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Original Research Article

Association of preoperative systemic inflammation score with clinicopathological feature in the early stage of carcinoma cervix

Syfun Naher[1]*, Shirin Akter Begum[2], Naznine Akter[3], Farhana Khatoon[2], Fatema Nihar[4], Subrina Meher[1], Fahmida Sultana[5], Mofazzal Hossen[6]

[1]Department of Obstetrics and Gynecology, Directorate General of Health Services (DGHS), Dhaka, Bangladesh
[2]Department of Gynecological Oncology, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, Bangladesh
[3]Department of Obstetrics and Gynecology, Institute of Health Technology, Dhaka, Bangladesh
[4]Department of Gynecological Oncology, National Institute of Cancer and Research Hospital (NICRH), Dhaka, Bangladesh
[5]Department of Obstetrics and Gynecology, Sheikh Sayera Khatun Medical College (SSKMC), Gopalganj, Bangladesh
[6]Department of Mathematics, Azimpur Government Girls School and College, Dhaka, Bangladesh

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***Correspondence:**
Dr. Syfun Naher,
E-mail: tonuhossen525@gmail.com

ABSTRACT

Background: Cervical cancer is a significant global health concern, particularly in its early stages (stage IA-IIA). Systemic inflammation's influence on cancer has been explored extensively in other tumor types, its association with clinicopathological features in early-stage carcinoma of the cervix remains a relatively underexplored area. This study aimed to evaluate the association of preoperative systemic inflammation score with clinicopathological features in the early stage of carcinoma cervix.
Methods: This was a cross-sectional study that was carried out in the department of gynecological oncology at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh during the period from June 2022 and July 2023. In our study, we included 90 cervical cancer stage IA-IIA patients who underwent primary radical hysterectomy with bilateral pelvic lymphadenectomy.
Results: Among all study participants, the mean age was 45.1±9.03 years. Majorities (65.6%) were found taking oral contraceptive pills. Higher SIS scores were strongly associated with larger tumor sizes, with mean tumor sizes of 1.45 cm (SIS 0), 1.99 cm (SIS 1), and 2.54 cm (SIS 2), respectively. Additionally, the incidence of lymphovascular space invasion (LVSI) demonstrated a pronounced increase with higher SIS scores, with 7.7% (SIS 0) and 92.3% (SIS 1-2) exhibiting LVSI. These associations were statistically significant ($p<0.05$).
Conclusions: The study findings conclude that there is an association of pretreatment systemic inflammation score SIS with tumor size, lymphovascular space invasion, and increased depth of stromal invasion. SIS preoperatively can predict the clinicopathological risk factor of cancer cervix.

Keywords: Clinicopathological feature, Early-stage carcinoma cervix, Systemic inflammation score

INTRODUCTION

Cancer ranks as a leading cause of death and a substantial barrier to increasing life expectancy in every country of the world.[1] The World Health Organization reports that in 2020, there were 604,000 cervical cancer diagnoses worldwide and 342,000 cervical cancer-related deaths.[2] Living in the world's poorest nations, young, uneducated women make up over 85% of those impacted.[3] India and China have the highest burden of cervical cancer, with two-thirds of cases.[4] According to the Global Cancer Observatory (GLOBOCAN) report, cervical cancer ranks

as the second most prevalent cancer (12%) among women in Bangladesh accounting for nearly 8,068 (10.6 per 100,000 women) new cases detection each year and causing 5,214 (7.1 per 100,000 women) fatalities.[5] Cervical cancer often follows a well-defined natural history, progressing from precancerous lesions to invasive carcinoma, making it amenable to early detection and intervention. Hence, the management of early-stage carcinoma of the cervix represents a critical juncture in the battle against this formidable disease.[6] Women with pathological risk factors (e.g., LNM, tumor-positive surgical margins, depth of stromal invasion, vascular thrombosis, tumor stage, and tumor differentiation) have a higher frequency of recurrence when compared to patients without those factors.[7] The World Health Organization (WHO) launched the global strategy to accelerate the elimination of cervical cancer in November 2020, with targets set to be achieved by 2030: vaccinate 90% of eligible girls against HPV, screen 70% of eligible women at least twice in their lifetime, and effectively treat 90% of those with a positive screening test or cervical lesion, including palliative care when needed. WHO strongly recommends HPV DNA detection as the primary screening test for both the general population of women and women living with HIV, emphasizing the importance of early detection and intervention in the fight against cervical cancer.[8] The development and spread of many malignancies, including cervical cancer, are significantly influenced by inflammation. Immune surveillance is associated with platelets and lymphocytes. Serum albumin is a negative acute-phase protein that is integrated with other markers to create new prognostic markers.[9] In cervical carcinogenesis, the hyperactivation of the inflammatory pathways plays an important role in tumorigenesis, the progression of the disease as well as in the initiation of other infections. Growth factors and cytokines influence the expression of cyclooxygenase-2 (COX-2), an inducible isoform of cyclooxygenases that is overexpressed in inflammatory conditions. Higher levels of COX-2 expression are closely related to a higher incidence of parametrial invasion and lymph node metastases in early-stage uterine cervical cancer.[10] Some studies have shown that platelet lymphocyte ratio is mostly related to tumor size, lymph node metastasis, and also with stromal infiltration, LVSI, and grading. Low albumin levels are associated with poor outcomes.[11] FIGO stage is the most important clinical prognostic indicator for cervical cancer patients, many patients with the same FIGO stage have different treatment outcomes due to tumor heterogeneity. Therefore, it is necessary to find other indicators to assist in predicting the prognosis of cervical cancer.[12] Systemic inflammatory biomarkers, such as the lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), have been reported as prognostic factors in various tumors.[13] The systemic inflammation score (SIS) for cervical cancer is based on PLR and serum albumin. Numerous malignancies, such as pancreatic, lung, oral cavity, colorectal, and cervical cancers, have been studied about SIS.[14] A study in China shows high CCSIS was correlated with a more advanced FIGO stage, poor tumor differentiation, presence of PLN, and LVSI. It also shows both albumin and PLR were independent prognostic factors for operable CA cervix and use of it could improve risk stratification and traditional clinicopathological analysis.[15]

