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Original Article

Preoperative Fibrinogen as a Biomarker Associated With Lymphovascular Space Invasion in Endometrial Carcinoma: A Cross-Sectional Study

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Abstract

Objective: Elevated fibrinogen levels have been associated with tumor progression in multiple malignancies; however, their relationship with lymphovascular space invasion (LVSI) in endometrial carcinoma remains insufficiently characterized. This study investigated the association between preoperative fibrinogen levels and LVSI and evaluated its potential as a preoperative biomarker.

Materials and methods: This cross-sectional analytical study included 152 patients with histologically confirmed primary endometrial carcinoma treated between August 2018 and August 2023 at Bangabandhu Sheikh Mujib Medical University and selected private clinics in Dhaka, Bangladesh. Preoperative plasma fibrinogen levels were measured using the Claus method. LVSI status was determined through histopathological examination of surgical specimens. Multivariable logistic regression and receiver operating characteristic (ROC) curve analyses were performed.

Results: LVSI was identified in 30.3% of patients. Mean preoperative fibrinogen levels were significantly higher in patients with LVSI compared to those without (414.66 ± 117.94 mg/dL vs. 277.27 ± 89.34 mg/dL; $p < 0.001$). In multivariable analysis, each 100 mg/dL increase in fibrinogen was associated with a 2.34-fold increase in the odds of LVSI (adjusted odds ratio 2.34; 95% confidence interval 1.52–3.60; $p < 0.001$). ROC analysis demonstrated good discriminatory performance (AUC 0.811; 95% CI 0.729–0.882). An optimal cut-off value of approximately 380 mg/dL yielded 65% sensitivity and 89% specificity.

Conclusion: Elevated preoperative fibrinogen levels are independently associated with LVSI in endometrial carcinoma and demonstrate good discriminatory performance. Fibrinogen may serve as a clinically accessible biomarker associated with LVSI and warrants further validation in larger prospective studies.

Keywords: Endometrial Carcinoma; Fibrinogen; Lymphovascular Space Invasion; Biomarker; Risk Stratification

Introduction

Endometrial carcinoma, a prevalent gynecologic malignancy, represents a significant health concern, especially in developed nations (1). Over the past few decades, the understanding of its pathophysiology has expanded considerably, yet the quest for optimal prognostic markers and therapeutic strategies continues (2). One area garnering increasing interest is the role of preoperative

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fibrinogen levels in the surgical management of endometrial carcinoma (3, 4). Fibrinogen, a glycoprotein involved in coagulation and inflammatory responses, has been implicated in tumorigenesis and cancer progression in various malignancies, including endometrial carcinoma (5, 6).

Fibrinogen is synthesized in the liver and released into the bloodstream, where it plays a pivotal role in hemostasis. However, beyond its traditional function in blood clotting, emerging evidence suggests that fibrinogen may influence cancer biology through several mechanisms (7, 8). It can promote tumor cell proliferation, invasion, and metastasis by interacting with integrins and growth factors (9). Additionally, fibrinogen can modulate the tumor microenvironment, facilitating angiogenesis and providing a scaffold for tumor cell migration (10).

Several studies have explored the prognostic significance of preoperative fibrinogen levels in endometrial carcinoma. Elevated fibrinogen levels have been associated with advanced disease stages, higher tumor grade, and poorer prognosis (11). For instance, a study demonstrated that patients with elevated preoperative fibrinogen levels had a significantly reduced overall survival compared to those with normal levels (12, 13). These findings suggest that fibrinogen could serve as a valuable biomarker for risk stratification in endometrial carcinoma, aiding in the identification of patients who may benefit from more aggressive surgical and adjuvant therapies (14).

The potential utility of preoperative fibrinogen levels extends beyond prognosis. In the context of surgical management, fibrinogen levels may provide insights into the extent of tumor spread and the likelihood of lymphovascular space invasion (LVSI) (15). LVSI is a critical factor in determining the need for lymphadenectomy, a procedure associated with significant morbidity. Accurate assessment of LVSI risk using fibrinogen levels could help tailor surgical interventions, minimizing unnecessary procedures while ensuring adequate treatment for high-risk patients (16).

