Immunohistochemistry Expression of L1CAM Based on Subtype and Grading Histopathological of Endometrial Carcinoma at Haji Adam Malik and Prof. Dr. Chairuddin P. Lubis Universitas Sumatera Utara Hospital 2018-2022

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ABSTRACT

Background
Endometrial cancer is a malignant neoplasm of epithelial cells that shows various proportions of glands with papillary and solid architecture with endometrioid cell differentiation resembling the endometrium. Endometrial cancer is the sixth most frequently diagnosed cancer in women with the majority of cases occurring in post-menopause average 61 years old. However, the incidence of endometrial carcinoma increases in pre-menopausal women and women less than 40 years old. Histopathological classification based on tumor morphology and tumor grade has played an important role in the management of endometrial carcinoma, allowing prognostic stratification into different risk categories, and guiding surgical and adjuvant therapy. There are several additional prognostic factors that can improve the prognostic stratification of endometrial carcinoma. Additional prognostic markers by examining immunohistochemical factors, such as L1 transmembrane cell adhesion molecule (L1CAM) expression. L1CAM has emerged as one of the most promising.
Method:
Descriptive study with 23 paraffin block samples from histerectomy was diagnosed as endometrium carcinoma at Haji Adam Malik and Prof. Dr. Chairuddin P. Lubis Universitas Sumatera Utara Hospital. Assessment was done using staining with hematoxylin and eosin (H&E) to determine subtype and grading endometrial carcinoma and appraise expression of endometrial tumor cells with L1CAM immunohistochemistry. L1CAM expression was positive if ≥ 10% was stained in the tumor membrane and cytoplasm and negative if < 10% was stained in the tumor membrane and cytoplasm.
Results
L1CAM immunohistochemistry on the 23 samples, based on the endometrial carcinoma subtype was most commonly found in the endometrioid carcinoma NOS subtype which expressed positively 46.7% and based on endometrial carcinoma grading it was high grade endometrial carcinoma in 88.2%.
Conclusion
Ekspression L1CAM immunohistochemistry was positive in high grade endometrial carcinoma.
Keywords: *Endometrial carcinoma, high grade, L1CAM*

INTRODUCTION

Endometrial carcinoma is an epithelial neoplasm with endometrioid cell differentiation that is most common in women in developed and industrialized countries, with the majority of cases occurring in post-menopausal women with an average age of 61 years. However, the incidence of endometrial carcinoma increases in pre-menopausal women and women less than 40 years of age.[1,2]

In recent years, there have been alarming changes in the epidemiology of endometrial carcinoma. According to statistical data from the Global Burden of Cancer Study (GLOBOCAN) in 2020, uterine corpus cancer is the sixth most frequently diagnosed cancer in women, the incidence is 3.0 per 100,000 with 417,000 new cases and 97,000 deaths.[3]

METHOD

This research is descriptive study with a cross sectional approach.The research was done at Haji Adam Malik Medan and Prof. Dr. Chairuddin P. Lubis, University of Sumatera Utara Hospital from 2018 to 2022. This study population consisted of all secondary data and paraffin blocks from patients who were histopathologically diagnosed with endometrial carcinoma that appropriate the inclusion and exclusion criteria. The sample size in this study was the entire affordable population selected using total sampling. The variables in this study were L1CAM immunohistochemical expression as the independent variable and endometrial carcinoma subtype and grading as the dependent variable.

