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Diabetes Mellitus and Elevated Preoperative Neutrophil to Lymphocyte Ratio in Surgically Treated Endometrial Cancer: An Exploratory Analysis from a Tertiary Cancer Center in Bangladesh

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Abstract

Introduction: Diabetes mellitus is an established metabolic risk factor for endometrial cancer and may influence tumor behavior through hyperglycemia, insulin resistance, oxidative stress, and chronic low-grade inflammation. The neutrophil-to-lymphocyte ratio (NLR), derived from routine complete blood count, is a simple marker of systemic inflammatory response and has been studied as a prognostic biomarker in endometrial cancer. The study aimed to assess the relationship between diabetes mellitus and elevated preoperative NLR in surgically treated endometrial cancer patients at a tertiary cancer center in Bangladesh.

Methods & Materials: This exploratory cross-sectional study included 31 histologically confirmed endometrial cancer patients who underwent primary surgery at the Department of Gynecological Oncology, National Institute of Cancer Research and Hospital, Dhaka, Bangladesh, between January and December 2020. Diabetes mellitus was recorded as a known clinical comorbidity. Preoperative NLR was calculated from the complete blood count and categorized as low (< 2.4) or high (2.4–20.0).

Results: Among 31 patients, 14, 45.2%, had elevated preoperative NLR. Diabetes mellitus was present in 16 patients, 51.6%. High NLR was more frequent among patients with diabetes mellitus than among non-diabetic patients, 62.5% versus 26.7%, respectively, although this difference did not reach conventional statistical significance on Fisher's exact test, $P = 0.073$. In exploratory multivariable analysis, diabetes mellitus was the only variable significantly associated with high NLR, with a reported OR of 7.40, 95% CI 3.79 to 71.76, $P = 0.001$.

Conclusion: Diabetes mellitus was associated with a higher frequency of elevated preoperative NLR among surgically treated endometrial cancer patients, and remained significant in exploratory multivariable analysis.

Keywords: Endometrial cancer, diabetes mellitus, neutrophil-to-lymphocyte ratio, systemic inflammation

Introduction

Endometrial cancer is one of the major gynecological malignancies worldwide, with rising clinical importance in both high-income and low- and middle-income settings. Its burden is closely linked with metabolic risk factors, particularly obesity, insulin resistance, and diabetes mellitus. Diabetes mellitus has been repeatedly associated with increased endometrial cancer risk, and this association appears to persist even after adjustment for body mass index in several analyses. Saed et al., in an updated systematic review and meta-analysis, reported that diabetes was associated with a significantly increased risk of endometrial cancer, while a more recent meta-analysis by Drab et al. similarly found higher endometrial cancer risk among women with diabetes.[1,2] In Bangladesh, Begum et al. also reported a significant association between diabetes mellitus and endometrial carcinoma, supporting the relevance of this relationship in the local clinical context.[3] Beyond cancer risk, diabetes mellitus may also influence endometrial cancer behavior and outcomes. In a systematic review and meta-analysis, McVicker et al. found that diabetes was associated with poorer overall survival, cancer-specific survival, and recurrence- or progression-free survival among patients with endometrial cancer.[4] Njoku et al., using a prospective database of women with endometrial cancer, also observed that type 2 diabetes mellitus was independently associated with increased overall mortality, cancer-specific mortality, and recurrence after adjustment for clinicopathological factors.[5] These findings suggest that diabetes should not be considered only as a background comorbidity in endometrial cancer; rather, it may represent a clinically meaningful metabolic and inflammatory condition that interacts with tumor biology. The biological basis of this relationship is complex and likely involves hyperglycemia, hyperinsulinemia, insulin-like growth factor signaling, altered cellular metabolism, oxidative stress, and chronic low-grade inflammation. Byrne et al. described hyperglycemia as a potentially important contributor to endometrial cancer pathogenesis, particularly through metabolic and growth-promoting mechanisms.[6] Wang et al. similarly reviewed several etiological links between diabetes mellitus and endometrial carcinoma, including insulin resistance and inflammatory pathways.[7] This inflammatory component is important because cancer progression is influenced not only by tumor-intrinsic factors but also by the systemic immune and inflammatory status of the host. The neutrophil-to-lymphocyte ratio (NLR), derived from routine complete blood count, has emerged as a simple marker of systemic inflammatory response. In diabetes mellitus, NLR has been associated with glycemic control and insulin resistance. Sefil et al. reported a relationship between increased NLR and elevated HbA1c in patients with type 2 diabetes mellitus, while Lou et al. found significantly higher NLR values in newly diagnosed diabetic patients and observed an association between NLR and insulin resistance.[8,9] More recent pooled and population-based analyses have also supported the association of NLR with glycemic dysregulation and type 2 diabetes mellitus.[10,11] These findings support the concept that raised glycemic status may be accompanied by an elevated systemic inflammatory profile. In endometrial cancer, preoperative NLR has been studied as a prognostic and clinicopathological biomarker. Cummings et al. reported that preoperative NLR and platelet-to-lymphocyte ratio were independent prognostic indicators in surgically treated endometrial cancer.[12] Cong et al. found that combined preoperative inflammatory ratios, including NLR, were associated with survival outcomes in a large cohort of surgically treated patients.[13] Meta-analyses by Ni et al. and Leng et al. further supported the prognostic value of pretreatment NLR in endometrial cancer.[14,15] Other studies have linked NLR with high-risk pathological features, including lymph node metastasis, cervical stromal involvement, deep myometrial invasion, and adverse histology.[16–18] However, limited data are available from Bangladesh regarding whether diabetes mellitus or raised preoperative glycemic status is associated