In addition to its prognostic and predictive value, fibrinogen has been incorporated into nomograms to improve clinical decision-making (17, 18). Nomograms are statistical tools that integrate multiple prognostic factors to predict clinical outcomes. Several nomograms have included fibrinogen levels along with other parameters such as age, tumor grade, and serum markers like CA-125. These models provide personalized risk assessments, guiding clinicians in selecting appropriate surgical and adjuvant treatments (19).

The mechanisms underlying the association between elevated fibrinogen levels and poor prognosis in endometrial carcinoma remain an area of active investigation (11). One hypothesis is that high fibrinogen levels reflect a systemic inflammatory state, which is known to promote cancer progression. Inflammation can enhance tumor growth and metastasis by increasing the production of cytokines, growth factors, and proteolytic enzymes (20). Furthermore, inflammation-induced hypercoagulability may facilitate tumor cell embolization and dissemination (21).

Another potential mechanism is the direct interaction between fibrinogen and tumor cells. Fibrinogen can bind to integrins on the surface of tumor cells, activating signaling pathways that promote cell survival, proliferation, and migration (22) (Figure 1). This interaction may also protect tumor cells from immune surveillance, contributing to immune evasion and disease progression (23). Moreover, fibrinogen can influence the tumor microenvironment by promoting angiogenesis and providing a structural framework for tumor cell invasion. Despite these insights, limited research has specifically explored the role of preoperative fibrinogen levels in endometrial carcinoma, particularly their relationship with LVSI, and the prognostic implications in surgical outcomes (24).

This study addresses this literature gap by investigating the association between preoperative fibrinogen levels and LVSI status in endometrial carcinoma patients. By focusing on this relationship, the study aims to assess whether fibrinogen can serve as a predictive marker for LVSI, which is a critical risk factor in endometrial carcinoma that can influence disease progression and recurrence. The objective of this research is to determine if elevated preoperative fibrinogen levels are associated with the presence of LVSI, thereby contributing to the development of non-invasive biomarkers for preoperative risk stratification in endometrial carcinoma management.

The novelty of this study lies in its potential to establish fibrinogen as a preoperative biomarker that could aid in surgical planning and risk assessment in endometrial carcinoma. Unlike traditional prognostic factors that may only be assessable postoperatively, preoperative fibrinogen levels could provide valuable insights into tumor aggressiveness before surgery, allowing clinicians to make informed decisions about surgical and adjuvant therapies.