Immunohistochemical expression of L1CAM was assessed in the membrane and cytoplasm of tumor cells. The L1CAM protein used was NP_ 076493 Rabbit Polyclonal Antibody with a dilution of 1:100 from the manufacturer Merck. According to the criteria published by Zeimet et al., cases were considered L1CAM positive if LICAM expression was ≥ 10% in the tumor membrane and cytoplasm and negative if L1CAM expression was < 10% in the tumor membrane and cytoplasm.[4]

The subtype and grading of endometrial carcinoma is the histopathological description of endometrial carcinoma which is based on the WHO Classification of Female Genital Tumours 5th edition in 2020. The histopathological subtype of endometrial carcinoma is endometrioid carcinoma NOS, serous carcinoma NOS, clear cell carcinoma NOS, undifferentiated carcinoma NOS, mixed cell adenocarcinoma, other endometrial carcinomas and carcinosarcoma NOS. Grading of carcinoma endometrium will be divided into two categories, namely low grade (endometrioid carcinoma FIGO grades 1 and 2) and high grade (endometrioid carcinoma FIGO grade 3, serous carcinoma, clear cell carcinoma, undifferentiated carcinoma, mixed carcinoma and carcinosarcoma, other endometrial carcinomas and carcinosarcoma NOS).[5,6]

This data will be analyzed using the SPSS Statistics for Windows version 21th computer program. Univariate analysis to obtain characteristics of research subjects. Categorical data will be assessed in percentage form (%) while numerical data uses the mean. The results will be presented in table form.

RESULTS

Of the 26 hysterectomy samples from this study, endometrial carcinoma was diagnosed in 2018 to 2022, at Haji Adam Malik Hospital Medan and Prof. Hospital. Dr. Chairuddin P. Lubis, only 23 samples could be used as research samples according to the inclusion and exclusion criteria.

Table 1. Frequency distribution of characteristics of endometrial carcinoma patients

Variable (n=23)	Frequency(f)	Percent (%)
Age		
• < 45 years old	2	8,7
• 45-55 years old	11	47,8
• > 55 years old	10	43,5
Parity history:		
• Nullipara	11	47,8
• Primipara	2	8,7
• Multipara	10	43,5
Contraceptive history:		
• Tidak menggunakan	19	82,6
• Menggunakan	4	17,4
Lymphovacular invasion		
• Positif	8	34,8
• Negatif	15	65,2
Myometrium invasion		
• < ½ miometrium	15	65,2
• > ½ miometrium	8	34,8
Staging FIGO		
• Stage I	18	78,3
• Stage II	2	8,6
• Stage III	3	13,1
• Stage IV	0	0
Subtype :		
• Endometrioid carcinoma NOS	14	60,9
• Serous carcinoma NOS	2	8,7
• Clear cell carcinoma NOS	2	8,7
• Undifferentiated carcinoma NOS	-	
• Mixed carcinoma	3	13,1
• Other endometrial carcinomas	1	4,3
• Carcinosarcoma NOS	1	4,3
Grade		
• Low grade	6	26,1
• High grade	17	73,9
Immunohistochemistry L1CAM :		
• Positive	15	65,2
• Negative	8	34,8

Based on clinical data in medical records (Table 1), in this study the distribution of endometrial carcinoma samples was highest in the age group 45-55 years (47.8%), followed by the age group > 55 years (43.5%), and the age group < 45 years (8.7%). The history of parity in endometrial carcinoma patients was highest in the nullipara group (47.8%), followed by multipara (43.5%) and primipara (8.7%). History of using contraception (17.4%) more less while not using contraception (82.6%).Tumor cell into the lymphovascular invasion (LVI) of endometrial carcinoma patients (34.8%) and those that did not invade (65.2%). Tumor cells that penetrate less than ½ the thickness of the myometrium (65.2%) and those that have penetrated more than ½ the thickness of the myometrium (34.8%).

In this study, the most common FIGO staging for endometrial carcinoma patients was stage I (78.3%), followed by stage III (13.1%), stage II (8.6%) and stage IV was not found in this study.The most common histopathological subtype of endometrial carcinoma is endometrioid carcinoma NOS (60.9%), followed by mixed carcinoma (13.1%), then serous carcinoma NOS (8.7%), clear cell carcinoma NOS (8.7%) and most Few other cases of endometrial carcinoma (mucinous carcinoma intestinal type) (4.3%), carcinosarcoma NOS (4.3%) and cases of undifferentiated carcinoma NOS were not found in this study.Histopathological grading of endometrial carcinoma based on the 2020 WHO classification is divided into two categories. In this study, the frequency distribution of endometrial carcinoma sufferers based on histopathological grading was mostly high grade (73.9%) while low grade (26.1%). Immunohistochemistry examination of endometrial carcinoma patients in this study found that L1CAM immunohistochemical expression was more positive (65.2%) while negative (34.8%).

