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Research Article

Impact of Preoperative Systemic Inflammation Score on Key Prognostic Risk Factors in Early Cervical Cancer

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Abstract

Background: Cervical cancer is the fourth most common malignancy in women across the world. Treatment decisions for early cervical cancer are guided by prognostic risk factors including tumor size, LVSI, depth of stromal invasion and nodal involvement. Systemic inflammation score (SIS) is a novel prognostic biomarker which is potential for different types of malignancies. But its role in early stage cervical cancer is unexplored. This study evaluate the impact of SIS on prognostic risk factors for early stage cervical cancer. *Methods:* This cross sectional study was conducted at Department of Gynecological Oncology, BSMMU, Dhaka, Bangladesh from July 2022 to June 2023. A total of 90 women with IA-IIA clinical stage cervical cancer are included in this study. SIS was categorized into 3 categories (0, 1, 2) and calculated. Chi-square tests and ANOVA were used to analyze associations between SIS and clinicopathologic parameters. *Results:* SIS was greatly correlated with adverse prognostic features. In 73.7% of patients tumors were >2 cm in patients with SIS 2 compared to 54.5% with SIS 1 and 18.4% with SIS 0 ($p<0.001$). SIS 2 was present in 92.3% of patients with positive LVSI and in 7.7% ($p=0.006$) of patients with SIS 0. Higher SIS levels were also associated with increased deepth of stromal invasion and pelvic lymph node metastases. *Conclusion:* SIS is associated with adverse prognostic factors in early stage cervical cancer. These results may help improve personalized treatment and outcomes through incorporation of SIS into risk assessment models.

Keywords

SIS, Prognostic Factors, Cervical Cancer, Tumor Size, LVSI

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1. Introduction

Cervical cancer is a common health problem globally, ranking as the fourth most frequent malignancy in women and constituting about 660,000 new cases and 350,000 deaths in 2022. [1] Despite efforts to increase vaccination and screening programmes access to preventive and curative care remains disproportionately high in low- and middle income countries (LMICs) where it is particularly high. Typical treatment for early stage cervical cancer detected generally through effective screening includes surgery or chemoradiotherapy, with relatively favorable survival rates. Although, within this group, there are some prognostic risk factors such as LVSI, tumor size, stromal invasion, parametrial involvement and lymph node metastasis that obviously have a great impact on outcome, so evaluation before surgery is necessary for approaching tailored treatment. [2] A clinical priority remains in identification of patients with higher likelihood of adverse outcomes allowing for individualized treatment and surveillance strategies. Though FIGO stage is the most important clinical prognostic indicator for cervical cancer patients, but same FIGO stage have different treatment outcomes. Therefore, find out other indicators to assist in predicting the prognosis of cervical cancer is necessary. [3] "Although the FIGO stage is the most important clinical prognostic indicator for cervical cancer patients, patients with the same FIGO stage may have different treatment outcomes. Therefore, identifying additional indicators to assist in predicting the prognosis of cervical cancer is necessary."

In recent years, systemic inflammation has been identified as a major determinant of cancer progression and is involved in numerous aspects of the cancer process—including tumor growth, angiogenesis, immune suppression and metastatic dissemination. [4] Several inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), and C reactive protein (CRP) have been studied as the potential prognostic factors in cancers of different origins including cervical. [3, 5] The systemic inflammation score (SIS; a composite biomarker that incorporates the levels of serum albumin and LMR) has recently demonstrated the potential for being an independent predictor of outcomes in a variety of malignancies including esophageal and gastric cancers. [6, 7] Despite the increased interest in its application the study of SIS in early cervical cancer remains uncertain with respect to the use of traditional clinicopathologic risk factors that are used to dictate the choice of therapeutic options.