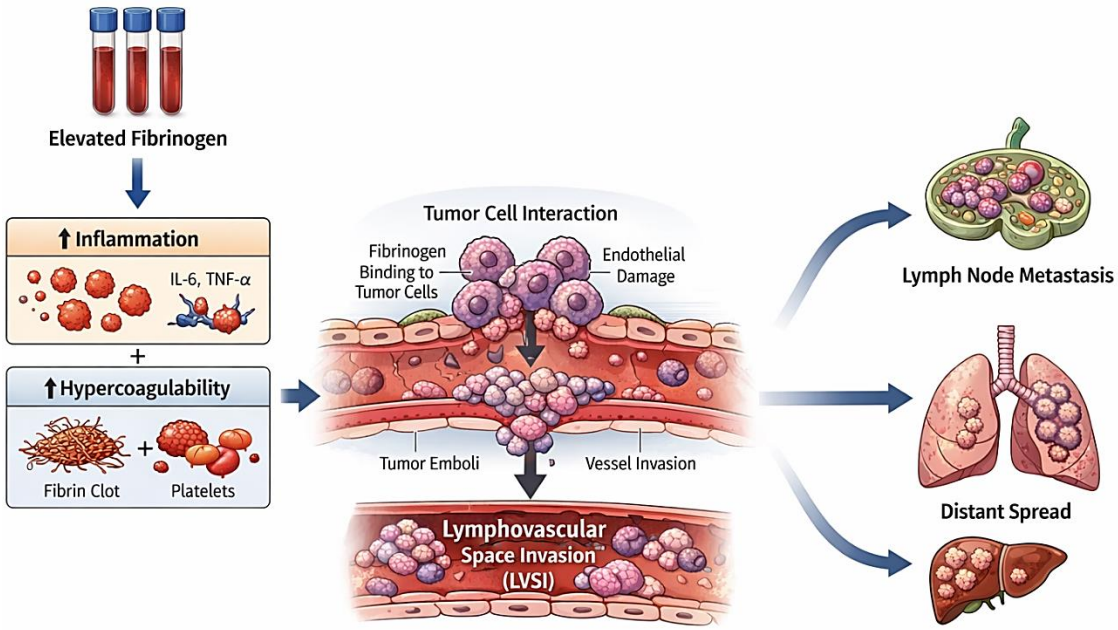

Figure 1: biological mechanism linking elevated preoperative fibrinogen levels to lymphovascular space invasion (LVSI) in endometrial carcinoma

By investigating this potential biomarker, the study contributes to advancing personalized medicine in gynecologic oncology, enhancing patient care by refining the stratification of endometrial carcinoma patients based on their risk profiles.

Materials and methods

Study Design and Setting: This cross-sectional analytical study was conducted between 1st August 2018 and 1st August 2023 at Bangabandhu Sheikh Mujib Medical University (BSMMU) and several private clinics across Dhaka city. The primary objective was to investigate the relationship between preoperative plasma fibrinogen levels and LVSI in patients diagnosed with endometrial carcinoma.

Study Population and Sampling: Patients were recruited using a convenience sampling method, which was necessary due to the relative rarity of endometrial carcinoma cases that met the inclusion criteria. Endometrial carcinoma with specific clinical profiles is not frequently encountered, and patients meeting the eligibility criteria are uncommon in routine clinical practice. To achieve a sufficient sample size and ensure meaningful statistical analysis, patients were enrolled from BSMMU and private clinics across various regions in Bangladesh. This approach enhanced the study's demographic diversity and increased the generalizability of the findings to a broader patient population within the country. Additionally, by including patients from both a large academic hospital (BSMMU) and private clinics, the study captured a spectrum of clinical profiles that reflects the overall endometrial carcinoma patient population in Bangladesh.

Inclusion and Exclusion Criteria: Inclusion criteria for this study encompassed all patients with a histologically confirmed diagnosis of primary endometrial carcinoma who were scheduled to undergo surgical treatment. Eligible patients were required to have completed preoperative blood tests, including fibrinogen level measurement, to ensure data consistency. Exclusion criteria included patients with recurrent endometrial carcinoma, those who had previously undergone hysterectomy, and those with active infections or coagulation disorders. These exclusions were necessary to eliminate potential confounding factors, as active infections or coagulation disorders could affect fibrinogen levels, thereby compromising the accuracy of our analysis of the relationship between fibrinogen and LVSI.

Data Collection and Variables: Data were collected through patient medical records and preoperative laboratory assessments. Demographic information included age, educational background, occupational status, and socioeconomic status, providing a comprehensive patient profile. Clinical variables relevant to endometrial carcinoma included tumor histology, grade, and depth of myometrial

invasion, cervical involvement, FIGO stage, and lymph node status.

The primary outcome of this study, LVSI status, was determined through histopathological analysis of surgically resected specimens. Cases were categorized as LVSI-positive if tumor cells were detected within endothelial-lined vascular or lymphatic spaces, indicating the presence of lymphovascular invasion. LVSI was coded as absent (0) or Present (1) based on histopathological findings.

