the most important aspects of the metastatic process is the relationship between tumor budding and the epithelial-mesenchymal transition (EMT). EMT is a transitional process of epithelial cells into mesenchymal, cells in which epithelial cells lose adhesion between cells and have the ability to migrate and invade, which are characteristics of mesenchymal cells.[17] Besides being characterized by a loss of E-cadherin expression, the EMT process is also characterized by an increase in matrix metalloproteinases which play role in degrading the extracellular matrix and basement membrane, which are prerequisites for invasion and metastasis processes.[10-15]

MMP-9 is one of the most widely observed types of MMP playing an important role in cancer cell invasion and tumor metastasis.[16] MMP-9 is involved in several biological processes, namely proteolytic degradation of the Extra Cellular Matrix (ECM), changes in interactions between cells and cells and ECM, cell surface protein cleavage and protein cleavage in the extracellular environment. MMP-9 plays a role in degrading the basement membrane because the basement membrane contains collagen, including Type IV collagen, which can be degraded by MMP-9. During tumor development, destruction of the basement membrane is usually an important step that favors tumor invasion and metastasis.[16-19] Because MMP-9 is an important factor for several cancers and several other MMP-9-associated diseases, targeting therapy at MMP-9 is of great value. important.[20]

Limited research has been done on the relationship between MMP-9 expression and tumor budding in malignancy. Some research that has been done is on colorectal cancer and breast cancer. In this study, it was found that high MMP-9 expression was associated with a high grade of tumor budding as well.[21-23]

MMP-9 expression has been found to be associated with the development of gynecological malignancies, including endometrial carcinoma. To date, studies conducted to assess MMP-9 expression in endometrial carcinomas are still limited and controversial. [24-26] The purpose of this study was to determine the relationship between MMP-9 immunohistochemical expression with the tumor budding index and histopathological grading in endometrial carcinoma.

METHODS

The research design is a cross-sectional analytic study. The study was

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conducted at the Laboratory of Anatomic Pathology, Faculty of Medicine, University of North Sumatra and the Anatomic Pathology Unit of RSUP H. Adam Malik Medan using paraffin blocks that had been diagnosed histopathologically as endometrial carcinoma. Sample calculation was carried out with a total sample of 38 samples including inclusion criteria, namely post-hysterectomy tissue diagnosed as endometrial carcinoma and completeness of medical record data in the form of age and exclusion criteria, namely missing or damaged paraffin blocks and medical record data in the form of incomplete age.

Age in this study was categorized into several groups based on epidemiological studies, namely <45 years old, 45-55 years old, and >55 years old.[7] The histopathological subtypes studied were endometrial carcinoma which was frequently found and grouped into endometrioid carcinoma NOS, serous carcinoma NOS, clear cell carcinoma NOS, undifferentiated carcinoma NOS, and mixed carcinoma NOS. Based on the WHO Classification of Female Genital Tumors in 2020, endometrial carcinoma grading is divided into two categories, namely low grade and high grade. For subtypes of endometrioid carcinoma FIGO grade 1 and 2 are included in the low-grade category, while endometrioid carcinoma FIGO grade 3, serous carcinoma, clear cell carcinoma, undifferentiated carcinoma, and mixed carcinoma are included in the high-grade category.[27]

Tumor budding was defined as a single tumor cell or a group of cells consisting of ≤4 tumor cells.[10-15] In this study, the tumor budding index was assessed in the peritumoral region. Assessment of tumor budding based on the International Tumor Budding Consensus Conference (ITBCC) is assessed in front of an invasive tumor with a measurement field of 0.785 mm2, which corresponds to the objective lens 20 times and is divided into three categories, namely: low budding (0-4 buds), intermediate budding (5-9 buds) and high budding (≥10 buds).[14]

Matrix metalloproteinase-9 (MMP-9) is a type of MMP that is able to degrade various components of the extracellular matrix (ECM) which plays an important role in cancer cell invasion and tumor metastasis. MMP-9 expression was carried out by immunohistochemistry using BZ-0898450-AP Rabbit Anti MMP-9 Polyclonal Antibody at 1:100 dilution (40C, overnight) from the manufacturer Bioenzy. MMP-9 can be displayed in tumor cells and stromal cells around the tumor environment.[16,24,28] The assessment was carried out semiquantitatively based on the intensity and percentage of tumor cells or stromal cells expressed. MMP-9 expression is characterized by brown cytoplasm, which is assessed in 10 fields of view of microscopic preparations with an objective lens magnification of 10 times.[29,30]

