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RESEARCH PAPER

Association Between Lymphovascular Space Invasion and Preoperative CA-125 Antigen and Fibrinogen in Patients with Endometrial Carcinoma

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Abstract

Background: Lymphovascular space invasion (LVSI) is the presence of tumor cells in a vascular space lined by endothelium. It is the crucial first step to tumor metastases. It has been suggested that LVSI is the strongest predictor of lymph node metastases, relapse of disease, and poor survival in endometrial carcinoma. Lymphovascular space invasion is an important predictor of lymph node involvement in endometrial carcinoma. Studies showed that LVSI can be predicted preoperatively by some biomarkers, which may be helpful regarding lymphadenectomy per-operatively in patients with endometrial carcinoma.

Objective: The aim of this study was to predict the risk of lymphovascular space invasion (LVSI) in women with endometrial carcinoma.

Methods: This is a cross-sectional analytical study done in the gynecological Oncology Department of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, between September 2018 and August 2019. A total of 35 patients with endometrial carcinoma admitted for surgery at the Department of Gynecological Oncology, BSMMU, were included in this study

Results: Among 35 patients with endometrial carcinoma, 12 patients were positive for LVSI, and 23 patients were negative for LVSI. It was found that depth of myometrial invasion, FIGO tumor stage, histological tumor type, tumor grade, and positive pelvic lymph nodes were associated with LVSI ($p<0.05$). However, age, patient's occupation, socioeconomic status, educational level, tumor size, and cervical involvement were not associated with LVSI ($p>0.05$). Receiver operating characteristic (ROC) curves revealed that the threshold values of CA-125 and fibrinogen correlated with LVSI were 34.15 U/mL and 300 mg/dl, respectively. Statistical analysis showed that CA-125 >34 U/mL ($p=0.026$) and fibrinogen ≥300 mg/dl ($p<0.001$) were significantly associated with LVSI.

Conclusion: There is a positive association between LVSI and preoperative serum CA-125 antigen and plasma fibrinogen in endometrial carcinoma patients. So, these biomarkers may help make decisions regarding lymphadenectomy during surgery for endometrial carcinoma patients.

Keywords: Endometrial Carcinoma; Lymphovascular Space Invasion; CA-125 Antigen; Fibrinogen.

Introduction

Endometrial carcinoma (EC) is the sixth most commonly occurring cancer in women and the fifteenth most commonly occurring cancer overall. There were over 380,000 new cases in 2018.[1] It is the most common malignancy of the female genital tract in developed countries.[2] There were 408 deaths from cancer of the corpus uteri in Bangladesh in the year 2018.[1]

EC is generally diagnosed early. More than 75% of EC cases are stage I at the time of diagnosis, and the 5-year overall survival (OS) rate for women with early-stage EC exceeds 80%.[3] However, depending on pathological factors, up to 30% of reported early-stage patients had pelvic regional recurrence disease, and 5-6% had distant recurrence.[4]

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The mainstay of treatment of endometrial carcinoma (EC) is surgery. Surgery includes total abdominal hysterectomy and bilateral salpingo-oophorectomy.[5] Because of limitations of clinical staging for endometrial carcinoma, the International Federation of Gynecology and Obstetrics (FIGO) recommended surgical staging in 1988.[6] In most cases of EC, surgical staging requires pelvic and para-aortic lymphadenectomy.[5]

Para-aortic lymphadenectomy is a part of comprehensive surgical staging in EC. But this is a major surgery for a group of patients, especially those who are elderly and obese.[5] However, this type of surgery is associated with higher cost and morbidity. So, it was suggested that para-aortic lymphadenectomy could be avoided in patients without risk factors (negative pelvic nodes, <50% myometrial invasion, and negative LVSI).[7,8]

The decision of lymphadenectomy mainly depends on histologic tumor characteristics like- histologic type, architectural grade, depth of myometrial invasion, cervical stromal invasion, lymphovascular space invasion (LVSI), and adnexal involvement.[9]

On the other hand, no preoperative scan is able to detect micro-metastases in lymph nodes. So, if accurate surgical staging is to be obtained, lymphadenectomy should be performed.[5]