The primary independent variable of interest was preoperative plasma fibrinogen level (mg/dL), measured from blood samples collected via peripheral venous puncture and analyzed within two hours of collection using the Claus method to ensure accuracy. Other independent variables included age, educational background, occupational status, and socioeconomic status, each coded to facilitate analysis. Age was categorized into two groups: <50 years and ≥50 years. Education level was recorded as No education, Primary, Secondary, and Higher. Occupational status was classified as not working or Working. Socioeconomic status, based on World Health Organization (WHO) standards, was coded into three groups according to monthly income: Lower middle class (6,827.79–26,851.99 Taka), Upper middle class (26,852–83,018.99 Taka), and Higher (above 83,018.99 Taka). Lymph node status was recorded as Negative or Positive, and fibrinogen level, a continuous variable, was analyzed to assess its association with LVSI presence.

Data Analysis: All statistical analyses were performed using Stata version 17 (StataCorp, College Station, TX, USA). Categorical variables were presented as frequencies and percentages, and continuous variables were expressed as means ± standard deviations. Associations between categorical variables and LVSI were examined using chi-square (χ^2) tests. Differences in mean preoperative fibrinogen levels between patients with and without LVSI were assessed using independent-sample t-tests. A two-sided p-value of <0.05 was considered statistically significant.

Multivariable logistic regression analysis was conducted to evaluate independent predictors of LVSI. Fibrinogen was treated as a continuous variable and scaled per 100 mg/dL increase to facilitate clinical interpretation. Variables included in the regression model were selected based on clinical relevance and findings from bivariate analysis. Adjusted odds ratios (AORs) with 95% confidence intervals (CIs) were reported. Model fit was assessed using the likelihood ratio test and pseudo-R^2 statistics. The discriminatory performance of preoperative fibrinogen for identifying LVSI was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) was calculated with 95% confidence intervals obtained through bootstrap resampling. The optimal cut-off value was determined using Youden's index. Sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were calculated at the identified threshold.

Ethical Approval: Ethical clearance for this study was obtained from the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University (BSMMU). All procedures followed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all participants before inclusion in the study, ensuring voluntary participation and confidentiality of patient information.

Results

A total of 152 patients with histologically confirmed primary endometrial carcinoma were included in the final analysis. The mean age of the study population was 54.47 ± 11.54 years, and the majority of patients (66.4%) were aged 50 years or older. Histopathological examination identified LVSI in 46 patients, corresponding to a prevalence of 30.3%, while 106 patients (69.7%) had no evidence of LVSI (Figure 2).

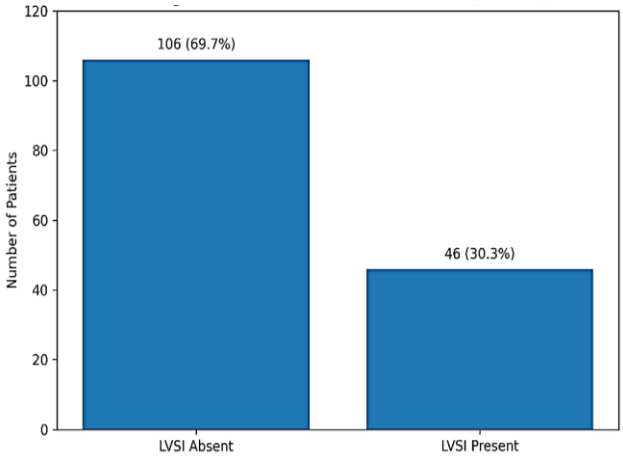

Figure 2: Prevalence of lymph vascular space invasion (LVSI) status among patients with endometrial carcinoma

Demographic and Clinical Characteristics: The demographic and clinical characteristics of the study are presented in Table 1. Over half of the participants (50.7%) belonged to the lower-middle-income category, and most patients (84.2%) were not currently working. Educational attainment varied, with 44.1% having completed secondary education. The mean preoperative plasma fibrinogen level in the overall cohort was 318.84 ± 117.07 mg/dL. Positive lymph node involvement was observed in 29.6% of patients.