MMP-9 intensity was categorized as follows: score 0 (not expressed), score 1 (weak), score 2 (moderate), and score 3 (strong). The percentage of MMP-9 is categorized as follows: score 0 (0%), score 1 (1-5%), score 2 (6-75%), and score 3 (76-100%). Then the expression was calculated from the addition of the intensity and percentage of MMP-9 expression which was categorized as negative expression (if the score was <3) and positive expression (if the score was ≥3).[29,30] The relationship between MMP-9 and the tumor budding index and histopathological grading was analyzed by Chi-Square test and Fisher's Exact. The statistical test is significant if the p value is <0.05.[29.30]

RESULTS

In this study, there were 38 samples of endometrial carcinoma.

Table 1. Frequency distribution of endometrial carcinoma patients based on age, subtype, tumor budding index, and histopathological grade.

Characteristics	Amount(n=38)	(%)
Age		
Mean ± SD = 55,5 ± 11,4 years old		
<45 years old	5	13.2
45-55 years old	13	34.2
>55 years old	20	52.6
Subtype		
Endometrioid carcinoma NOS	35	92.1
Serous carcinoma NOS	1	2.6
Clear cell carcinoma NOS	2	5.3
Undifferentiated carcinoma NOS	0	0
Mixed carcinoma NOS	0	0
Tumor budding Index		
Low	22	57.9
Intermediate	7	18.4
High	9	23.7
Histopathological grade		
Low grade	26	68.4
High grade	12	31.6

SB: Standard Deviation, NOS: Not Otherwise Specified

Data on the frequency distribution of endometrial carcinoma patients based on age in this study had a mean age of 55.5 years with a standard deviation of 11.4 years. The youngest is 31 years old and the oldest is 84 years. The age distribution of endometrial

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carcinoma patients with the highest prevalence was the >55 years age group with 20 cases (52.6%), followed by the 45-55 years age group with 13 cases (34.2%), and the least in the age <45 years, namely 5 cases (13.2%).

The most common subtype of endometrial carcinoma in this study was endometrioid carcinoma NOS, with 35 cases (92.1%), followed by clear cell carcinoma NOS with 2 cases (5.3%), and serous carcinoma NOS with 1 case (2, 6%), whereas for undifferentiated carcinoma NOS and mixed carcinoma NOS were not found.

Assessment of tumor budding based on the International Tumor Budding Consensus Conference (ITBCC) is divided into three categories. In this study, the frequency distribution of endometrial carcinoma patients based on the highest tumor budding index was low budding with 22 cases (57.9%), followed by high budding with 9 cases (23.7%), while for intermediate budding the least was as many as 7 cases (18.4%).

Histopathological grading of endometrial carcinoma based on WHO classification in 2020 is divided into two categories. In this study, the highest frequency distribution of endometrial carcinoma patients based on histopathological grading was low grade with 26 cases (68.4%), compared with high grade with 12 cases (31.6%).

Table 2. Frequency distribution of endometrial carcinoma patients based on matrix metalloproteinase-9 (MMP-9) immunohistochemical expression.

MMP-9 Expressions	Amount (n)	Percentage (%)
Negative	22	57.9
Positive	16	42.1
Total	38	100

MMP-9: Matrix Metalloproteinase-9

In this study, the highest frequency distribution of endometrial carcinoma patients based on matrix metalloproteinase-9 (MMP-9) immunohistochemical expression was negative expression in 22 cases (57.9%), compared to positive expression in 16 cases (42.1%).

Table 3. Correlation between Matrix Metalloproteinase-9 (MMP-9) immunohistochemical expression and tumor budding index in endometrial carcinoma.

MMP-9	Tumor budding index						p-value*
	Low		Intermediate		High		
	N	%	N	%	N	%	
Negative	13	59.1	7	31.8	2	9.1	0.021
Positive	9	56.3	0	0	7	43.7	

*Fisher's Exact Test

Table 4. Correlation between Matrix Metalloproteinase-9 (MMP-9) immunohistochemical expression and histopathological grading in endometrial carcinoma.