LVSI is a crucial first step to tumor metastases and is defined as the presence of tumor cells in a vascular space lined by endothelium.[10,11] It has been suggested that LVSI is the strongest predictor of LN metastases in EC.[12] LVSI appears to be an independent risk factor for recurrence and death from EC of all histologic types.[13] Also reported that LVSI is highly associated with lymph node (LN) metastasis and recurrence in endometrial cancer.[14] A multivariate analysis also confirmed that LVSI is an independent risk factor for LN metastases (p<0.001).[14]

The development of noninvasive preoperative tests with better performance instead of histopathological examination is needed to identify patients with LVSI as well as pelvic and para-aortic lymph node metastases. Recently, a retrospective study of Zhou et al. reported that LVSI could be predicted by a preoperative increase in serum CA-125 antigen and plasma fibrinogen levels. This may help in decision-making whether lymphadenectomy should be performed or omitted during the surgical staging of EC.[15] The association of elevated CA-125 levels with advanced and recurrent endometrial carcinoma was first reported at 1984.[16]

Serum CA-125 antigen is a circulating glycoprotein that has been widely accepted and used in the diagnosis and follow-up of patients with epithelial ovarian carcinomas.[17] Interest in its application in endometrial malignancies began to emerge in 1980s.CA- 125 appears to be a significant independent predictor of advanced stage endometrial carcinoma as well as LN metastases.[16] Preoperative serum CA-125 level is an important predictor for patients with EC, and it should be taken into consideration when surgical management is determined, especially if lymphadenectomy is undertaken in patients with clinical stage I.[18] A preoperative CA-125 assay for women with uterine cancer is a relatively inexpensive, reproducible and objective test which provide prompt valuable information regarding the risk of metastatic disease and overall likelihood of long term survival. Patients with a low likelihood of metastatic or nodal disease (favorable tissue type and CA-125 level <28U/mL) and significant co-morbidities may benefit by avoiding an extended complete staging procedure. Alternatively, a high level of CA-125 may require prompt imaging and a multidisciplinary approach to plan individualized management.[19] In another study, it was also observed that preoperative serum CA-125 level is a clinically valuable tool for individualizing patient management and for predicting prognosis in EC patients since it is correlated with clinical stage and is an independent predictor of survival. So, the investigators suggested that preoperative assessment of CA-125 should be incorporated into the initial preoperative evaluation of EC patients.[20]

Fibrinogen is an essential coagulation factor that is converted to fibrin by activated thrombin, and this fibrin is the final product of the hemostatic pathway. Dvorak noted that elevated fibrinogen levels were frequently observed in patients with malignant disease.[21] Recently, the plasma fibrinogen level was found to correlate with clinicopathological factors and prognosis in colon cancer, endometrial cancer, gastric cancer, and so on.[22-24] The investigator of a retrospective multicenter study suggested that plasma fibrinogen can be used as an independent prognostic parameter for disease-free survival (DFS) and overall survival (OS) of patients with EC.[25]

Till now, few studies are available covering preoperative factors to predict LVSI, which is most importantly

associated with LN metastasis. So, the aim of this study was to evaluate serum CA-125 and plasma fibrinogen levels preoperatively and establish their association with LVSI in patients with EC.

Materials and Methods

This cross-sectional analytical study was carried out in the Department of Gynecological Oncology, Bangabandhu Sheikh Mujib Medical University, Dhaka, from September 2018 to August 2019. All consecutive patients of endometrial carcinoma proven histologically and who were selected and admitted for surgery at the Department of Gynecological Oncology, BSMMU, Dhaka, were included in the study. Purposive sampling was applied.

Post-hysterectomy diagnosis of endometrial carcinoma, recurrent cases of endometrial carcinoma, endometrial carcinoma patients with active infection or coagulation disorder, and patients who had no willingness to participate in the study were excluded from the study.

Data were collected by interviewing the patients, from their lab investigations, and from final histopathology reports using a structured questionnaire containing all the variables of interest.

