Association Between Body Mass Index (BMI) And Histopathologic Grade Of Endometrioid Endometrial Carcinoma (EEC)

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Abstract- Endometrioid Endometrial Carcinoma (EEC) is one of the malignant primary epithelial tumors in the endometrium, a glandular neoplasm that shows acinar, papillary or partially dense configuration and potentially affects the myometrium. Histopathological grading is based on the degree of structural differentiation and cell atypia. BMI is a body mass index calculated by comparing body weight with height, calculated by dividing body weight in kilograms with height in meters squared. The exact cause of EEC is unknown, most of the EEC cases associated with endometrial exposure to chronic estrogen stimulation will cause excessive proliferation resulting in endometrial hyperplasia which is a precursor to the occurrence of EEC. This study used endometrial tissue samples to assess the relationship BMI and histopathological grading of EEC. As many as 31 paraffin blocks fixed by formalin from EEC patients were examined and assessed for histopathological grading. The basic characteristics of the sample are obtained through medical records or pathology archives. the relationship between BMI and histopathological grading EEC was analyzed using SPSS version 22. The results of the analysis showed that there was no significant relationship between BMI and histopathological grading of EEC (p> 0.05).

Index Terms- Endometrioid Endometrial Carcinoma (EEC), Body Mass Index (BMI), Grading histopathology

I. Introduction

Endometrial carcinoma is the most common carcinoma of the female reproductive tract in developed countries and is the third most common cause of death in carcinoma in women. In 2012, endometrial carcinoma occurred in 320,000 women and caused 76,000 deaths worldwide.1 In developed countries, 75% of cases of endometrial carcinoma occur in patients around 60 years of age during the post-menopausal period, so the most common symptom is post-bleeding menopause. Evidence about the relationship between the Body Mass Index (BMI) is high, and the risk of endometrial cancer, including subtypes in Asian populations is still limited. In Indonesia, the latest study found the prevalence of endometrial carcinoma in Cipto Mangunkusumo Hospital (RSCM) Jakarta reached 7.2 cases per year. The age of patients tends to be younger, which is as much as 63.9% at the age of ≥50 years and as much as 12.5% at the age of ≤40 years. The most common type based on histopathology type is endometrioid endometrial carcinoma (EEC) of around 75-80%, serous papillary carcinoma 5-10% and clear cell carcinoma 3-5%. Serous papillary carcinoma and clear cell carcinoma are aggressive types. [2,3,4,5]

Excess Estrogen is allegedly the cause of endometrial carcinoma. Ovaries produce and release estrogen, but fat tissue also has the power to convert some hormones into estrogen. The more fat tissue, the more hormones that are converted to estrogen, increasing estrogen levels in women and at the risk of EEC.[6]

Some experts argue, there is a correlation between weight gain and EEC events. According to Arem, et al. (2013) there may be an association of obesity with the risk of EEC and women with EEC with normal weight may have better survival than obesity. [7,8]

BMI is a measure of weight adjusted for height, calculated as weight in kilograms divided by square of height in meters (kg / m2). Research has shown that BMI levels correlate with body fat and with future health risks. High BMI predicts future morbidity and mortality. Therefore, BMI is the right measure for obesity screening and its health risks.[9]

Some studies suggest that increasing weight and obesity can increase the risk of EEC. The risk was greatest in women who had a ≥35% increase in normal BMI or women who averaged ≥1% increase in normal BMI during the period from the age of 21 years. In Japanese and Americans, a 5% increase in normal BMI increases the risk of EEC.[10]

Differentiation of malignancy for EEC according to the World Healt Organization (WHO) is made based on structural histopathology and cell atypia. These grading are grouped according to the degree of differentiation of the EEC seen from the growth patterns of non-squamous or non-morula solids. Core grades are determined by variations in the size and shape of the nucleus, chromatin distribution, and size of nucleoli.[11]

II. Material and Methods

Sample selection

This study was conducted in a cross-sectional manner in the Anatomy Pathology Department, Medan H. Adam Malik General Hospital and included 31 EEC cases, which aimed to assess

whether there was a relationship between BMI and EEC histopathological grading. All samples are obtained through surgical procedures. The inclusion criteria were EEC cases with adequate clinical data, fixed tissue blocks with undamaged formalin-fixed with adequate tumor tissue. Detailed clinical data obtained from medical records or pathology records consisting of age, and BMI status or body weight and height, can then be calculated the number of BMI of these patients. Histopathological grading was determined independently by the researchers through a slide examination of hematoxylin and eosin.