Pathogenesis of cervical cancer is intimately associated with inflammatory processes, which are initiated by persistent infection with oncogenic human papillomavirus (HPV) strains. HPV induced chronic inflammation leads to genetic instability, immune evasion and neoplastic progression. [8] Elevated inflammatory biomarkers in systemic inflammatory responses have been assumed to create a pro tumorigenic environment allowing for growth of the disease. Earlier studies have shown prognostic scores based upon inflammation, such as SIS, may provide biological aggressiveness information of tumors and are cost effective, noninvasive predictors of outcome. [9] Despite the analysis largely of advanced disease, Zheng et al. noted that there was prognostic value in the SIS in cervical cancer patients. [10] This highlights the need to evaluate its merits in the context of early stage cases, typically characterized by an often tradeoff between potential benefits and the risks of overtreatment regarding adjuvant therapies.

Standard risk stratification in early cervical cancer is mainly driven by clinicopathologic parameters including tumor size, depth of stromal invasion, LVSI and nodal status. [11] They affect the recurrence rate and indicate the use of adjuvant therapies, radiation and chemotherapy respectively. [12] On the other hand, systemic inflammatory markers have the potential to enhance the precision with which prognosticating hinges on these traditional parameters. For example, patients with elevated SIS may have more aggressive disease phenotypes, even in the absence of detectable clinicopathologic risk factors, and warrant closer monitoring or further intervention. In contrast, patients with low SIS and favorable clinicopathologic profiles could avoid unnecessary adjuvant treatments and thereby lessen treatment related morbidity and improved quality of life. [13]

Systemic inflammation in early cervical cancer is a relatively under investigated area that is important for prognosis. Although inflammation based indices have been extensively applied to other solid malignancies such esophageal, renal, lung cancer, their application in early cervical cancer has not been previously demonstrated given its potential to predict outcome, and treatment response for advanced disease. [14, 15] In this gap in the literature, studies are needed to see whether including SIS into existing risk assessment strategies could make clinical decision-making and patient outcomes better.

The impact of preoperative systemic inflammation score was evaluated in prognostic risk factors in early cervical cancer. This research will provide evidence of SIS as a valuable means of risk stratification by investigating the relationship between SIS and clinicopathologic parameters including tumor size, LVSI, parametrial involvement and nodal metastasis. It also discusses possible ways SIS could extend prognostic models to provide a more patient specific, patient centric approach to treatment planning and post treatment management.

2. Objective

The objective of this study were to evaluate the impact of

preoperative systemic inflammation score on prognostic risk factors in early cervical cancer.

3. Methodology & Materials

This cross-sectional study was conducted at the Department of Gynecological Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from July 2022 to June 2023. A total of 90 women with the early operable stage (lA -IIA) of cervical cancer who admitted in the Department of Gynecological Oncology BSMMU, Dhaka, Bangladesh for radical hysterectomy with bilateral pelvic lymphadenectomy are included in this study. Purposive type of non-random sampling was done according to the availability of the study subjects who fulfilled the inclusion criteria.

3.1. Inclusion Criteria

1. Histopathologically diagnosed cervical cancer patients
2. Clinical staging suggestive of early-stage, who underwent radical hysterectomy and bilateral pelvic lymphadenectomy
3. Had given consent to participate in the study.

3.2. Exclusion Criteria

1. Known case of acute or chronic infection
2. Undergoing fertility saving surgery
3. Received neoadjuvant chemotherapy
4. Received preoperative corticosteroid
5. With hematologic, autoimmune or infectious diseases
6. With multiple primary site cancer
7. Cervical cancer stage IIB -IVB

3.3. Eligibility Criteria for Study Participants

The study aimed to evaluate the impact of the preoperative systemic inflammation score (SIS) on prognostic risk factors in early-stage cervical cancer. To achieve this, participants were carefully selected based on specific eligibility criteria to ensure the reliability and accuracy of the results. The study included women with histopathologically confirmed cervical cancer who were in early clinical stages (IA to IIA), as determined by FIGO staging. Participants were eligible if they were scheduled to undergo radical hysterectomy and bilateral pelvic lymphadenectomy, aligning their treatment with the study's focus on early-stage disease. Ethical considerations were prioritized, and only those who provided informed consent were enrolled. To minimize confounding factors, the study excluded patients with conditions or treatments that could impact systemic inflammation scores. This included those with acute or chronic infections, hematologic or autoimmune diseases, or other infectious conditions. Patients who had received neoadjuvant chemotherapy, preoperative corticosteroids, or were undergoing fertility-sparing surgery were also excluded. Additionally, individuals with multiple primary site cancers or advanced cervical cancer (stages IIB to IVB) were not included. These criteria ensured that the study population was representative of early-stage cervical cancer cases while maintaining the integrity of the findings.