Patients were enrolled in the study based on inclusion and exclusion criteria using a structured questionnaire. Informed written consent was taken from the respondents, and the study protocol was approved by the institutional ethics committee. For safeguarding confidentiality and protecting anonymity, each of the patients was given a special ID number. The number was followed in each and every step of the procedure. After admission, an interview and thorough physical examination were done. Investigations were done and based on which patients were selected for surgery. Preoperative serum CA-125 and plasma fibrinogen levels were measured. Fibrinogen measurement: Blood samples (citrated plasma) for evaluation of plasma fibrinogen levels were taken by peripheral venous puncture before surgery. Clotting reagents (from Access-2) were used to determine plasma fibrinogen levels by the Clause method. Blood was centrifuged at 300 g for ten minutes within one hour of collection. Plasma was separated and frozen or tested within two hours of dilution (1:10 in Owrens buffer). CA-125 measurement: Was measured before surgery by means of Chemiluminescence microparticle immunoassay using an ARCHITECT i2000SR system. 3cc of blood was collected from peripheral venous puncture and kept in a non-citrated container for the measurement of serum CA-125 level. After the operation, specimens were submitted to the pathology lab for review by the pathologist for histopathological type, tumor differentiation or grade, LVSI, pelvic lymph node metastasis, depth of myometrial invasion, and cervical involvement. When there was difficulty in identifying LVSI (LVSI was indeterminant), then immunohistochemistry was performed. A tumor was considered LVSI positive when tumor emboli were noted within a space clearly lined by endothelial cells. The questionnaires were filled out, and data was collected on a data collection sheet, including variables of interest. All the data were rechecked and edited after collection. The patients were then divided into a positive LVSI and a negative LVSI group. The demographic, biochemical (biomarkers), and histopathological characteristics of the two groups were compared. The threshold values of significant factors were calculated to predict LVSI.

Descriptive statistics (Frequency observation and percentages) were used for the general description of the socio-demographic profile of patients and of the surgicopathological prognostic factors. Data were analyzed between two groups (LVSI positive and LVSI negative), including the following variables: age, occupation, level of education, socioeconomic status, depth of myometrial invasion, tumor size, FIGO stage, histologic tumor type, tumor grade, cervical involvement, pelvic lymph node metastasis, CA-125, and fibrinogen level. They were compared using χ^2 tests. The results of the measurements of CA-125 and fibrinogen were used to obtain receiver operating characteristic (ROC) curves for predicting LVSI. With the use of these curves, the threshold values of these two variables were set. The area under the curve (AUC) indicated which percentage (%) of LVSI could be correctly diagnosed with an optimum cutoff value of CA-125 or fibrinogen. Sensitivity, specificity, positive and negative predictive values, and false positive and false negative rates were also calculated. The significance level was set at $p<0.05$ and confidence interval (CI) at 95%. SPSS for Windows version 25 was used for data management and statistical analysis.

Results

Among 35 patients, LVSI was present in 12 (34.3%) and absent in 23(65.7%) patients with endometrial carcinoma. Over half (51.4%) of the tumors had <50% myometrial invasion.71.4% of the tumors were>2 cm

in size, and 17.1% had cervical involvement. Patients with e"50% of myometrial invasion had LVSI in 75.0% of cases compared to 25.0% of cases with <50% of myometrial invasion. p=0.028, which was significant. In patients with cervical involvement, LVSI occurred in about one-third (33.3%%) of the patients with endometrial carcinoma (EC), as opposed to 66.7% when there was no cervical involvement (p = 0.066). FIGO stage was found to be associated with LVSI, and stages III & IV were found to be most frequently associated with LVSI (p < 0.001). Type II endometrial carcinoma demonstrated a significant presence in patients with LVSI (p = 0.021). Grade-3 carcinoma was also significantly higher in patients with LVSI than in patients without LVSI (p = 0.035). In patients with positive pelvic lymph nodes, LVSI was positive in 75% of cases. Lymph node-positive cases were significantly associated with LVSI (p = <0.001).

