ORIGINAL RESEARCH

The prognostic role of mitosis index, stage and grade of endometrial cancer in Dr. Soetomo General Academic Hospital Surabaya, Indonesia, in 2018-2020

Farida Umi Choviva[1], Willy Sandhika[2,3]*, Pungky Mulawardhana[4]
[1]Midwifery Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[2]Department of Anatomic Pathology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.
[3]International Association of Pathologist, Indonesia Division.
[4]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

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***Corresponding author:**
Willy Sandhika
willysand@fk.unair.ac.id

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ABSTRACT

Objective: This study aimed to analyze the correlation between the mitotic index and the stage and grade of endometrial cancer.

Materials and Methods: We collected pathology reports of endometrial cancer from the Pathology Laboratory at Dr. Soetomo General Hospital in Surabaya, Indonesia, covering cases diagnosed between 2018 and 2020. A total of 106 cases of endometrial cancer were included in this study. For each case, detailed records of the cancer stage, grade, and mitotic index were recorded. The mitotic index, an indicator of cell proliferation, was quantified, and its correlation with cancer stage and grade was assessed. To determine the strength and direction of these relationships, we performed a Spearman rank correlation statistical analysis for non-parametric data.

Results: Our findings indicated a significant positive correlation between the mitotic index and the stage of endometrial cancer. An increase in the mitotic index, reflecting a higher proliferation rate of cancer cells, was associated with a more advanced cancer stage, suggesting that the mitotic index could potentially serve as a prognostic marker for assessing tumor progression in endometrial cancer. However, our analysis revealed no significant correlation between the mitotic index and the histological grade of endometrial cancer, implying that the grade, which typically reflects the differentiation status and morphological characteristics of the tumor cells, is independent of the proliferation rate as measured by the mitotic index.

Conclusion: The mitotic index is positively correlated with the stage of endometrial cancer but does not show a correlation with the histological grade. These findings highlight the potential use of the mitotic index in staging endometrial cancer.

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Highlights:

1. Mitotic index and grade are prognostic factors for endometrial cancer, but both are independent.
2. Stage and mitotic index associated with cell proliferation affect the prognosis of endometrial cancer.

INTRODUCTION

Endometrial carcinoma is the sixth most common cancer, accounting for about 5% of all cancer cases in women. According to the World Health Organization, the global rate of cancer was 50%, reaching 15 million by 2020. Endometrial cancer is estimated to have 417,000 incidents and 97,000 deaths worldwide.[1]

Endometrial carcinoma is generally thought to have a good prognosis, but more than 20% of women with endometrial cancer die from it.[2] Mortality is directly linked to poor prognostic factors that drive tumor recurrence.[3] Significant prognostic factors in endometrial cancer are the stage of cancer, the grade, and the mitosis index.[4,5] The grade and the stage are independent prognostic factors. High histopathological graduation and staging are associated with low long-term survival rates.[6] The mitosis index is used as a simple way to measure proliferation in the microscopic examination of endometrial cancer.[7] With a useful and simple method for analyzing cell proliferation, it can br analyzed quickly.[8] In uncontrolled proliferation of epithelial cells, the resulting cancer development affects the size of endometrial cancer. The size of endometrial cancer determines the clinical stage according to the TNM classification, which indicates that the higher the tumor size, the higher the stage and the worse the prognosis. The degree of histological differentiation of cancer can help predict the rate of the tumor growth rate is. In general, the slower the growth, the better the prognosis.[9] Proliferation also affects the growth rate of endometrial cancer tissue.[10] The growth rate of endometrial cancer can be predicted by determining the grade of the cancer. In general, the slower the growth, the better the prognosis.[11] This study aimed to show whether there is a correlation between mitotic index with stage and grade of endometrial cancer. By a relatively simple method calculating the mitotic index, it was found that the prognosis can be established earlier and provide faster information for treatment recommendations and better future collection of outcome and survival data.[7,8,12]

MATERIALS AND METHODS

The method of this study was analytic observation with a cross-sectional study design. The sample of this study was taken from some endometrial cancer patients who did post-surgical staging and visited the Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from January 2018 to December 2020. As many as 106 patients had endometrial cancers. The patients had two primary or unclear primaries during this period, and no medical records were excluded. The samples were obtained by total population sampling. The staging, grade, and mitotic index variables were observed in medical records in each case. The result of the study was analyzed with the Spearman rank statistic formula to obtain a correlation between the variables. Health Research Ethics Committee, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia No. 1732/125/4/X/2022, approved this study ethically.