3.4. Data Collection

Subjects were selected according to the availability of the respondents. A preformed semi-structured questionnaire obtained relevant history and clinical information. After taking informed written consent from the patients following introducing and informing the study purpose and objectives, data were collected by face-to-face interview ensuring privacy and confidentiality by using the questionnaire. All other required data were collected from history sheet, investigation papers, per-operative findings and follow up records. After that, all data were compiled, modified, and finalized.

3.5. Ethical Consideration

Ethical clearance for the study was taken from the Institutional Review Board and concerned authority, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. Written consent of all the study subjects was taken free of duress and without exploiting any weakness of the subjects. The entire study subject was thoroughly appraised about the nature, purpose and implications of the study as well as the entire spectrum of benefits and risks of the study. The interest of the study subjects was not compromised to safeguard their rights and health. As this study needs only 5 ml of blood of study subjects, the chances of complications are very unlikely. But if any complications like slight discomfort, mild pain, weakness or vertigo occur they were treated with assurance and analgesics. Subjects were assured about their confidentiality and freedom to withdraw them from the study anytime.

3.6. Statistical Analysis of Data

Statistical analyses were carried out by using Windows-based Microsoft Excel and Statistical Package for Social Sciences (SPSS-27) where required. Systemic inflammation score was categorized to 0, 1 and 2 based on cut-off value as normal and low obtained through PLR and serum albumin level. In this study, a serum PLR value of 128.3 was taken as the cut-off point. Values above this threshold were categorized as high PLR, while values below it was considered as low PLR. This cut-off value was based on the research conducted by Zheng et al. in 2016. [7] The descriptive statistics of the study was presented in tables, figures or frequency, percentage, mean ± SD as per the requirement of qualitative and quantitative variables. Chi-square tests were done to observe the association between SIS score and clinicopathological features in early stage of cervical cancer. ANOVA and post-hoc tests were conducted to assess the relationship between SIS scores and tumor size. The p-value <0.05 was considered statistically significant.

4. Results

Table 1. Distribution of systemic inflammatory score of the study population (n=90).

SIS Score	Frequency(n)	Percentage(%)
0	38	42.22
1	33	36.67
2	19	21.11

Table 1 shows that 38(42.22%) of the women had SIS score of 0, 33(36.67%) of respondents had SIS score of 1 and the rest of 19(21.11%) had SIS score of 2.

Table 2. Comparison of histopathological subtypes of cervical cancer patients stratified by cervical cancer systemic inflammation score (n=90).

SIS Score	Histological Subtype		Total	P-value
	Squamous p-value (n = 71)	Non-squamous (n = 19)		
0	30(42.3%)	8(42.1%)	38(42.2%)	
1	27(38.0%)	6(31.6%)	33(36.7%)	0.787a
2	14(19.7)	5(26.3%)	19(21.1)	

a = chi-square test

Table 2 shows, among patients with an SIS score of 0, 30 (42.3%) had squamous type, while 8 (42.1%) had non-squamous type of cervical cancer. In the SIS score 1 group, 27 (38.0%) had squamous, whereas 6 (31.6%) had non-squamous type cervical cancer. For those with an SIS score of 2, 14 (19.7%) exhibited squamous type, and 5 (26.3%) had non-squamous type cervical cancer. But these differences were statistically not significant (p=0.787).

Table 3. Comparison of tumor size and lymphovascular space invasion (LVSI) of the respondents stratified by cervical cancer systemic inflammation score (n=90).

