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

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Article Info	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.

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 rates by 50%, reaching 15 million by 2020. Endometrial cancer is estimated to have 417,000 incidents and 97,000 deaths due to the disease 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 so that it can analyze quickly.[8] In the uncontrolled proliferation of epithelial cells causing cancer development that affects the size of endometrial cancer, the size of endometrial cancer determines the clinical stage according to the TNM classification, which indicates the higher the tumor size, the higher the stage and the worse the prognosis. The degree of histological differentiation of cancer can help predict how fast 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 aims 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 is 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 is analytic observation with a cross-sectional study design. A 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, 106 patients have endometrial cancers. Patients had two primary or unclear primaries during this period, and no medical records were excluded. The samples were obtained by total population sampling. This observational analytical study reviews anatomic pathology results in Surabaya from 2018 to 2020. The staging, grade, and mitotic index variables were seen 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 aged 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 have a grade III of 40 patients (37.73%), based on the characteristics of the degree of differentiation histology 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 was under the 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 menstruation naturally. No clear physiological or pathological exists without clinical intervention.[16] There is no definitive research on the cause of endometrial cancer being more frequent in menopausal women, but the hypothesis that women with older menopausal age have higher hormone levels and a long time of estrogen exposure before menopause has been suggested as an essential etiology in addition to that in menopausal women it occurs Progesterone deficiency associated with anovulatory cycles can also increase the risk of endometrial cancer.[13]

The study's results found that the stage and grade of endometrial cancer at the Dr. Soetomo general hospital are high, illustrating that the prognosis of endometrial cancer patients is poor. This can be influenced because, according to the profile of the Dr. Soetomo General Hospital, Surabaya, it is a type A hospital that is an eastern referral area. Hence, 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 every day. In Indonesia, the 2018 Riskesdas data states that only 20% of Indonesians care about health.[17] With inadequate public health awareness in Indonesia, patients come to health workers at an advanced level, making patients have a poor prognosis.

The characteristics of the mitosis index from the total sample of 106 obtained the minor data with the mitosis index two and the highest data for the mitosis index 55, 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.

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).

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

At the levels of grades I, II, and III, the standard deviation values are pretty high because they are higher than the average half-value, which indicates that at grade I, II, and III, the mitosis index values vary greatly, as demonstrated by the presence of the lowest and highest range of mitosis indexes of any very wide of grade.

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 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 widespread (table 3).

Tabel 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 are pretty high because they are higher than the average half-value, which indicates that in stages II and III, the mitosis index values are 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 is a typical standard deviation compared to the average; the lower the standard deviation, the better because the sample is homogeneous, but this is due to the small number of samples.

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 obtained from the results of the analysis with a p-value of 0.076 ($p > 0.05$), it can be concluded that there is 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 is obtained at $p > 0.001$ (p 0.05), it can be concluded that there is a relationship between mitosis and the stage of endometrial cancer. The correlation coefficient value of 0.370 indicates the turning of the relationship between the mitotic index and a 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 is 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] The more cells proliferate, the larger the size of the tumor, so to measure cell growth by cell division, the activity of mitosis is defined. The mitotic index can measure it.[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 mitosis index and the stage has a reasonably tight distortion due to the probability caused by the mitotic index, whose examination is limited to the cell cycle phase with significant observing variability in its identification. Since the area of one high-power field can vary up to 3–5 times in different microscopes, the mitosis index is a more reliable marker and can be used to assess 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 endometrial cancer.[24] Lower gland formation and higher proliferation were expected to result in a higher mitosis index. However, this study found no link between the mitotic index and the grade. Histological degrees decrease the tumor growth rate, affecting the prognosis. The slower its growth, the better the forecast.[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 this is not possible to perform 6 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 Hospital, some patients had a poor prognosis. This is an unusual thing to happen because, in general, endometrial cancer has a good prognosis due to symptoms that are typical of endometrial cancer. Limitations of research vary due to the subjectivity of the observers themselves. This affects the research results, which makes the relationship relatively weak.

CONCLUSION

These data demonstrate a correlation between the mitotic index and the stage of endometrial cancer and no correlation between the mitotic index and the grade of endometrial cancer. Increase. The mitosis index does not correlate with the grade, but there is a correlation between the mitotic index and endometrial cancer stage in the Dr. Soetomo General Hospital Surabaya in 2018–2020.

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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