MMP-9	Histopathological grading				p value*
	Low		High		
	N	%	N	%	
Negative	19	86.4	3	13.6	0.005
Positive	7	43.8	9	56.2	

*Chi-Square Test

The results of the statistical test analysis showed that there was a significant relationship between matrix metalloproteinase-9 (MMP-9) immunohistochemical expression and the tumor budding index in endometrial carcinoma with a value of p=0.021 (p<0.05).

Based on statistical test analysis, it was shown that there was a significant relationship between matrix metalloproteinase-9 (MMP-9) immunohistochemical expression and histopathological grading of endometrial carcinoma with a value of p = 0.005 (p <0.05).

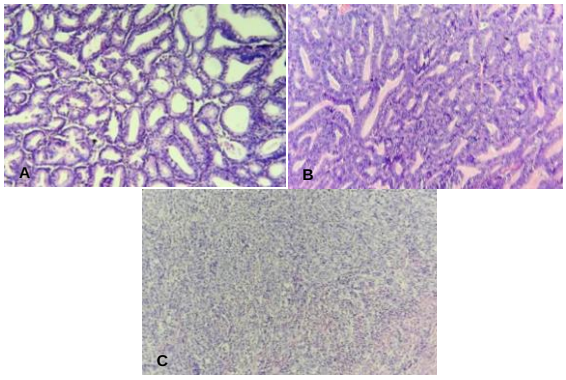

Figure 1. Histopathological grading of endometrial carcinoma. A. Endometrioid carcinoma NOS FIGO grade I (Low grade). B. Endometrioid carcinoma NOS FIGO grade II (Low grade). C. Endometrioid carcinoma NOS FIGO grade III (High grade). (HE 100 times).

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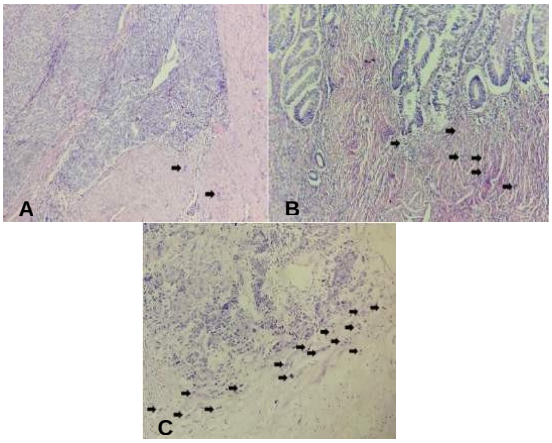

Figure 2. Tumor budding index in endometrial carcinoma. A. Low budding. B. Intermediate budding. C. High budding. (HE 200 times).

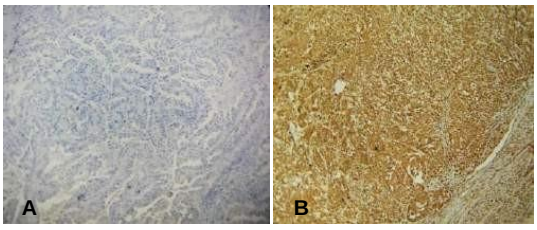

Figure 3. MMP-9 expression in endometrial carcinoma. A. Negative. B. Positive. (HE 100 times).

DISCUSSION

Most patients with endometrial carcinoma in this study were found in the age group >55 years old. These results are in line with a study that was conducted at Haji Adam Malik General Hospital Medan in 2012-2015 by Christian where the most patients were found at >55 years old (45.8%).[7] According to the literature, the risk of endometrial carcinoma increases in women with advancing age associated with prolonged exposure to estrogen, which is most common in postmenopausal women. Estrogen has a proliferative effect on the endometrium, which causes endometrial hyperplasia. Unmonitored proliferation causes dysplasia and then results in endometrial carcinoma.[2,27,31] Although the ovaries stop producing the hormones progesterone and estrogen at menopause, small amounts of estrogen are still produced naturally in adipose tissue. It is this estrogen in the fatty tissue that has a greater influence after menopause than before menopause in terms of causing endometrial carcinoma. Hormone replacement therapy with estrogen alone without combining it with progesterone in postmenopausal patients can also stimulate the endometrium and may lead to the development of endometrial carcinoma.[2,27,31,32] In addition, the late age of menopause also causes prolonged exposure to estrogen and is an important risk factor for endometrial carcinoma.[31,32]