Parameter		SIS Score			p-value
		0 (n=38)	1 (n=33)	2 (n=19)	
Tumor size	2-4 cm	7 (18.4%)	18 (54.5%)	14 (73.7%)	<0.001
	<2 cm	31 (86.6%)	15 (45.5%)	5 (26.3%)	
Mean ±SD		1.45 ±0.78	1.99 ±0.83	2.54 ±0.79	
LVSI	Present	1 (7.7%)	12 (92.3%)		0.006
	Absent	37 (48.1%)	40 (51.9%)		

Table 3 illustrates those women with an SIS score of 0 had a mean (SD) tumor size of 1.45±0.78 cm, which increased to 1.99±0.83 cm in women with an SIS score of 1 and increased significantly further to 2.54±0.79 cm in patients with a SIS score of 2. This progressive increase in tumor size with higher SIS scores is statistically significant as indicated by the p-value (p<0.001). It also demonstrates that among women with an SIS score of 0, 7.7% had LVSI, while the majority consisting of 48.1% had no LVSI. Conversely, in the SIS score range of 1 to 2, a significantly higher proportion, 92.3%, had an LVSI present, compared to 51.9% who did not have an LVSI. This difference in distribution was statistically signif-

icant (p = 0.006).

Depth of stromal invasion: Among women with an SIS score of 0, 30.2% exhibited invasion of half thickness or more, while a majority of 59.5% displayed stromal invasion of less than half thickness. In contrast, within the SIS score range of 1-2, a significantly higher proportion, specifically 69.8%, demonstrated invasion of half thickness or more, while 40.5% had stromal invasion of less than half thickness. This difference in distribution was statistically highly significant (p = 0.006).

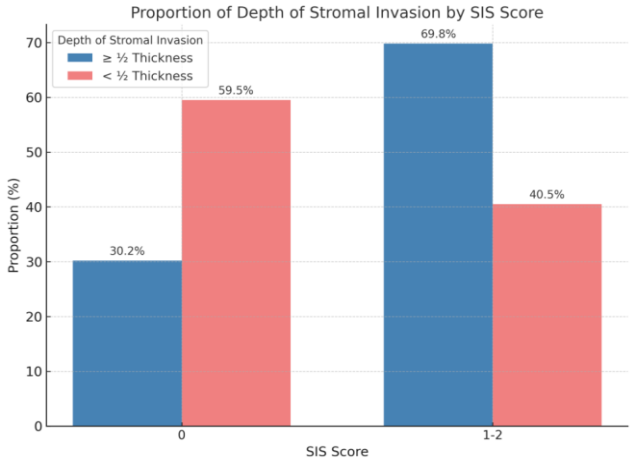

Figure 1. *Comparison of depth of stromal invasion by cervical cancer systemic inflammation score (n=90).*

Table 4. *Comparison of pelvic lymph nodes (PLN) metastases by cervical cancer systemic inflammation score (n=90).*

SIS Score	PLN		Total (n=90)	p-value
	Present (n=8)	Absent (n=82)		
0	1 (12.5%)	37 (45.1%)	38 (42.2%)	0.132
1-2	7 (87.5%)	45 (54.9%)	52 (57.8%)	

Table 4 exhibits that among women with an SIS score of 0, 12.5% exhibited PLN metastases, while a +majority of 45.1% did not have PLN involvement. Conversely, within the SIS score range of 1-2, a significantly higher proportion, specifically 87.5%, showed PLN metastases, while 54.9% did not have PLN involvement (p>0.05).

5. Discussion

The results of this study highlight the prognostic value of the systemic inflammation score (SIS) in early cervical cancer and the correlation with relevant clinicopathological factors including tumor size, lymphovascular space invasion (LVSI), depth of stromal invasion and metastasis to pelvic lymph nodes (PLN). The Systemic Inflammation Score (SIS) is based on serum albumin and PLR. SIS score 0 for increased albumin and decreased PLR, score 1 for either decreased albumin or increased PLR and score 2 for both decreased albumin and increased PLR.