When patients were stratified according to LVSI status, marked differences in preoperative fibrinogen levels were observed. Patients without LVSI had a mean fibrinogen level of 277.27 ± 89.34 mg/dL, whereas those with LVSI had a substantially higher mean level of 414.66 ± 117.94 mg/dL.

Table 1: Demographic and clinical characteristics of the study population

Characteristic	Overall (N=152)
Age Group	
<50 years	51 (33.6%)
≥50 years	101 (66.4%)
Age (years), mean ± SD	54.47 ± 11.54
Education Level	
No education	20 (13.2%)
Primary	41 (27.0%)
Secondary	67 (44.1%)
Higher	24 (15.8%)
Working Status	
Not working	128 (84.2%)
Working	24 (15.8%)
Income Category	
Lower middle class	77 (50.7%)
Upper middle class	62 (40.8%)
Higher	13 (8.6%)
Monthly income (Taka), mean ± SD	34,763 ± 24,546
Preoperative Fibrinogen (mg/dL)	318.84 ± 117.07
Lymph Node Status	
Negative	107 (70.4%)
Positive	45 (29.6%)

The absolute mean difference of approximately 137 mg/dL was highly statistically significant ($p < 0.001$). This difference reflects a clinically meaningful elevation rather than a marginal statistical variation. The distribution of fibrinogen levels according to LVSI status is illustrated in Figure 3. The box-and-whisker plot demonstrates a clear upward shift in fibrinogen values among LVSI-positive patients, with higher median levels and broader upper quartiles compared to the LVSI-negative group. Although some overlap is present, the overall distribution pattern suggests a strong biological gradient between fibrinogen concentration and vascular invasion.

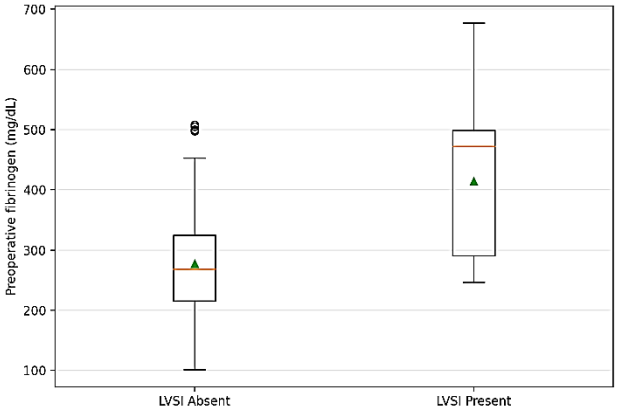

Figure 3: Box-and-whisker plot of preoperative fibrinogen levels according to of lymph vascular space invasion (LVSI) status

To determine whether fibrinogen independently predicted LVSI, multivariable logistic regression analysis was performed showing in Table 2. Fibrinogen was modeled per 100 mg/dL increase to enhance clinical interpretability and avoid misinterpretation associated with small per-unit effects. After adjustment for age group, working status, income category, and lymph node status, fibrinogen remained independently associated with LVSI. Each 100 mg/dL increase in preoperative fibrinogen was associated with a 2.34-fold increase in the odds of LVSI (adjusted odds ratio 2.34; 95% confidence interval 1.52–3.60; $p < 0.001$). Positive lymph node status was also independently associated with LVSI (adjusted odds ratio 5.63; 95% confidence interval 2.19–14.47; $p < 0.001$). Socioeconomic variables did not retain statistical significance in the adjusted model. The overall regression model demonstrated good explanatory performance, with a statistically significant likelihood ratio test ($p < 0.001$) and a pseudo-R^2 of approximately 0.33, indicating moderate model fit.

The discriminatory ability of preoperative fibrinogen for predicting LVSI was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) was 0.811 (95% confidence interval 0.729–0.882), indicating good overall discrimination.