Body Mass Index (BMI)

BMI is a body mass index calculated by comparing body weight with height, calculated by dividing body weight in kilograms with height in meters squared.

$$BMI = \frac{\text{Weight Loss (Kilograms)}}{\text{Body Height (Meter)}^2}$$

BMI Category

BMI	Weight Status
< 18.5	Underweigth
18.5 – 24.9	Normoweight
25.0 – 29.9	Overweight
30.0 and above	Obesity

Grading

Histopathological grading is based on the degree of structural differentiation and cell atypia.15 This grading is grouped according to the degree of differentiation of EEC seen from the following non-squamous or non-morula solid growth patterns as follows: GI (5% or less), G-II (6 -50%), G-III (> 50%). The core grade is determined by variations in core size and shape, chromatin distribution, and nucleoli size. The grade-I core is oval, slightly enlarged, and has evenly spread chromatin. The grade-III nucleus showed a striking and pleomorphic enlargement, with irregular coarse chromatin and a prominent eosinophilic nucleoli. Grade-II core images between grade-I and grade-III. Mitotic activity is an independent variable but generally increases with an increase in core grade. [11,12,13,14,15,16]

Statistical analysis

Statistical analysis was carried out using the SPSS version 22.0 software package (SPSS Inc., Chicago) with 95% confidence intervals and Microsoft Excel 2010. Variable categories were presented in frequency and percentage. The Kruskal-Wallis test was applied to find the relationship between BMI and EEC histopathology grading. P values> 0.05 were considered insignificant.

III. RESULT

The average age for Endometrioid Endometrial Carcinoma (EEC) patients is 53.4 (± 14.1) with the youngest patients aged 21-26 as many as 1 case (3.2%) and the oldest age is the 81-86 age group year with a total sample of 1 case (3.2%), and the age of most patients was in the age group 51-56 years with a total sample of 9 cases (29.0%). Characteristics based on EEC patient age are summarized in table 1.

Table 1. Characteristics of EEC patients based on age

BMI	Number of cases	Percentage (%)
Age, mean ± SD, years	53,4 ± 14,1	
21 – 26	1	3,2
27 - 32	2	6,5
33 – 38	1	3,2
39 – 44	2	6,5
45 – 50	6	19,3
51 – 56	9	29,0
57 – 62	2	6,5
63 – 68	2	6,5
69 – 74	4	12,9
75 – 80	1	3,2
81 - 86	1	3,2
total	31	100

Frequency distribution of EEC patients based on histopathological grading obtained data on frequency of EEC patients with histopathological grading of Grade I were 14 people (45.2%), Grade II was 8 people (25.8%), and Grade III was 9 people (29.0%) shown in table 2.

Table 2. Grading of EEC patients histopathology.

Grading	Total (n)	Percentage (%)
Grade I	14	45,2
Grade II	8	25,8
Grade III	9	29,0
total	31	100

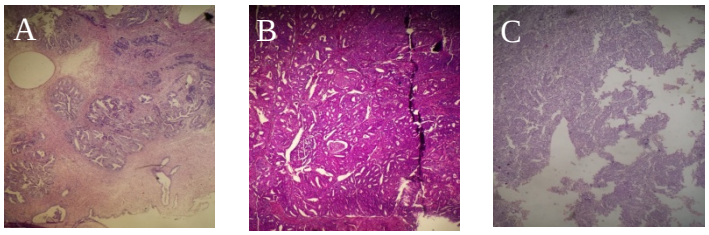

Figure 1. EEC A. Gr I, B. Gr II, C. Gr III

Characteristics of EEC patients based on the BMI category in EEC patients obtained data namely underweight with the number of 2 people (6.5%), normoweight as many as 15 people (48.4%), overweight as many as 8 people (25.8%), and obesity as many as 6 people (19.3%) listed in table 3.

Table 3. BMI category in EEC patients

BMI	Total (n)	Percentage (%)
Underweigth	2	6,5
Normoweight	15	48,4
Overweight	8	25,8
Obesity	6	19,3
total	31	100

Based on the WHO classification, EEC consists of grade I, grade II and grade III. And BMI consists of 4 categories of underweight, normoweight, overweight and obesity. The frequency distribution of all EEC patients based on BMI and histopathological grading can be seen in table 4.