RESULTS AND DISCUSSION

One hundred and six patients were enrolled in this study. Most of the samples were women with endometrial cancer aged 45-65 (59.43%), and there were stage characteristics in endometrial cancer. Most 40 patients (37.74%) were in stage III, while 4 (3.77%) were in stage IV. Most endometrial cancer patients in Dr. Soetomo, General Hospital Surabaya had a grade III of 40 patients (37.73%), based on the characteristics of the degree of histology differentiation in endometrial cancer obtained. (Table 1).

Table 1. Patients' characteristics in this study

No.	Variables	Total	N (%)
1.	Age		
	<45 years old	12	11.32%
	45-60 years old	63	59.43%
	>60 years old	31	29.25%
	Total	106	100%
2.	Stage		
	I	37	34.91%
	II	25	23.58%
	III	40	37.74%
	IV	4	3.77%
	Total	106	100%
3.	Grade		
	I	32	30.19%
	II	34	32.08%
	III	40	37.73%
	Total	84	100%

This study revealed that most patients were diagnosed with endometrial cancer at 45-60 years old. At that age, the average woman experiences menopause. This result alligned with a previous research, which showed that age affects endometrial cancer. When a woman is over 46.5 years the risk of cancer increases with her menopausal age.[13] There are differences in the age of menopause in every country in the world due to differences in lifestyle, geographical, ethnic, and socioeconomic locations that affect the period of menopause.[14] Women with lower socioeconomic status experience significantly earlier menopause.[15] According to WHO 2022 and the Ministry of Health in Indonesia, the menopause period age is 45-55 years after 12 consecutive rounds without natural menstruation. [16] There is currently no definitive research identifying why

endometrial cancer is more prevalent among menopausal women. However, one prominent hypothesis suggests that women who experience menopause at an older age have prolonged exposure to higher levels of estrogen before menopause, contributing to cancer risk. Additionally, progesterone deficiency, which is common in menopausal women due to anovulatory cycles, may further elevate the risk of developing endometrial cancer.[13]

The study's results found that the stage and grade of endometrial cancer at the Dr. Soetomo General Academic Hospital are high, illustrating that the prognosis of endometrial cancer patients is poor. This might be because Dr Soetomo Hospital is a Type A referral hospital for eastern region of Indonesia, the patients treated are more varied, and many patients have degrees of histological differentiation and advanced stages. It can also be seen that Indonesia is a developing country. Most developing countries have low public health quality because public awareness about health is also low. In Indonesia, the 2018 Basic Health Research data states that only 20% of Indonesians care about health.[17] With inadequate public health awareness in Indonesia, patients come to health facilities at an advanced level, making patients have a poor prognosis.

The characteristics of the mitosis index from the total sample of 106 showed the highest was 55 while the lowest index was 2, with an average of 18.41 and a standard deviation of 10.599. The mitosis index has a high standard deviation because its value is higher than the average value, which suggests that the data of the mitotic index is highly variable, supported by the presence of mitotic index data from 2 to 55 (Table 2).

The various mitotic indices are due to the time of identification of mitotic indices limited to the cell cycle phase of tissue retrieval and the substantial variability of observers in their title because the area of one high-power field can vary up to 3-5-fold in different microscopy.[18] These factors allow subjectivity so that the data obtained has a varied mitotic index.

The lowest mitosis index is 2, found in patients with a grade II, whereas the mitotic index should not be found at grade II because it has a high level. The highest mitosis index of 55 was found in patients with a grade III, but a shallow mitotic index of 4, which should not be found in grade III (Table 2).

At the levels of grades I, II, and III, the standard deviation values were quite high because they were higher than the average half-value, which indicated that at grade I, II, and III, the mitosis index values varied greatly, as demonstrated by the presence of the lowest and highest range of mitosis indexes of any very wide of grade (Table 2).

Table 2. Mitotic index versus grade of endometrial cancer.

No.		Min	Max	*Mean*	SD	Total
1.	Grade I	4	42	15.75	9.119	32
2.	Grade II	2	46	19.15	11.988	34
3.	Grade III	4	55	19.90	10.305	40

The lowest mitosis index of 2 was found in patients with stage I. The highest mitotic index of 55 was found in stage III, but in stage III there was the presence of a shallow mitosis index of 4, which should not be found in stage III because, at stage III, the spread of cancer has been wide (Table 3).

Table 3. Mitotic index versus stage of endometrial cancer.

No.		Min	Max	Mean	SD	Total
1.	Stage I	2	34	14.05	8.086	37
2.	Stage II	5	46	17.24	10.293	25
3.	Stage III	4	55	22.68	11.555	40
4	Stage IV	18	32	23.25	6.702	4

In stages, I, II, and III, the standard deviation values were high because they were higher than the average half-value, which indicated that in stages II and III, the mitosis index values were highly variable, as demonstrated by the presence of the lowest and highest ranges of mitosis indexes in each very distant stage. In stage IV, there was a typical standard deviation compared to the average; the lower the standard deviation, the better because the sample was homogeneous, but this is due to the small number of samples (Table 3).