with elevated NLR among surgically treated endometrial cancer patients. The present exploratory analysis was therefore conducted to assess the relationship between diabetes mellitus or raised glycemic status and elevated preoperative NLR in endometrial cancer patients treated surgically at a tertiary cancer center in Bangladesh.

Methods & Materials

This exploratory cross-sectional study included 31 histologically confirmed endometrial cancer patients who underwent primary surgery at the Department of Gynecological Oncology, National Institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh, between January and December 2020. Eligible patients were aged 30–70 years and planned for surgery. Patients with acute inflammatory disease, autoimmune disorders, recurrent or multiple malignancies, or prior neoadjuvant chemotherapy were excluded. Of 37 initially assessed patients, 31 were confirmed histopathologically and included through purposive sampling. Written informed consent was obtained, and ethical approval was granted by the NICRH ethics committee. Data were collected using a structured questionnaire and medical records, including demographic, clinical, hematological, and histopathological information. The primary exposure variable for the present analysis was known diabetes mellitus, recorded as present or absent in the clinical dataset. Body mass index, hemoglobin level, tumor stage, grade, histological subtype, tumor size, lymph node metastasis, deep myometrial invasion, and lymphovascular space invasion were also recorded. Complete blood count was done within 7 days before surgery. Absolute neutrophil and lymphocyte counts were obtained using an automated hematology analyzer, and the absolute neutrophil count was divided by the absolute lymphocyte count to calculate the neutrophil-to-lymphocyte ratio (NLR). The cutoff used in the thesis to classify patients into low (< 2.4) or high NLR (> 2.4). Histopathological examination of surgical specimens and final clinico-pathological data were obtained from pathology reports. The data were analyzed using SPSS version 22.0. Continuous variables were represented as mean ± standard deviation and categorical variables as counts and percentages. The correlation of diabetes mellitus with high NLR was evaluated using Fisher's exact test due to limited sample size. Exploratory multiple logistic regression was performed to discover the factors related with high NLR. Statistical significance was considered at $P < 0.05$. Multivariable findings were considered exploratory due to the limited sample size.

Results

A total of 31 surgically treated patients with histologically confirmed endometrial cancer were included in this exploratory analysis. Preoperative NLR was categorized using a cut-off value of 2.4, with 17 patients, 54.8%, classified in the low NLR group and 14 patients, 45.2%, classified in the high NLR group.

Among the 31 patients, 16 patients, 51.6%, had recorded diabetes mellitus, while 15 patients, 48.4%, had RBS <7.8 mmol/L. Most patients had stage I disease, 18 patients, 58.1%, followed by stage III disease in 11 patients, 35.5%. High-risk pathological features were also observed, including grade 3 tumor in 11 patients, 35.5%, lymph node metastasis in 12 patients, 38.7%, deep myometrial invasion in 16 patients, 51.6%, and lymphovascular space invasion in 9 patients, 29.0% [Table 1].

Elevated preoperative NLR was more frequent among patients with diabetes mellitus. Among 16 diabetic patients, 10 patients, 62.5%, had high NLR. In comparison, among 15 non-diabetic patients, 4 patients, 26.7%, had high NLR. This difference did not reach conventional statistical significance on Fisher's exact test, $P = 0.073$ [Table 2].