Table 4. BMI Distribution Based on Patients Grading

No	BMI	Grading						P-value*
		Grade 1		Grade 2		Grade 3		
		n	%	n	%	n	%	
1.	Underweight	1	50,0	1	50,0	0	0	0,563
2.	Normoweight	5	33,3	4	26,7	6	40,0	
3.	Overweight	4	50,0	2	25,0	2	25,0	
4.	Obesity	4	66,6	1	16,7	1	16,7	

*p>0,005

Based on table 4, it is stated that patients with underweight category have 1 case (50.0%) in grade 1 histopathological grading and 1 case (50.0%) in grade 2 and not even 1 case (0%) in grade 3. Furthermore in the normoweight category, there were 5 cases (33.3%) in grade 1 and 4 cases of histopathology grading (26.7%) in grade 2 and found 6 cases (40.0%) grade 3. While in the overweight category, there were 4 cases (50.0%) in grade 1 and 2 cases of histopathology grading (25.0%) in grade 2 and found 2 cases (25.0%) grade 3. And in the obesity category, there were 4 cases (66.6%).) in grade 1 histopathology grading, 1 case (16.7%) in grade 2 and 1 case (16.7%) in grade 3.But the results of the analysis of the relationship between BMI and histopathological grading of EEC patients in this study obtained p-value = 0.563 (p> 0.05) which showed no significant relationship.

IV. DISCUSSION

EEC is a malignant primary epithelial tumor in the endometrium, a glandular neoplasm that shows acinar, papillary or partially dense configurations and potentially regarding myometrium.[17] Most cases of EEC are often associated with endometrial exposure to estrogen stimulation. In this study it was found from 31 samples of EEC patients that many occurred in the age range of 51 - 56 years (29.0%). This situation is in accordance with Sofian A (2010) study where the age of EEC patients at the age of ≥50 years.3 While in the Nevadunsky NS (2014) study, the results of the study showed that the average age of patients with EEC was 67.1 years with a standard deviation of ± 11.9 years. [18]

From this study also found that the highest rate of EEC patients was grade I as many as 14 people (45.2%). This is in accordance with the study of Nevadunsky NS (2014) which also stated that the highest number of EEC patients was grade I as many as 380 people (64.3%)[18]. While in the study of O.G. Trifanescu found the highest number of EEC patients in grade III histopathology. [19]

Characteristics of EEC patients based on the BMI category in EEC patients from this study, found the normoweight category as the highest number with 15 people (48.4%). While in the study of Nevadunsky NS (2014) the highest number was in the category of obesity (66.3%).[17]

Some experts argue, there is a relationship of weight gain with the EEC event where excess estrogen is allegedly the cause. This excess produced estrogen will be stored cumulatively, considered to increase the risk of EEC.[21] Various factors known to affect EEC development include (1) obesity, (2) diabetes, (3) hypertension, (4) infertility, and (5) exposure against unopposed estrogen (estrogen used in replacement / estrogen therapy without progestin administration to prevent side effects). Prolonged estrogen replacement therapy and ovarian tumors that secrete estrogen increase the risk of endometrioid endometrial carcinoma.

The relationship between BMI and histopathological grading of EEC patients in this study found that the category of obesity with grade I histopathology grading was the highest incidence (66.6%). This is in accordance with the results of the Nevadunsky NS (2014) study which also obtained the category of obesity with grade I histology grading as the highest incidence (60.9%) 30. But the results of the analysis of the relationship between BMI and histopathological grading of EEC patients in this study obtained p-value = 0.563 (p> 0.05) which showed no significant relationship. This may be the data of BMI or body weight and height of the patients who came to RSUP HAM Medan, assessed at the same time. While the possibility of patients suffering from EEC has occurred long before the patient came to RSUP HAM Medan.

But from this study there is an interesting one although statistically the relationship between BMI and EEC histopathology grading is not significant. The consistency of the characteristics of overweight and obesity seems consistent in grade 1 with the highest incidence and decreasing with increasing histopathological grading of EEC. There is a tendency of overweight and obesity most often found in grade 1. While in grade 2 and grade 3 the incidence rate decreases. This may occur because of the patient's health condition which is decreasing due to the disease, or perhaps due to the patient's psychological state of the illness. Side effects of therapy also cannot be excluded as a cause of a decrease in the patient's BMI category along with the course of the disease.

V. CONCLUSION

There is no significant relationship between BMI and EEC histopathology grading.

COMPETING INTERESTS

The author has no financial interests relevant to the product or company described in this article.

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ETHICAL APPROVAL

Health Research Ethical Committee, University of Sumatera Utara, Medan, Indonesia approved this study.

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