Accuracy of plasma fibrinogen in predicting LVSI in patients with endometrial carcinoma: The sensitivity of the test in differentiating LVSI cases from those who did not have LVSI 10/12 x 100 = 83.3% and specificity of the test in correctly detecting those who did not have LVSI is 17/23 x 100 = 73.9%. The positive and negative predictive values of the test are 62.5% and 89.5%, respectively, while the percentages of false positives and false negatives are 37.5% and 10.5%, respectively. Among the study population, 45.71% showed a raised level (≥300 mg/dl) of plasma fibrinogen, whereas 42.86% exhibited a raised level (>34 U/mL) of serum CA-125. The sensitivity (83.3%), positive predictive value (62.5%), and negative predictive value (89.5%) of fibrinogen were higher than CA-125, which were 75.0%, 60.0%, and 85.0%, respectively, in the case of CA-125.

Table I: Association between demographics and LVSI

Demographic Characteristics Frequency %	LVSI		*p*-value
	Present (n=12 34.3%)	Absent (n=23 65.7%)	
Age (yrs.)			
≥50(n=27, 77.1%)	9(75.0%)	18(78.3%)	0.571
< 50 (n=8, 22.9%)	3(25.0%)	5(21.7%)	
Occupation			
Unemployed (n=9, 25.7%)	3(25.0%)	6(26.1%)	0.405
House-wife (n=23, 65.7%)	9(75.0%)	14(60.9%)	
Service-holder (n=3, 8.6%)	0(0.0%)	3(13.0%)	
Socio economic status			
Lower middle class (n=19, 54.3%)	9(75.0%)	10(43.48%)	0.076
Upper middle class (n=16, 45.7%)	3(25.0%)	13(56.52%)	
Level of education			
Illiterate (n=5, 14.3%)	1(8.3%)	4(17.4%)	0.571
Primary to SSC (n=21, 60%)	10(83.4%)	11(47.8%)	
HSC & higher (n=9, 25.7%)	1(8.3%)	8(34.8%)	

*Data were analyzed using Chi-square (χ^2).
*Mean age =55.6 ± 11.6 yrs.; range = (30-77) yrs.
*Socioeconomic status (WHO): Lower middle class (6827.791-26851.99 Tk/month)
Upper middle class (26858.64-83018.22 TK/month)

Table II: Association between myometrial invasion and lymphovascular space invasion (LVSI)

Myometrial Invasion (%)	LVSI		*p*-value
	Present	Absent	
≥50 (n=170)	9 (75.0%)	8(34.8%)	0.028
<50 (n=18)	3(25.0%)	15(65.2%)	

*Data were analyzed using Chi-square (χ^2)

Table III: Association of FIGO stage, histological type, and grade with LVSI

Histological findings FIGO	LVSI		*p- value*
	Present (n = 12)	Absent (n = 23)	
Stage			
Stage I & II (n=22)	2(16.7%)	20(87.0%)	<0.001
Stage III & IV (n=13)	10(83.3%)	3(13.0%)	
Histopathological Type			
Type I (n=28)	7(58.3%)	21(91.3%)	0.021
Type II (n=7)	5(41.7%)	2(8.7%)	
Grade			
Grade 1 & Grade 2 (n=25)	6(50.0%)	19(82.6%)	0.035
Grade 3 (n=10)	6(50.0%)	4(17.4%)	

*Data were analyzed using Chi-square (χ^2)

Table IV: Association between positive pelvic lymph nodes (PLNs) and Lymphovascular space invasion (LVSI)

Positive Pelvic Lymph Node (PLN)	LVSI		*p*-value
	Present	Absent	
Yes (n = 12)	9 (75.0%)	3 (13.0%)	<0.001
No (n = 23)	3 (25.0%)	20 (87.0%)	

*Data were analyzed using Chi-square (χ2).