Table 2. Frequency distribution of L1CAM immunohistochemistry expression in subtype endometrial carcinoma.

Subtype	L1CAM expression			
	Positive		Negative	
	(n)	(%)	(n)	(%)
Endometrioid carcinoma NOS	7	46,7	7	87,5
Serous carcinoma NOS	2	13,3	0	0
Clear cell carcinoma NOS	2	13,3	0	0
Undifferentiated carcinoma NOS	0	0	0	0
Mixed carcinoma	3	20,0	0	0
Other endometrial carcinomas	0	0	1	12,5
Carcinosarcoma NOS	1	6,7	0	0
Total	15		8	

In this study, positive L1CAM immunohistochemistry expression was found in the endometrial carcinoma subtype endometrioid carcinoma NOS (46.7%), mixed carcinoma

(20.0%), serous carcinoma NOS and clear cell carcinoma NOS (13.3%) and carcinosarcoma (6, 7%). Negative L1CAM immunohistochemical expression was found in endometrioid carcinoma subtype s (87.5%) and other subtypes of endometrial carcinoma NOS (12.5%).

Table 3. Distribution of L1CAM immunohistochemistry expression in grading endometrial carcinoma patients .

Grading	L1CAM expression			
	Positive		Negative	
	(n)	(%)	(n)	(%)
Low grade	0	0	6	100
High grade	15	88,2	2	11,8

Frequency distribution of L1CAM immunohistochemistry expression in grading endometrial carcinoma is highest expression in high grade endometrial carcinoma patients 88.2%, while L1CAM immunohistochemistry expression was negative in low grade endometrial carcinoma patients 100% and patients with high grade endometrial carcinoma 11,8%.