The most important findings of this study was the link between SIS and tumor size. Women with a SIS score of 2 had considerably larger tumors (mean size 2.54 ± 0.79 cm) than those with SIS ratings of 1 (1.99 ±0.83 cm) and 0 (1.45 ±0.78 cm), with a p-value of <0.001.

LVSI has long been considered as a potential adverse prognostic factor in cervical cancer. Researchers found that LVSI positive patients showed a higher rate of lymph node metastasis (LNM), were more likely to have local or distal relapse and usually had shorter overall survival (OS). [16].

Gemer et al. conducted an assessment of different clinical and Zheng et al. conducted pathologic risk factors that could impact the utilization of multimodality treatment for early cervical cancer. [2, 7] Their findings revealed that 89% of patients with tumors measuring 2 cm or larger and exhibiting lymphovascular space invasion (LVSI) received radiotherapy, while 76% of patients with tumors of 2 cm or more and a depth of invasion exceeding 10 mm underwent radiotherapy. [2].

There was statistically significant relationship between depth of stromal invasion and SIS (p=0.006), as women with higher SIS score have greater depth of stromal invasion. In particular, the stromal invasion of half or more depth (SIS) was found in 69.8% of patients with a SIS score of 1 or 2, and in 30.2% of those patients with a SIS score of 0. As it relates to prognosis thus as well as the decision about adjuvant treatment, stromal invasion depth is a predictor that has implications for recurrence risk and survival outcome. [11].

In this study, patients with higher SIS scores were more likely to have PLN metastases (87.5% of patients with SIS score 1-2 had PLN metastases vs. 12.5% with a SIS score 0, p>0.05). This differs from past studies where the inflammation markers were strongly related to lymph node involvement in cervical cancer. [4, 7] In the present study, this lack of statistical significance may be due to having a relatively small sample size or limited number of patients with documented PLN metastases. The prognostic value of SIS for lymph node metastasis and the ultimate outcome of the disease is not clearly defined and further research with larger cohorts is indicated.

A similar study by Zheng et al. demonstrated that high SIS was associated with advanced tumor stage, poor differentiation, and worse survival outcomes in cervical cancer patients. [7] Similarly, Xu et al. highlighted the predictive utility of SIS for overall survival in cervical cancer. [3] These findings reinforce the potential of SIS as a universal prognostic marker across different cancer types.

6. Conclusion

Systemic inflammation score (SIS) demonstrates the potential for this as a significant prognostic tool in early stage cervical cancer. Strong elevated SIS levels were strongly associated with adverse clinicopathologic risk factors like larger tumor size, higher LVSI rate, deeper stromal invasion, and pelvic lymph node metastases. By making SIS as a part of routine clinical practice, clinical risk prediction could be improved, overtreatment reduced, and patient outcome goals improved, especially in low resource settings.

7. Limitations and Recommendations

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community. These findings should be validated in future larger, multicenter studies to confirm their clinical utility. Combining SIS with other biomarkers and molecular profiling techniques may offer a more complete picture of tumor biology and improve the accuracy of risk stratification models to lead to more accurate, patient specific treatment strategies.

Abbreviations

BSMMU Bangabandhu Sheikh Mujib Medical University

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Ethical Approval

The Institutional Ethics Committee approved the study.

Author Contributions

Syfun Naher: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing

Naznine Akter: Investigation, Methodology, Resources, Software, Visualization

Riffat Ara Sharmin: Data curation, Project administration, Validation, Writing – review & editing

Rita Roy: Data curation, Investigation, Writing – review & editing

Fawzia Hossain: Funding acquisition, Methodology, Resources, Software

Jakanta Faika: Conceptualization, Project administration, Visualization, Writing – original draft, Writing – review & editing

Khandker Tafriha Rahman: Validation, Writing – original draft

Asim Kumar Saha: Formal Analysis, Software

Mofazzal Hossen: Data curation, Formal Analysis

Conflicts of Interest

There are no conflicts of interest.

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