In this study, we used the Spearman rank test to find the correlation between two variables. Based on the correlation between the mitosis index and the degree of histological differentiation of endometrial cancer, we obtained a p-value of 0.076 (p >0.05), indicating that there was no relationship between the index of mitosis and the degree of histological differentiation of endometrial cancer. When the correlation between the mitosis index and the stage of endometrial cancer was obtained at p >0.001 (p 0.05), it can be concluded that there was a relationship between mitosis and the stage of endometrial cancer. The correlation coefficient value of 0.370 indicated the turning of the relationship between the mitotic index and the weak stage, as well as obtaining a positive value in the correlation coefficient so that the connection between the mitosis index and the stage of endometrial cancer was aligned. The higher the mitosis index, the higher the stage of endometrial cancer.

In this study, there was a correlation between the mitosis index and the stage of endometrial cancer at Dr. Soetomo General Academic Hospital, Surabaya, in 2018–2020. With fairly tight rotation values and the direction of the relationship, the higher the mitosis index, the greater the stage in endometrial cancer patients. TNM stage is classified according to tumor size, metastasis, and tumor spread tumor, which refers to the size and breadth of the primary tumor.[19] Tumor size and tumor growth induce angiogenesis. Angiogenesis is triggered due to uncontrolled proliferation.[20] As cellular proliferation increases, tumor size correspondingly enlarges. To assess cell growth through division, mitotic activity is evaluated. This can be quantified using the mitotic index, which provides a measure of cell division rates.[21] This study demonstrated a correlation between the mitosis index and cancer stage with directional correlations. In gynecological cancer such as breast cancer, the prognosis is greatly influenced by the proliferation of cancer cells seen from the histopathology results which are assessed based on the mitotic index.[22] In other cancers, it has also been shown that there is a correlation between the mitotic index and the stage of the bladder tumor, which is explained by a significant increase in the proliferative activity of tumor cells in proportion to the increase in the stage of the bladder tumor.[18] This is comparable to this study which found a correlation between mitotic index and stage.

The correlation between the mitotic index and tumor stage shows considerable variability, likely due to the dependency of the mitotic index on specific phases of the cell cycle, as well as variability in identifying these phases. Additionally, differences in high-power field area, which can vary up to three- to five-fold across different microscopes, impact measurement consistency. Despite these factors, the mitotic index remains a reliable marker for assessing cellular proliferation.[18]

The grade assesses the cell morphology suspected as part of the tumor tissue based on the similarity of malignant cell shapes with the cells of origin.[23] The fewer glands formed, the greater the grade and the poorer the prognosis of the endometrial cancer.[24] Lower gland formation and higher proliferation were expected to result in a higher mitosis index. However, this study found no correlation between the mitotic index and the grade. Histological degrees decrease the tumor growth rate, affecting the prognosis. The slower its growth, the better the prediction.[11] The mitosis index also affects the tumor growth rate in the presence of cell proliferation.[10] The mitosis index is a significant prognostic indicator.[7] The grade has also been established as one of the prognostic factors.[4] This indicates that the mitosis index and the degree of histological differentiation equally affect the prognosis and tumor growth rate, but they are neither interrelated nor independent.

Mitosis has long been used as a simple way to measure proliferation in routine areas. This simple measurement method can practically save costs, time and workload. This method can be used as a practical tool in a developing countries, where there are less possibilities to perform six multiple repeat biopsies and the patient was often lost to follow-up.[8] This mitotic index is associated with the well-established prognostic parameters, that is, tumor grade and stage.[6] Thus, adding this marker to existing protocols can increase the objectivity and reliability of accurate diagnosis, patient management, and tumor progression compared with conventional grade and stage.[8]

At Dr. Soetomo General Academic Hospital, certain patients exhibited a poor prognosis, which is atypical, as endometrial cancer generally has a favorable prognosis due to its characteristic symptoms that aid in early detection. Variability in research outcomes may arise from observer subjectivity, impacting study results and weakening the observed relationships.

CONCLUSION

These data indicate a correlation between the mitotic index and the stage of endometrial cancer, while no correlation is observed between the mitotic index and cancer grade. At Dr. Soetomo General Academic Hospital in Surabaya, Indonesia, from 2018 to 2020, the mitotic index was associated with endometrial cancer stage but showed no relationship with cancer grade.

DISCLOSURES

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Conflict of interest

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Author contribution

All authors have contributed to all processes in this research, including preparation, data gathering and analysis, drafting, and approval for publication of this manuscript.

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