Table 2: Multivariable Logistic Regression Analysis for Independent Predictors of lymph vascular space invasion (LVSI)

Variable	Adjusted Odds Ratio	95% Confidence Interval	P-Value
Fibrinogen (Per 100 Mg/Dl Increase)	2.34	1.52 – 3.60	<0.001
Positive Lymph Node Status	5.63	2.19 – 14.47	<0.001
Working (vs Not Working)	0.41	0.09 – 1.89	0.250
Upper Middle Income (vs Lower)	0.62	0.18 – 2.10	0.440
Higher Income (vs Lower)	0.21	0.02 – 2.01	0.170

As shown in Figure 4, the ROC curve lies well above the line of no discrimination across thresholds, demonstrating consistent separation between LVSI-positive and LVSI-negative patients.

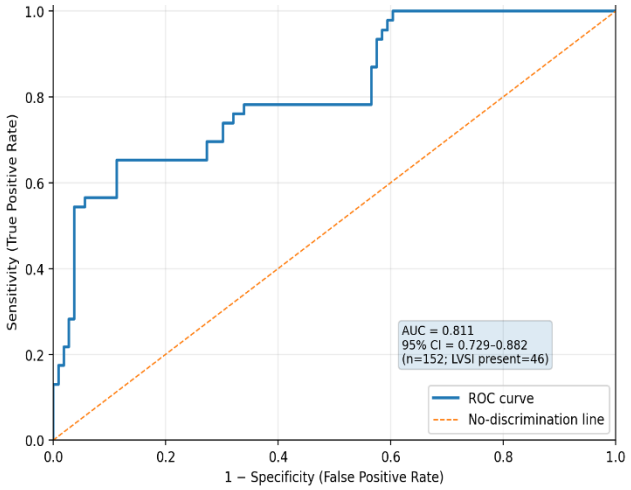

Figure 4: Receiver operating characteristic (ROC) curve of preoperative fibrinogen for predicting lymph vascular space invasion (LVSI)

The optimal cut-off value determined using Youden's index was approximately 380 mg/dL. At this threshold, fibrinogen demonstrated a sensitivity of 65% and a specificity of 89%. The corresponding positive likelihood ratio was 5.9, while the negative likelihood ratio was 0.39. The relatively high specificity and positive likelihood ratio suggest that elevated fibrinogen levels are more effective for identifying patients at increased risk of LVSI than for excluding it.

Discussion

This study demonstrates a strong and independent association between elevated preoperative fibrinogen levels and the presence of LVSI in patients with endometrial carcinoma. LVSI was identified in 30.3% of patients in this cohort and was significantly associated with higher circulating fibrinogen concentrations. Patients with LVSI exhibited a mean fibrinogen level approximately 137 mg/dL higher than those without LVSI, representing a clinically meaningful difference rather than a marginal statistical variation. These findings suggest that systemic inflammatory and coagulative activity, reflected by fibrinogen elevation, may be linked to tumor aggressiveness in endometrial carcinoma (25).

The discriminatory performance of fibrinogen further strengthens its potential clinical relevance. ROC curve analysis demonstrated good discrimination (AUC=0.811; 95% CI 0.729–0.882), indicating that fibrinogen meaningfully differentiates between LVSI-positive and LVSI-negative patients. Using Youden's index, an optimal cut-off of approximately 380 mg/dL yielded a sensitivity of 65% and a specificity of 89%. The relatively high specificity and positive likelihood ratio (5.9) suggest that markedly elevated fibrinogen levels are particularly informative for identifying patients at increased risk of LVSI. When fibrinogen was incorporated into a multivariable prediction framework alongside lymph node status, model discrimination improved modestly (AUC ≈ 0.84), suggesting additive predictive value.

The independent predictive value of fibrinogen was confirmed in multivariable logistic regression analysis. When modeled per 100 mg/dL increase to enhance interpretability, each increment was associated with a 2.34-fold increase in the odds of LVSI, even after adjustment for demographic factors and lymph node status. This effect size indicates a substantial association and supports fibrinogen as more than a statistically significant variable; rather, it reflects a biologically meaningful gradient of risk. Positive lymph node status also remained independently associated with LVSI, consistent with established evidence that vascular invasion is closely linked to nodal dissemination and more aggressive disease behavior (26).