In this study, it was found that the youngest was 31 years old and the oldest was 84 years old. According to the literature, endometrial carcinoma is rare in young women.[34,35] Usually tumors in this age group are of low grade, non-myoinvasive, and have a good prognosis.[33,34] Endometrial carcinoma in this age group may be sporadic or familial. associated with Lynch syndrome or Cowden syndrome. Risk factors that can occur include menarche at an early age, nulliparity, infertility, and polycystic ovarian syndrome where this condition causes prolonged exposure to estrogen. In addition, an unhealthy lifestyle can lead to obesity, metabolic syndrome, and diabetes mellitus, where this condition causes fat tissue in the body to convert androgens into estrogens, thereby increasing the risk of endometrial cancer.[31-34]

The most common subtype of endometrial carcinoma in this study was endometrioid carcinoma NOS. These results are in line with research conducted by Prendergast, Lapińska, Ignatov, and Zhang et al., which also found that the most common subtype was endometrioid carcinoma compared to non-endometrioid carcinoma.[35-38] Based on the WHO Classification of Female Genital Tumors 2020, endometrioid carcinoma is the most common subtype of endometrial carcinoma, which is around 70-80% of all cases, followed by serous carcinoma which is around 10%, and clear cell carcinoma which is found in <10% of all cases. Meanwhile, undifferentiated carcinoma is rare, which is about 2% of all endometrial carcinomas. Mixed carcinoma is rare, with the most common being mixed endometrioid and serous carcinoma which accounts for approximately 10% of endometrial carcinoma.[27]

Tumor budding has been suggested as a useful prognostic marker in some tumors, but research on tumor budding in endometrial carcinoma is still very limited.[10] In this study, the frequency distribution of endometrial carcinoma patients based on the highest tumor budding index was low budding. This result is in line with a study conducted by Koyuncuoglu, who found that the category of budding tumors was lower grade.[10] In the study conducted by Klutz et al., there were more categories of positive budding tumors than negative budding tumors.[13] This

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result is not in line with the research conducted by Rau et al., where in that study, the most categories were negative budding tumors. However, in this study, tumor budding was significantly associated with depth of invasion, lymph node involvement, grading, and invasion of blood vessels.[39] Research on tumor budding is being extensively developed in several organs where tumor budding is considered a promising prognostic biomarker and is easier to detect, performed by hematoxylin-eosin (HE) staining, which is used to predict disease progression and survival unfavorably.[10-12] During local cancer growth, some of these cell clusters detach from the main tumor body and invade the surrounding stroma. This phenomenon is considered the histological basis of the formation of metastases and further tumor invasion.[10]

The frequency distribution of endometrial carcinoma patients based on histopathological grading in this study was mostly low grade. This is in line with studies conducted by Ignatov, Rau et al., and Zhang et al., which found that the most common grade of endometrial carcinoma was low grade.[37-39] According to the literature, endometrioid carcinoma is the most common subtype of carcinoma of the uterine corpus, i.e., approximately 70-80% of all cases, whereas low-grade endometrioid carcinoma (FIGO grades 1 and 2) accounts for 80%-90% of this subtype.[3,27] Low-grade endometrioid carcinoma is generally confined to the uterus when diagnosed and has a relatively good prognosis compared to high-grade which has a much worse prognosis and is often diffuse at diagnosis.[3]

In this study, the distribution of the frequency of endometrial carcinoma patients based on matrix metalloproteinase-9 (MMP-9) immunohistochemical expression was mostly negative compared to positive. This result is almost the same as a study conducted by Yu et al. in which the highest expression of MMP-9 was found to be weak expression compared to high expression.[25] However, it is different from the research conducted by Grybos and Aglund et al., who found more positive expression of MMP-9.[26,40] Several important processes of carcinogenesis, which include migration, invasion, metastasis, and angiogenesis, are closely related to the extracellular environment. MMP-9 plays an important role in ECM remodeling and membrane protein cleavage, which has been found to be widely associated with cancer pathology.[16] Molecular changes that lead to tumor formation lead to breakdown of intercellular junctions, ECM breakdown and cleavage of basement membrane components by modulation of MMP activity, induce the process of epithelial-mesenchymal transition (EMT) and promote cell motility and invasion.[16,24] Loss of MMP-9 expression in cases of endometrial carcinoma that have been studied has different possible explanations, including when the case studied is a low-grade malignancy. In this study the results showed that most cases were low grade. Another possibility is the presence of desmoplastic stroma in cases of malignancy caused by fibroblast proliferation which in turn will produce collagen. The stroma is sometimes replaced by homogeneous collagen in which fibroblasts become less prominent resulting in decreased or negative expression of MMP-9.[41]