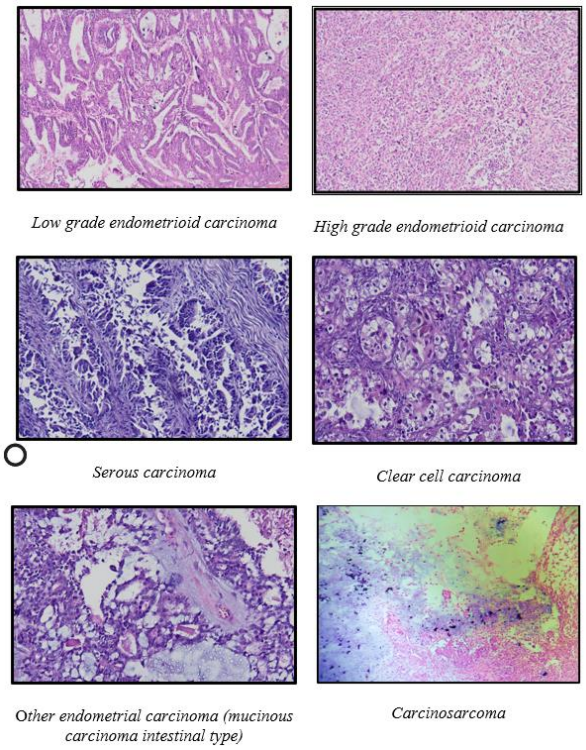

Figure 1. Microscopic images of endometrial carcinoma subtypes

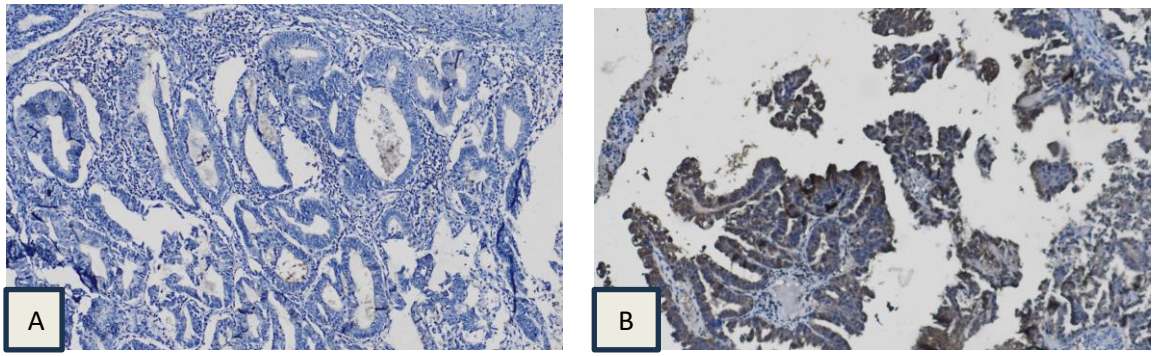

Figure 2. L1CAM immunohistochemistry expression in endometrial carcinoma. A. Negative expression. B. Positive expression (≥10%).

DISCUSSION

In this study, found that the most endometrial carcinoma patients were found in the 45-55 year age group 47.8% followed by > 55 year olds 43.5% and < 45 year olds 8.7%, the average age was The occurrence of endometrial carcinoma was 53.3 years, where the youngest age was 38 years and the oldest age was 69 years with a median age of 54 years. This is different from research conducted at Haji Adam Malik General Hospital Medan in 2012-2015 by Christian where most endometrial carcinoma patients were found at ages > 55 years 45.8%, followed by ages 45-55 years 31.3% and the fewest were patients aged < 45 years 22.9% and research conducted by Yuzar et al where most endometrial carcinoma patients were aged > 55 years 52.6%, followed by the age group 45-55 years 34.2%, and the least common in the age group < 45 years 13.2%.[7,8] In the literature, explain that endometrial carcinoma is the most common cancer in post-menopausal women of age the average was 61 years and the median for endometrial carcinoma patients was 64 years with a range of 34-94 years.[4,5] In this study, endometrial carcinoma patients shifted slightly in the fifth decade of age. This shift may be caused by changes in lifestyle, obesity, nulliparity, hypertension, anovulatory cycles, diabetes, lack of physical activity, unopposed estrogen therapy, long-term use of tamoxifen, Lynch syndrome, Cowden syndrome, and a family history of breast, ovarian, or colon cancer.[2,9] However, this study did not obtain data on the disease history of endometrial carcinoma patients such as diabetes or hypertension and also did not calculate body mass index. So the risk factors for endometrial carcinoma patients at a younger age cannot be clearly revealed. In general, due to changes in lifestyle today, namely reduced physical activity, obesity often occurs, giving rise to degenerative diseases such as hypertension and diabetes. This is an increased risk factor for endometrial carcinoma.

The results of this study showed that 47.8% with a history of nulliparity suffered from endometrial carcinoma. This is in line with the literature[5,6], where nulliparity is a strong independent risk factor for the occurrence of endometrial carcinoma. Nuliparity is only

significant if endometrial carcinoma develops before menopause and not after. This shows that estrogenic hormonal disorders that prevent fertilization also encourage malignant changes in the endometrium.[10] Nuliparity conditions cause the endometrium to always be exposed to the hormone estrogen which causes hyperplasia of the endometrium and will become a precursor to endometrial malignancy.