Therefore, in this study, we aimed to evaluate the association of preoperative systemic inflammation score with clinicopathological features in the early stage of carcinoma cervix.

METHODS

This was a cross-sectional study that was carried out in the department of gynecological oncology at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh during the period from June 2022 and July 2023. In our study, we included 90 cervical cancer stage IA-IIA patients who underwent primary radical hysterectomy with bilateral pelvic lymphadenectomy.

These are the following criteria to be eligible for enrolment as our study participants: a) patients aged more than 18 years; b)patients histopathologically diagnosed with cervical cancer; c) patients with clinical staging and imaging (MRI) features suggestive of early-stage, who underwent radical hysterectomy; d) patients who were willing to participate were included in the study and a) patients undergoing fertility saving surgery; b) patients received neoadjuvant chemotherapy or preoperative radiotherapy or preoperative corticosteroid; c) patients with hematologic, autoimmune or infectious diseases; d) patients with cervical cancer stage IIB -IVB; e) patients with multiple primary site cancer; f) patients with any history of acute illness (e.g., renal or pancreatic diseases, ischemic heart disease, asthma, COPD etc.) were excluded from our study.

Data collection

After obtaining informed written consent from the patients following the introduction and informing the study's purpose and objectives, data were collected from a total of 90 histologically confirmed women with early-stage (IA-IIA) cervical cancer. Clinical examinations were performed to assess the extent of the disease (FIGO staging), and imaging studies focusing on magnetic resonance imaging (MRI) results confirmed the presence of early-stage cervical cancer. Postoperatively, histopathology reports were collected to confirm the diagnosis and provide comprehensive information about tumor characteristics that included pathological types, lymphovascular space invasion (LVSI), and pelvic lymph node metastasis (PLN). In all the study subjects 5 ml of blood was drawn aseptically from an ante-cubital vein from each study subject preoperatively. Complete blood count and serum albumin level were assayed in the department of laboratory medicine, BSMMU, Shahbag, Dhaka. From the test results, PLR was calculated by

absolute platelet count divided by absolute lymphocyte count. The SIS score was obtained from the PLR and serum albumin levels in the blood of the patients.

Statistical analysis

All data were recorded systematically in preformed data collection form. Quantitative data was expressed as mean and standard deviation and qualitative data was expressed as frequency distribution and percentage. Chi-square tests were done to observe the association between SIS score and clinicopathological features in the early stage of cervical cancer. ANOVA and post-hoc tests were conducted to assess the relationship between SIS scores and tumor size. A p value <0.05 was considered as significant. Statistical analysis was performed by using SPSS 27 (Statistical Package for Social Sciences) for Windows version 10. The study was approved by the ethical review committee of Bangabandhu Sheikh Mujib Medical University.

RESULTS

This cross-sectional study was carried out to determine the association of preoperative systemic inflammation score (SIS) with clinicopathological features in the early stage of carcinoma cervix. A total number of 90 women with histopathologically confirmed early-stage cervical cancer were included in this study. The results were presented in tables and figures.

Table 1: Distribution of sociodemographic characteristics of the study population.