In this study, a significant association was found between MMP-9 immunohistochemical expression and the tumor budding index in endometrial carcinoma. Very little research has been done on the relationship between MMP-9 expression and tumor budding in malignancy, where studies analyzing the relationship between the two in endometrial carcinoma have never been done before. However, few studies have been conducted on other malignancies. Research conducted by Sriwidyani et al. on breast carcinoma found a significant association between high-grade tumor budding and high MMP-9 expression.[22] Research conducted by Guzińska on colorectal cancer obtained similar results where it was said that if there is a budding tumor in the invasive front of colorectal cancer, it indicates a higher invasive potential, and these results are indicated by a strong relationship between MMP-9 expression in buds.[21] Budding tumors were identified as representative of the EMT process. Tumor cells in tumor budding show loss of normal expression of E-cadherin on the membrane, which is characteristic of mesenchymal cells as in the EMT process. Besides being characterized by a loss of E-cadherin expression, the EMT process is also characterized by an increase in MMP, which plays a role in degrading the extracellular matrix and basement membrane, which are prerequisites for invasion and metastasis processes.[14] When genetic and epigenetic changes occur, cancer cells lose contact between cells, and matrix and cell, and break away from the main tumor body, expanding filopodia into adjacent interstitial components. The budding tumor itself may play a role in degrading the extracellular matrix (ECM). This

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is supported by the overexpression of matrix metalloproteinases (MMP-2 and MMP-9) and plasminogen-activator receptors in high-grade tumor budding in malignancy based on several studies.[19]

This study also found a significant association between MMP-9 immunohistochemical expression and histopathological grading of endometrial carcinoma. This is in line with the study of Yu et al., in which it was found that high MMP-9 expression was associated with high histopathological grading of endometrial carcinoma and correlated with the progression of endometrial carcinoma.[25] Similar results were obtained by Aglund et al., who found that there was a relationship between expression of MMP-9 and histopathological grading of endometrial carcinoma. In that study, it was said that MMP-9 could act as a marker of clinical behavior of endometrial carcinoma and might further be associated with a tendency for disease recurrence. Thus, MMP-9 may potentially be useful in making decisions about the need for adjuvant therapy.[40] The study by Nezza et al. also found that MMP-9 is related to the histopathological grading of endometrial carcinoma. This study shows that increased MMP-9 expression and the development of endometrial carcinoma are closely related. The presence of MMP-9 in endometrial carcinoma produces changes in the microenvironment that encourage tumor invasion and metastasis.[42] However, it is different from the study conducted by Grybos, where in this study MMP-9 expression did not show differences from each grade. In that study, no correlation was seen between MMP-9 expression and clinical or pathological parameters of endometrial carcinoma.[26] MMP-9 is a type of matrix metalloproteinase that facilitates invasion and destruction of the extracellular matrix and further proliferation after metastases are formed, where this is required for cancer spread and metastasis.[24] MMP-9 appears to be a promising therapeutic target for cancer treatment. The correlation between MMP-9 activity and tumor angiogenesis has led to many therapeutic development programs because tumor growth will be limited without the ability to form a blood supply. The use of antiangiogenic therapeutic agents will allow for the prevention of tumor-associated neoangiogenesis. The use of MMP inhibitors as a target for angiogenesis could be an effective method. In addition, such angiogenesis-inhibiting therapy could be used alongside standard chemotherapy to help reduce mortality and morbidity and prolong survival in endometrial carcinoma patients.[24,43]

CONCLUSION

In this study, there was a significant relationship between MMP-9 immunohistochemical expression, tumor budding index, and histopathological grading in endometrial carcinoma, where MMP-9 immunohistochemical expression increased with a tumor budding index and high histopathological grade.

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