The results of this study showed that 17.4% used contraception and 82.6% did not use contraception. The results of this study do not indicate that using contraception is one of the risk factors for endometrial carcinoma. However, if we examine the data obtained, several samples of endometrial carcinoma sufferers of the endometrioid carcinoma subtype have a history of using contraceptives in the form of pills or injections. Based on the literature, endometrioid carcinoma is hypothesized to develop due to prolonged estrogen stimulation. Excess estrogen stimulates endometrial cell proliferation, thereby increasing the occurrence of endometrial carcinoma and the accumulation of cellular mutations. This so-called “unopposed estrogen” hypothesis is especially supported by epidemiological data showing a significantly increased risk of endometrial carcinoma in oral estrogen users.[5,6]

FIGO stage, age, histopathological grade, depth of myometrial invasion and lymphovascular invasion are the most important predictors and final outcome in patients with endometrioid carcinoma and its variants.[5] In this study, endometrial carcinoma patients with blood vessel invasion 34.8% and did not invade 65.2%. Currently, lymphovascular invasion (LVI) is widely used as a research variable to determine prognosis, although LVI is not related to staging. Blood vessel invasion carries a more adverse prognosis than lymph vessel invasion, although most pathologists do not routinely differentiate it. The presence of LVI can cause recurrence around the pelvis, distant metastases, and reduce overall survival. Prominent lymphovascular invasion is used in the treatment algorithm, and the distinction between focal and extensive lymphovascular invasion (≥ 5 vessels) may have prognostic significance.[5,11]

In the results of this study, cases that invaded less than ½ the thickness of the myometrial 65.2% and cases that invaded more than ½ the thickness of the myometrial 34.8%. According to the literature, the risk of spread to lymph nodes and recurrence is related to the depth of myometrial invasion. Invasion of more than half of the myometrium is significantly associated with reduced survival for endometrial carcinoma patients. The depth of myometrial invasion is one of the criteria for determining staging based on FIGO and UICC.[5] FIGO and UICC staging for endometrial carcinoma patients is based on the depth of myometrial invasion (< ½ myometrial thickness or ≥ ½ myometrial thickness) and involvement of the endocervical stroma, adnexa and lymph nodes.[11] The results of this study are staging of endometrial carcinoma based on FIGO, where stage I is the most found (78.3%). Stage I includes tumors that have invaded less than ½ the thickness of the myometrial wall or those that have invaded

more than ½ the thickness but have not invaded the cervix or uterine serosal wall. The prognosis for endometrial carcinoma sufferers will be better. Stage II was found in 8.6%, where the tumor cells had invaded the cervical area. The prognosis is worse than stage I. Stage III was found 13.1%, where the tumor cells had invaded the serous layer of the uterine wall. The prognosis is worse than stages I and II.[5] Based on the literature, it is shown that survival is not compromised in patients with myometrial invasion of less than ½ the thickness of the myometrium and no metastases to lymph nodes or other organs.[12] Postoperatively, patients are classified as low risk, intermediate, or high based on the pathological stage of surgery. Patients with tumors confined to the endometrium or minimally invasive were defined as low risk and did not require further therapy. Patients with pelvic metastases or involvement of para-aortic, adnexal or intraperitoneal lymph nodes were defined as high risk and received postoperative radiation. Despite treatment with surgery and radiotherapy, 50% of stage III tumors will recur. Half of these patients died with distant metastases, with lung metastases occurring in approximately 36% of patients. Patients who were not included in the low or high risk categories were included in the intermediate risk category. Management for this patient is TAH-BSO. Postoperative radiation should be considered even though there are no conclusive studies showing a survival benefit for these patients.[12,13]

In this study, the most common subtypes of endometrial carcinoma were endometrioid carcinoma (60%), mixed carcinoma (13.1%), serous carcinoma (8.7%), clear cell carcinoma (8.7%), other endometrial carcinoma (mucinous carcinoma). intestinal type) (4.3%) and carcinosarcoma (4.3%). This is in line with the literature[4,8,9,13] where their research results show that the subtype of endometrial carcinoma is the most common. According to the literature, it is found that endometrioid carcinoma is the most frequently found subtype, namely 70-80%.[8] The mixed carcinoma subtype is 3-10%, where the most common type of mixed carcinoma is a mixture of endometrioid carcinoma and serous carcinoma, followed by mixed between endometrioid carcinoma and clear cell carcinoma.[15] This is parallel with literature, where research results showed that endometrioid carcinoma NOS 92.1%, followed by clear cell carcinoma NOS 5.3%, and serous carcinoma NOS 2.6%. In this study, the mixed carcinoma subtype consisted of endometrioid carcinoma with serous carcinoma. The serous carcinoma subtype is 10% of cases, clear cell carcinoma is less than 10%, carcinosarcoma is 5%, and other endometrial carcinoma is very rare at less than 1%.[8]