Table V: Comparison of performance indices between serum CA-125 and plasma fibrinogen in predicting LVSI

Performance Index	CA-125	Fibrinogen
Sensitivity	75.0%	83.3%
Specificity	73.9%	73.9%
PPV	60.0%	62.5%
NPV	85.0%	89.5%
FPR	40.0%	37.5%
FNR	15.0%	10.5%

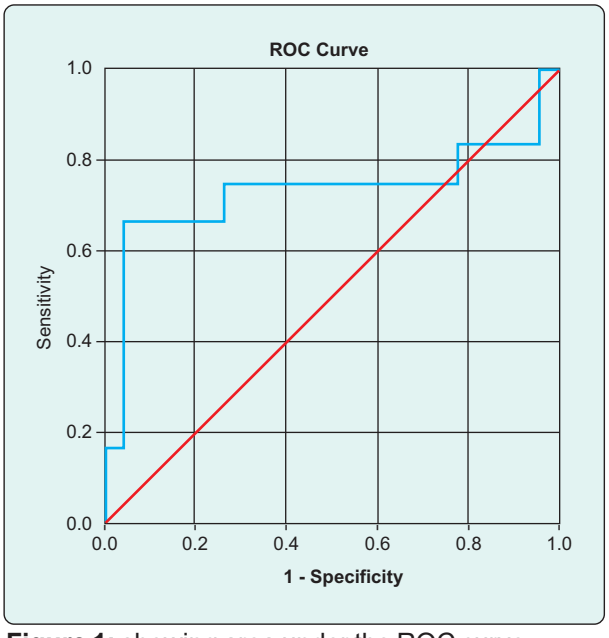

Figure 1: showing area under the ROC curve

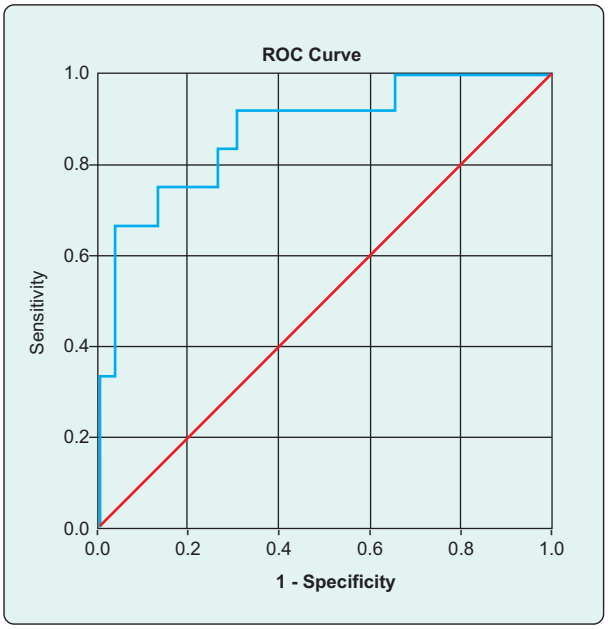

Figure 2: showing area under the ROC curve

Discussion

In this study, among 35 patients with endometrial carcinoma, LVSI was present in 12 (34.3%) and absent in 23(65.7%) patients. In the current study, 77.1% of the patients were ≥50 years of age, with a mean age of 55.6±11.6 years and a range of 30-77 years. It also found that the women who underwent surgery for endometrial carcinoma were mostly (57%) ≥50 years

of age (Range 50-70 years).[26] In this present study, no significant association was observed between the age of the patients and LVSI (p=0.571). This result is comparable with another study where the investigators also observed a positive rate of LVSI in endometrial carcinoma had no relationship with age (p=0.411).[27] But Lim found that 55.2% of the patients were >50 years of age, and this age group was significantly associated with LVSI (p=0.001).[28] This study showed that 48.6% of the patients had ≥50% of myometrial invasion by the tumor. In other studies, ≥50% of myometrial invasion was seen in 36%, 60%, and 34% of cases.[29-31] In the present study, ≥50% of myometrial invasion was associated with 75% of LVSI, whereas only 25% of LVSI was present when myometrial invasion was<50%. The myometrial invasion was significantly associated with LVSI (p=0.028). This result is consistent with another recent study, where LVSI was present in 47.6% of cases when myometrial invasion was ≥50% and myometrial invasion was significantly associated with LVSI (p<0.001).[15] In another study,>50% of myometrial invasion was significantly associated with LVSI (p<0.001). In this study, a tumor diameter>2 cm was found in 71.4% of patients with EC. However, tumor size was not significantly associated with LVSI (p=0.056). This result is comparable with another study where tumor diameter was not associated with LVSI (p=0.731).[15] On the other hand, Laufer et al.[32] found that tumor diameter was significantly associated with LVSI in patients with endometrial carcinoma (p<0.001). In the current study, it was revealed that cervical involvement was associated with only 33.3% of LVSI occurrence, and cervical involvement was not significantly associated with LVSI(p=0.066). This result is also comparable with the result of another study where no significant association was noted between cervical involvement and LVSI(p=0.767).[28] On the contrary, confirmed that cervical involvement was significantly associated with LVSI in patients with endometrial carcinoma (p<0.001).[27] In this study, the result showed a statistically significant association of the FIGO stage with LVSI (p<0.001). This result is comparable with another study where the FIGO tumor stage was significantly associated with LVSI (p<0.001). In the present study, type II endometrial carcinoma demonstrated a significant association with LVSI (p=0.021). In another study, type II tumors were mostly associated with LVSI (p=0.029).[15] On the contrary, another one study failed to show any association between histological tumor type and LVSI (p=0.229).[27]