Characteristics	Frequency (n=90)	Percentage
Patient's age (years)		
30-44	42	46.7
45-59	38	42.2
≥60	10	11.1
Mean±SD	45.14±9.03	
Level of education		
Illiterate	24	26.7
Upto primary	37	41.1
SSC/equivalent	23	25.6
HSC and above	6	6.7
Occupation		
Housewife	73	81.1
Service holder	9	10.0
Govt. service	6	6.7
Wage earner	2	2.2
Monthly income status (in Taka)		
≤15000	24	26.7
15,001-30,000	53	58.9
>30,000	13	14.4

Table 1 shows the distribution of respondents according to socio-demographic parameters. Nearly half (46.7%) of the respondents were between 30-44 years with a mean age of 45.1±9.03 years. Most respondents (41.1%) had attained education up to the primary level, and 81.1% were housewives (81.1%). The majority (58.9%) of the participants' monthly income was 15,001-30,000 Tk and were middle class.

Table 2: Distribution of the study population according to their contraceptive history.

Parameters	Frequency	Percentage
Oral contraceptive pill use		
Yes	59	65.6
No	31	34.4
Duration of OCP use (n=59)		
≥5 years	43	72.9
<5 years	16	27.1

Table 2 shows the distribution of the respondents according to their contraceptive history, where the majority (65.6%) were found taking oral contraceptive pills and 72.9% of women were taking OCP for more than 5 years.

Table 3: Distribution of hematological parameters of the study population (n=90).

Parameters	Frequency	Percentage
Platelet to lymphocyte ratio (PLR)		
≥128.3	34	37.8
<128.3	56	62.2
Mean±SD	139.46 ± 104.61	
Serum albumin level (mg/dl)		
≥3.5	52	57.8
<3.5	38	42.2
Mean±SD	3.60 ± 6.07	

Table 3 shows the distribution of responders based on their PLR, with 37.8% of the respondent's PLR level over ≥128.3, and the mean PLR was 139.46±104.61. 57.8% of the respondents had a serum albumin level of ≥3.5 mg/dl, with an average serum albumin level of 3.60±6.07 mg/dl.

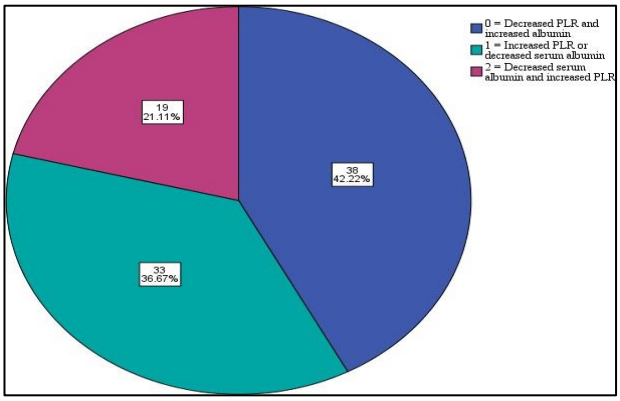

Figure 1: Distribution of systemic inflammatory score of the study population (n=90).

The pie chart shows that among 90 women 38 (42.2%) of them had an SIS score of 0, 33 (36.7%) of respondents had an SIS score of 1 and the rest of 19 (21.1%) had an SIS score of 2.

Table 4: Comparison of tumor size of the respondents stratified by cervical cancer systemic inflammation score (n=90).

Tumor size	SIS score			P value
	0 (n=38)	1 (n=33)	2 (n=19)	
2-4 cm	7 (18.4)	18 (54.5)	14 (73.7)	<0.001[b]
<2 cm	31 (81.6)	15 (45.5)	5 (26.3)	
Mean±SD	1.45±0.78	1.99±0.83	2.54±0.79	

[b]=one-way ANOVA

Table 5: Pair-wise comparison of mean (±SD) SIS score by tumor size (n=90).

SIS score (I)	SIS score (J)	Mean difference (I-J)	SE	P value	95% CI	
					Lower bound	Upper bound
0	1	-0.545	0.189	0.005	-0.923	-0.168
	2	-1.092	0.224	<0.001	-1.538	-0.646
1	0	0.545	0.189	0.005	0.168	0.923
	2	-0.547	0.229	0.019	-1.004	-0.902
2	0	1.092	0.224	<0.001	0.646	1.538
	1	0.547	0.229	0.019	0.090	1.004

Table 6: Comparison of lymphovascular space invasion (LVSI) by cervical cancer systemic inflammation score (n=90).

SIS score	LVSI		Total (n=90)	P value
	Present (n=13)	Absent (n=77)		
0	1 (7.7)	37 (48.1)	38 (42.2)	0.006[a]
1-2	12 (92.3)	40 (51.9)	52 (57.8)	

[a]=chi-square test

Table 7: Comparison of depth of stromal invasion by cervical cancer systemic inflammation score (n=90).