In this study, immunohistochemistry expression of L1CAM in the endometrioid carcinoma subtype showed L1CAM positive in 46.7% and in non-endometrioid carcinoma in 53.3%. These findings are parellel with the literature[4,16] where they observed a lower percentage of L1CAM positivity in the endometrioid carcinoma subtype.[4,16,17,18] This study may inform that L1CAM expression is associated with the presence of non-endometrioid and carries prognostic value for histologically classified endometrioid carcinoma. The mucinous subtype

does not express positively with L1CAM, which is because mucinous endometrial carcinoma produces MUC1 which can weaken the activity of L1CAM. So it does not express positively when L1CAM staining is carried out.

Based on the literature[5], endometrial carcinoma grading is divided into two categories, namely low grade and high grade. For endometrioid carcinoma subtypes FIGO grades 1 and 2 are included in the low grade category, while endometrioid carcinoma FIGO grade 3, serous carcinoma, clear cell carcinoma, undifferentiated carcinoma, mixed carcinoma, other endometrial carcinomas and carcinosarcoma NOS. included in the high grade category. L1CAM immunohistochemical expression was more positive in high grade endometrial carcinoma grading in 88.2% while negative in 22.8% and there were high grade that expressed negatively in 11.8%, namely endometrial carcinoma subtype other carcinoma NOS and endometrial carcinoma grade 3 in a 38 year old patient. This suggests that L1CAM immunohistochemical expression is associated with aggressive carcinoma subtypes and tumor progression. This is in line with the literature[4,16], where in this study in serous endometrial carcinoma the immunohistochemical expression of L1CAM often appeared. If L1CAM immunohistochemical expression is present in endometrioid carcinoma, this is associated with poorly differentiated tumors, absence of estrogen and progesterone receptors, and loss of E-cadherin expression.[19] This study shows that L1CAM immunohistochemistry is expressed in high grade endometrial carcinoma. One of the reasons why L1CAM is not expressed positively in high grade endometrial carcinoma is the patient's young age (pre-menopausal age). In young patients, endometrial carcinoma is caused by endometrial hyperplasia caused by continuous exposure to the hormone estrogen which can cause endometrioid carcinoma. In general, endometrioids that still have estrogen receptors will not express positively on L1CAM immunohistochemical examination.

L1CAM has several extracellular and intracellular functions in cancer, both in intact and cleaved forms, because it has an influence on cell migration, cell survival, angiogenesis, and tumor development.[20-24] It is known that the epithelial-to-mesenchymal transition (EMT) plays an important role in the invasion and metastasis of endometrial cancer.[19,25] Several studies have shown that L1CAM expression induces an EMT-like transition that increases metastatic potential, without changing the invasive ability. Comparable to EMT, L1CAM expression is dependent on TGF-β and SLUG.[16,19]

CONCLUSION

Endometrial carcinoma patients is mostly in the 45-55 year age group, with a history of parity were nulliparous and not using contraception. Endometrial carcinoma patients without lymphovascular invasion and nvasion of tumor cells to reach less than ½ the thickness of the endometrial were found.

Based on FIGO staging, stage I is the most common, and subtype is endometrioid carcinoma NOS more common. Distribution of L1CAM immunohistochemical expression based on the most endometrial carcinoma subtype is the endometrioid carcinoma NOS subtype which expressed positive at 46.7% and distribution of L1CAM immunohistochemical expression based on grading of endometrial carcinoma, the most high grade endometrial carcinoma.

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Conflict of Interest

None to declare.

Open access

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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