The biological plausibility of these findings is supported by previous oncologic research.

Fibrinogen, beyond its classical role in coagulation, functions as an acute-phase reactant and plays a role in tumor progression through multiple mechanisms. Elevated fibrinogen has been associated with tumor cell adhesion, proliferation, angiogenesis, and immune modulation in several malignancies, including gastric and ovarian cancers (27). Fibrin matrices may facilitate tumor cell anchoring within vascular structures, thereby promoting invasion and metastatic spread. The present study extends these mechanistic insights to endometrial carcinoma and supports the hypothesis that systemic inflammatory and coagulative pathways contribute to lymphovascular invasion (28).

Importantly, this study offers practical clinical implications. LVSI is a well-recognized marker of aggressive disease and influences decisions regarding lymphadenectomy, adjuvant therapy, and postoperative surveillance. However, LVSI is typically determined only after definitive surgical pathology. The identification of a readily available, inexpensive preoperative biomarker associated with LVSI may therefore enhance risk stratification before surgery. Preoperative fibrinogen measurement could assist clinicians in identifying patients who may benefit from more comprehensive surgical staging or closer postoperative monitoring. While fibrinogen alone does not provide definitive diagnostic certainty, its relatively strong rule-in capacity at higher thresholds suggests potential value as part of a broader preoperative assessment model. Although socioeconomic variables showed associations with LVSI in unadjusted analyses, these relationships did not persist after multivariable adjustment. This finding suggests that the association between fibrinogen and LVSI is unlikely to be primarily explained by socioeconomic disparities and instead reflects tumor-related biological processes.

This study has several limitations. First, the cross-sectional design limits our ability to establish causation between elevated fibrinogen levels and LVSI in endometrial carcinoma. Additionally, the use of convenient sampling rather than random selection may introduce selection bias, affecting the generalizability of our findings. The data were collected from a single academic center and a few private clinics, which may not fully represent the broader population of endometrial carcinoma patients. Although we controlled for key confounders, other unmeasured factors, such as comorbidities and lifestyle influences, could impact both fibrinogen levels and LVSI status, potentially affecting the results. The sample size, though sufficient for primary analysis, limited the ability to conduct more detailed subgroup analyses. Furthermore, fibrinogen levels can be influenced by conditions such as inflammation and infection, which were not entirely accounted for in this study. Lastly, as the study only measured preoperative fibrinogen levels, it does not provide information on changes in fibrinogen over time or its association with long-term outcomes. Future studies with larger, more diverse populations and a longitudinal approach are needed to validate the role of fibrinogen as a prognostic marker in endometrial carcinoma.

Conclusion

This study demonstrates a significant and independent association between elevated preoperative fibrinogen levels and LVSI in patients with endometrial carcinoma. Patients with LVSI exhibited substantially higher fibrinogen levels, and each 100 mg/dL increase in fibrinogen was associated with more than a twofold increase in the odds of LVSI. Receiver operating characteristic analysis further indicated good discriminatory performance (AUC=0.811), with a threshold of approximately 380 mg/dL demonstrating high specificity. These findings suggest that preoperative fibrinogen may serve as a clinically accessible biomarker associated with LVSI. Although fibrinogen alone does not provide definitive diagnostic certainty, its discriminatory capacity and biological plausibility support its potential role in preoperative risk assessment frameworks. Integration of fibrinogen into broader predictive models may enhance the identification of patients at increased risk of LVSI. However, external validation in larger and multi-center study is required before routine clinical adoption. Further research should explore the incorporation of fibrinogen into comprehensive risk stratification algorithms aimed at improving individualized management of endometrial carcinoma.

Conflict of Interests

Authors declare no conflict of interests.

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