Additionally, the current study also observed that grade 3 carcinomas were significantly associated with LVSI (p=0.035). Also found that grade-3 tumors were significantly associated with LVSI (p<0.001).[33] In this study, pelvic lymph node metastasis was found in 75% of cases with LVSI and lymph node metastasis was significantly associated with LVSI (p<0.001). This result is consistent with a good number of previous studies where the investigators (p<0.001), (p=0.003), (p<0.001), and (p=0.0001) also observed that lymph node metastasis was significantly associated with LVSI.[10,11,25,31] Found that pelvic lymph node was positive approximately nine times more in patients with LVSI. Before determining the accuracy of CA-125 in diagnosing LVSI, an optimum cutoff value for CA-125 was determined using a Receiver Operating Characteristic (ROC) curve. The best cutoff value for optimum sensitivity without much compromising the specificity obtained was 34.15U/ml. Area under the curve (AUC) is 0.732 [95%CI=0.513-0.951], p=0.026. The area under the curve (AUC) indicated that 73.2% of the LVSI could be correctly diagnosed with CA-125 level >34 U/mL in patients with endometrial carcinoma.

At a cutoff value of 34 U/mL, the sensitivity of CA-125 was 75%, and specificity was 73.9%. The positive and negative predictive values of the test were 60% and 85%, respectively, while the percentage of false positive and false negative rates were 40% and 15%, respectively. So, it could be concluded that the expression level of CA-125 could indicate the risk of LVSI occurrence in women with endometrial carcinoma. In another recent study, it was found that the cutoff value determined by the ROC curve of CA-125 was 21.2 U/mL, with a sensitivity of 76.5% and a specificity of 69.4% for predicting LVSI. In this study, 45.71% of patients showed raised plasma levels (e™300 mg/dl) of fibrinogen, whereas 42.86 % exhibited raised serum levels (>34 U/mL) of CA-125. In the current study, fibrinogen showed better sensitivity (83.3%) than CA- 125(75.0%) in determining LVSI. Its positive predictive value (62.5%) and negative predictive value (89.5%) were also higher than CA-125(PPV-60%, NPV-85%). So, fibrinogen is a better predictor than CA-125 in determining LVSI in patients with endometrial carcinoma. On the contrary, in a recent study, CA-125 showed better sensitivity (76.5%) and specificity (69.4%) than fibrinogen

(sensitivity=71.4%, specificity=63.5%) in predicting LVSI. So, they concluded that the performance of CA-125 is better than fibrinogen in predicting LVSI in endometrial carcinoma.[15]

Conclusion

The study findings suggested that the presence of LVSI could be predicted by serum CA-125 level >34 U/mL and plasma fibrinogen level ³300 mg/dl in women with endometrial carcinoma. So, the determination of these biomarkers preoperatively may provide an idea about the status of LVSI and, thereby, pelvic lymph node status. So, these biomarkers could help improve surgical staging, including lymphadenectomy in clinical stage I endometrial carcinoma.

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