Table 1: Baseline clinicopathological profile of the study participants, $n = 31$

Variables	*n* (%)
Preoperative NLR group	
NLR <2.4	17 (54.8)
NLR >2.4	14 (45.2)
Diabetes Mellitus	
Present	16 (51.6)
Absent	15 (48.4)
BMI	
<18.5 kg/m²	3 (9.7)
18.5 to 24.9 kg/m²	17 (54.8)
>25 kg/m²	11 (35.5)
Hemoglobin	
10 to 12 g/dL	8 (25.8)
8 to 10 g/dL	22 (71.0)
<8 g/dL	1 (3.2)
FIGO stage	
Stage I	18 (58.1)
Stage II	1 (3.2)
Stage III	11 (35.5)
Stage IV	1 (3.2)
Tumor size	
<2 cm	10 (32.3)
>2 cm	21 (67.7)
Tumor grade	
Grade 1	6 (19.4)
Grade 2	14 (45.2)
Grade 3	11 (35.5)
Histological subtype	
Endometrioid adenocarcinoma	20 (64.5)
Papillary serous adenocarcinoma	11 (35.5)
Lymph node metastasis	
Present	12 (38.7)
Absent	19 (61.3)
Deep myometrial invasion	
Present	16 (51.6)
Absent	15 (48.4)
Lymphovascular space invasion	
Present	9 (29.0)
Absent	22 (71.0)

Table 2: Association between raised glycemic status/DM and elevated preoperative NLR

Diabetes Mellitus	NLR <2.4, *n* (%)	NLR >2.4, *n* (%)	*P*-value
Diabetes Present	6 (37.5)	10 (62.5)	**0.073**
Diabetes Absent	11 (73.3)	4 (26.7)	
Total	17 (54.8)	14 (45.2)	

Percentages in the NLR columns are row percentages. The *P* value was calculated using Fisher's exact test. NLR, neutrophil-to-lymphocyte ratio.

In the exploratory multivariable model, diabetes mellitus was the only variable that remained significantly associated with high preoperative NLR. Patients with diabetes mellitus had a reported 7.40-fold higher odds of elevated preoperative NLR, 95% CI 3.79 to 71.76, $P = .001$. Other variables, including BMI, hemoglobin level, hypertension, tumor stage, tumor size, tumor grade, lymph node metastasis, deep myometrial invasion, and lymphovascular space invasion, were not statistically significant in the reported model [Table 3].

Discussion

This exploratory cross-sectional study observed a higher frequency of elevated preoperative neutrophil-to-lymphocyte ratio (NLR) among diabetic patients with surgically treated endometrial cancer. In this cohort of 31 histologically confirmed cases, 14 patients, 45.2%, had high preoperative NLR, defined as NLR > 2.4. Diabetes mellitus was present in 16 patients, 51.6%, and high NLR was more frequent in diabetic than non-diabetic patients, 62.5% versus 26.7%, respectively. Although this difference did not reach conventional statistical significance on Fisher's exact test, $P = 0.073$, the thesis-reported exploratory multivariable analysis identified diabetes mellitus as the only variable significantly associated with high NLR, with a reported OR of 7.40, 95% CI 3.79 to 71.76, $P = .001$. These findings suggest a possible relationship between diabetes mellitus and elevated systemic

Table 3: Exploratory multivariable analysis of factors associated with high preoperative NLR

Variable	Regression coefficient	Standard error	*P*-value	Reported OR	95% CI
DM	1.40	0.75	**.001**	7.40	3.79 to 71.76
BMI	0.222	0.126	.176	1.29	Not significant
Hemoglobin	0.207	0.149	.178	1.12	Not significant
Hypertension	0.014	0.224	.943	1.10	Not significant
Stage of tumor	0.346	0.254	.515	0.69	Not significant
Tumor size	0.162	0.194	.386	0.52	Not significant
Tumor grade	0.025	0.126	.892	0.20	Not significant
Lymph node metastasis	0.058	0.549	.915	0.48	Not significant
Deep myometrial invasion	–0.327	0.172	.076	0.30	Not significant
Lymphovascular space invasion	–0.163	0.190	.361	0.29	Not significant