SIS score	Depth of Stromal Invasion		Total (n =90)	P value
	≥½ thickness (n=53)	<½ thickness (n=37)		
0	16 (30.2)	22 (59.5)	38 (42.2)	0.006[a]
1-2	37 (69.8)	15 (40.5)	52 (57.8)	

Table 4 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 was statistically significant as indicated by the p value (p<0.001).

Table 5 reveals statistically significant variations in mean values among different SIS score comparisons. SIS score 0 compared to score 1 shows a mean difference of -0.545, signifying that tumors with score 1 were, on average, 0.545 units smaller in size than those with score 0, with a significance level of 0.005. Conversely, comparing SIS score 0 to score 2 exhibits a larger mean difference of -1.092 (p<0.001), indicating the substantial impact of stromal invasion on tumor size.

Table 6 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 significant (p=0.006).

Table 7 shows that 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.

DISCUSSION

Surgery is preferred for the early stage of cervical cancer, though radiotherapy provides equally good results. Radiotherapy or CCRT is preferred in patients likely to require postoperative radiotherapy to avoid treatment-related morbidity. This study was conducted among 90 purposively selected cervical cancer women to determine the association of SIS with the clinicopathological features in patients with early-stage cervical cancer.

The majority of women with early cervical cancer in the study were aged 30-44 (46.7%), followed by 45-59 (42.2%), and ≥60 (11.1%) years. The mean age was 45.14±9.03 years. A patient's age is also one of several critical factors considered when determining the most appropriate treatment approach for cervical cancer. A comparable study in South India revealed a median age of 40 years and a mean age of 41.8±11.5.[16] The American Cancer Society reports that the majority of cervical cancer diagnoses occur in women between the ages of 35 and 44, with an average age of 50 at diagnosis. It hardly ever appears in women under the age of twenty.[17] The majority of women in the study had primary-level education (41.1%), were housewives (81.1%), and had a monthly income between Tk. 15,001 and Tk. 30,000. A systematic review by Murfin et al found an association between education, income levels, and the uptake of cervical screening and HPV vaccination among women.[18]

In this study, 65.6% of the women with early cervical cancer had given history of taking oral contraceptive pills. Among the OCP users who had reported early cervical cancer, 72.9% of them had taken OCP for a duration of ≥5 years. For women who have taken oral contraceptives for five years or longer, the risk of cervical cancer is greater than for women who have never taken them. A woman's risk of developing cervical cancer increases with the length of time she utilizes oral contraceptives. According to one study, the risk doubled with 10 years or more of use, increased by 60% with 5-9 years, and increased by 10% with less than 5 years.[19] The systemic inflammation score was used to distinguish patients with different oncological outcomes combining PLR and serum albumin levels. In the present study, tumor size 2-4 cm was more in women who had an SIS score of 2 (73.7%) compared to the SIS score of 1 (54.5%) and 0 (18.4%), these variations in the distribution of women with cervical cancer was statistically significant ($p<0.001$). Gemer et al conducted an assessment of different clinical and pathologic risk factors that could impact the utilization of multimodality treatment for early cervical cancer. 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.[20] LVSI has long been considered a potential adverse prognostic factor in cervical cancer. Researchers discovered that individuals with LVSI typically had a lower overall survival (OS), a greater probability of lymph node metastasis (LNM), and a higher likelihood of local or distant relapse.[21] In this study, 92.3% of patients with an SIS score range of 1-2 exhibited the presence of LVSI, while the occurrence of LVSI was notably lower (7.7%) among patients with an SIS score of 0 ($p=0.006$). In the current study, more than ½ depth stromal infiltration was noted in a higher proportion of women (69.8%) with an SIS score range of 1-2, followed by 30.2% with an SIS score of 0. A similar study by Zheng et al showed high CCSIS was correlated with more advanced FIGO stages, poor tumor differentiation, and the presence of PLN and LVSI.[9] Preoperative SIS is a simple and useful prognostic factor for postoperative survival in patients with cervical cancer. Xu et al also enumerated that the preoperative SIS is a simple and useful prognostic factor for postoperative survival in patients with cervical cancer.[12]

Our study was a single-center study. We took a small sample size due to our short study period. After evaluating those patients, we did not follow up with them for the long term and did not know other possible interference that may happen in the long term with these patients.

CONCLUSION

The findings of this study reveal a significant association between the systemic inflammation score (SIS) and clinicopathological features in early-stage carcinoma cervix. A higher SIS score is correlated with larger tumor size, the presence of LVSI, and increased depth of stromal invasion. Therefore, a high SIS score can be a valuable guide for considering monotherapy as a preferred therapeutic approach over surgical interventions, thereby contributing to an individualized treatment strategy for patients from a clinical perspective.

Further study with a prospective and longitudinal study design including a larger sample size needs to be done to validate the findings of our study.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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