inflammatory response in endometrial cancer, although the small sample size requires cautious interpretation. The present finding is consistent with the limited direct literature examining diabetes, inflammatory cell ratios, and endometrial cancer together. Bing, Tsui and Ding, in a retrospective cohort of surgically treated endometrial cancer patients, found that NLR was significantly associated with diabetes mellitus and FIGO stage.[19] Their study also reported that diabetes mellitus and high monocyte-to-lymphocyte ratio were associated with cancer mortality. Although their strongest prognostic marker was MLR rather than NLR, their observation supports the present study's central finding that diabetes mellitus may be linked with altered systemic inflammatory indices in endometrial cancer patients. The association between diabetes and elevated NLR is biologically plausible. Diabetes mellitus is characterized by chronic low-grade inflammation, oxidative stress, endothelial dysfunction, insulin resistance, and altered innate and adaptive immune responses. Sefil et al. reported that patients with poorly controlled type 2 diabetes mellitus had higher NLR and that NLR was positively correlated with HbA1c.[8] Lou et al. also found higher NLR among newly diagnosed diabetic patients, with a significant association between NLR and insulin resistance.[9] Shiny et al, in an Asian Indian population, showed a graded increase in NLR with worsening glucose intolerance, which is particularly relevant to South Asian populations where diabetes and insulin resistance are common at comparatively lower BMI levels.[20] More recent pooled and population-based findings have also supported an association between NLR and glycemic control or type 2 diabetes mellitus.[10,11] These findings collectively support the interpretation that the higher NLR observed in patients with raised glycemic status may reflect systemic inflammatory activation related to dysglycemia. The endometrial cancer literature also supports the relevance of NLR as a preoperative biomarker. Cummings et al. (2015) reported that preoperative NLR and platelet-to-lymphocyte ratio predicted survival in surgically treated endometrial cancer. Cong et al., in a large surgical cohort, found that preoperative NLR, PLR, and MLR were associated with survival outcomes.[13] Meta-analyses by Ni et al. and Leng, Wu and Zhang further showed that elevated pretreatment NLR was associated with poorer prognosis in endometrial cancer.[14,15] The present study did not include survival or recurrence follow-up, so it cannot evaluate prognostic impact. However, the finding that high NLR was common in the cohort and associated with glycemic abnormality adds a possible metabolic-inflammatory dimension to the use of NLR in preoperative assessment. Several studies have also linked NLR with high-risk pathological features in endometrial

cancer. Aoyama et al. found that pretreatment NLR was associated with lymph node metastasis, while Dong, Cheng and Wang reported that elevated NLR was associated with advanced stage, higher histological grade, and lymph node metastasis.[16,21] Muangto et al. observed that NLR was associated with deep myometrial invasion, although NLR and PLR were not useful as broad predictors of malignant potential.[17] These studies indicate that NLR may reflect aggressive tumor biology in some settings. In the present analysis, several high-risk pathological features were present, including grade 3 tumor, lymph node metastasis, deep myometrial invasion, and LVSI; however, diabetes mellitus was the only variable that remained significant in the exploratory multivariable model. This finding should not be taken to mean that pathological factors are unimportant, but rather that the current model was limited by the very small sample size and the number of variables entered. The findings should therefore be interpreted as hypothesis-generating. NLR is a non-specific marker and may be influenced by infection, obesity, inflammatory disease, medications, renal disease, hematologic disorders, and other comorbidities. Although patients with acute inflammatory disease and autoimmune disorders were excluded, residual confounding cannot be excluded. Another important issue is exposure definition. The original dataset recorded diabetes mellitus or raised glycemic status using RBS > 7.8 mmol/L versus RBS < 7.8 mmol/L, and this may not be equivalent to confirmed diabetes mellitus based on fasting glucose, HbA1c, oral glucose tolerance testing, or medication history. Despite these limitations, the study identifies a clinically relevant signal: among surgically treated endometrial cancer patients in this tertiary Bangladeshi cancer center, raised glycemic status or diabetes mellitus was associated with elevated preoperative NLR. Larger prospective studies with standardized diabetes classification, HbA1c assessment, inflammatory marker panels, and survival follow-up are needed to clarify whether glycemic dysregulation contributes independently to systemic inflammation and clinical outcomes in endometrial cancer.

Limitations of the Study

This study was limited by its small sample size and single-center design, which may restrict the generalizability of the findings. Diabetes mellitus or raised glycemic status was categorized from the available dataset using random blood sugar, rather than standardized HbA1c, fasting glucose, oral glucose tolerance testing, or detailed antidiabetic treatment history. Survival and recurrence outcomes were not assessed, so the prognostic impact of diabetes-associated NLR elevation could not be determined.

Conclusion

Diabetes mellitus was associated with a higher frequency of elevated preoperative neutrophil-to-lymphocyte ratio among surgically treated endometrial cancer patients in this tertiary cancer center cohort. Although the unadjusted Fisher's exact comparison did not reach conventional statistical significance, exploratory multivariable analysis identified diabetes mellitus as the only factor significantly associated with high NLR. These findings suggest a possible metabolic-inflammatory relationship between diabetes mellitus and systemic inflammatory response in endometrial cancer, but they should be interpreted as hypothesis-generating and require confirmation through larger prospective studies using standardized diabetes assessment, broader inflammatory marker evaluation, and clinical outcome follow-up.

Ethical Approval

The study was approved by the Institutional Ethics Committee.

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