Original Research Article

Efficacy of the albumin-to-fibrinogen ratio as a predictive marker of advanced-stage cervical cancer

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ABSTRACT

Background: Cervical cancer is the fourth most prevalent cause of mortality from cancer in women worldwide. Inflammation is a significant predictor of cancer. Indications of inflammation include a high fibrinogen level and a low albumin level. Increased fibrinogen levels have been connected to the development and spread of cancer as well as a pro-inflammatory condition. The albumin/fibrinogen ratio (AFR), which is a combination of albumin and fibrinogen, has been proposed as a novel marker of inflammation. Therefore, this study aimed to evaluate the efficacy of the albumin-to-fibrinogen ratio as a predictive marker of advanced-stage cervical cancer.
Methods: This was a prospective observational study conducted in the department of gynecological oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh during the period from July 2022 to June 2023. In our study, we included 70 women with biopsy-proven cervical cancer attending the inpatient and outpatient departments of the gynecological oncology department at BSMMU.
Results: The mean age of the patients was 45.37±9.54 years. The mean albumin to fibrinogen ratio was lower in the advanced-stage group (9.77±1.21) compared to that in the early-stage group (10.74±1.54) and the difference between the two groups was statistically highly significant (p=0.005). Considering 10.7 as the cut-off value (by ROC curve) we found the sensitivity, specificity, PPV, and NPV for AFR<10.7 was 85.71%, 62.86%, 69.77%, and 81.48%, respectively.
Conclusions: Our study findings show that the albumin-to-fibrinogen ratio (AFR) emerges as a promising prognostic marker to differentiate between advanced and early-stage cases and could aid in clinical decision-making.

Keywords: Albumin to fibrinogen ratio, Cervical cancer, Efficacy, Predictive marker

INTRODUCTION

Cervical cancer is the fourth most prevalent cause of mortality from cancer in women worldwide.[1] Approximately 85% of cervical cancer deaths occur in poor or developing countries, with low- and middle-income countries having a death rate 18 times greater than affluent countries.[2] In Bangladesh, no national cancer registry is no national cancer registry that can give comprehensive nationwide statistics. More than 50 million women in Bangladesh are at risk of developing cervical cancer due to a combination of risk factors such as early marriage, early initiation of sexual activity, multiparity, STDs, and low socioeconomic status, and despite widespread national screening facilities, it remains inadequate in comparison to developed countries.[3,4]

Inflammation is a significant predictor of cancer. Tumor-related inflammatory factors are closely related to the prognosis of cancer patients. In a variety of human tumor forms, a few index systems associated with inflammation are useful predictors. The albumin/fibrinogen ratio (AFR), which is a combination of albumin and fibrinogen, has been proposed as a novel marker of inflammation.[5]

The protein albumin, which is a necessary component of blood plasma, is produced by the liver. Among its many functions, it maintains osmotic pressure, controls immunological reactions and carries various substances. Low serum albumin levels, which are commonly observed in cancer patients, are associated with poor outcomes. This decrease in albumin levels is caused by several factors, including malnutrition, inflammation, and cancer-related alterations in protein metabolism.[6,7]

In contrast, fibrinogen is a glycoprotein that promotes blood coagulation and wound healing. The body's response to damage during acute-phase events, including inflammation or tissue destruction, causes fibrinogen levels to increase.[8] Elevated levels of fibrinogen have been linked to pro-inflammatory conditions and the onset and progression of cancer.[9]

Cervical cancer is known as a long-term consequence of infection with specific strains of the human papillomavirus.[10] About 10% of people with the illness develop precancerous lesions, which subsequently progress into cervical cancer.[11] Three double-blind clinical trials found that in women with no prior HPV infection, vaccination with the non-violent vaccine reduced cervical cancer incidence by 98.2% and surgery rates by 97.8%.[12]

Screening is critical for preventing and diagnosing cervical cancer, but traditional cytology-based approaches have limitations such as difficult sample collection, low sensitivity, and time-consuming processing.[13] Human papillomavirus (HPV) testing, while useful, may not differentiate between temporary and persistent infections.[14] An efficient, cost-effective, and user-friendly biomarker is required to effectively predict cervical cancer. The staging technique most frequently used for cervical cancer is that of the International Federation of Gynecology and Obstetrics (FIGO). Stage I disease is divided into two categories: IA and IB. Stage IA is only visible under a microscope. Any pretty obvious lesion is promoted to IB right away.[15]

Combining two indications, the albumin-to-fibrinogen ratio (AFR) tells us how the body balances the acute-phase responses and immunological responses during cancer. The albumin-to-fibrinogen ratio (AFR) has shown diagnostic use in several human cancer types; nevertheless, the outcomes of the literature currently in print regarding the application of AFR in cervical cancer stage prediction have been mixed.[5,16]

Therefore, this study aimed to evaluate the efficacy of the albumin-to-fibrinogen ratio as a predictive marker of advanced-stage cervical cancer.

METHODS

This was a prospective observational study conducted in the department of gynecological oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh during the period from July 2022 to June 2023. In our study, we included 70 women with biopsy-proven cervical cancer attending the inpatient and outpatient departments of the gynecological oncology department at BSMMU.

These are the following criteria to be eligible for enrolment as our study participants: a) women aged more than 18 years; b) women diagnosed with cervical cancer confirmed by histopathology report; c) women who were willing to participate were included in the study and a) women with a history of previous surgery, chemotherapy or radiation treatment for cervical disease, neoplasia or any other cancer; b) women with coagulopathy or received anticoagulant before enrolment; c) women with known hematological diseases, autoimmune, infectious diseases or concomitant malignant tumors; d) women with known HIV infection; e) women 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

Thorough clinical examination including general examination, systemic examination and routine gynecological examination was done in all subjects, and staging by clinical examination was done and categorized as early stage (FIGO stage I-IIA) and advanced stage (FIGO stage IIB-IV). Data was collected from the patients on variables of interest using the semi-structured questionnaire designed for interviews, observations, hematological investigations, and from the history sheet of the patients. 5 ml of blood was drawn, on the same day of clinical staging of cervical cancer, from the antecubital vein for measurement of serum albumin and fibrinogen level using a sterile needle and syringe and sent for analysis, which was then sent for analysis to the department of biochemistry and molecular biology and the department of hematology, BSMMU. The albumin to fibrinogen ratio (AFR) was calculated by dividing the total serum albumin level by the serum fibrinogen level for each participant.

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. The albumin-to-fibrinogen ratio (AFR) was categorized based on the cut-off value as normal and low obtained through the receiver

operating characteristic curve. An unpaired t-test was done to find out the difference in mean albumin to fibrinogen ratio between the two study groups. Chi-square tests were done to observe the association between albumin to fibrinogen ratio and stages of cervical cancer. 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

Table 1 shows, that the majority (47.1%) of the patients were within the 30-44 years age group, the mean age of the patients was 45.37±9.54 years. Most (85.7%) of the patients were married, and 84.3% were housewives. Over half (52.9%) of the participants had post-coital bleeding, followed by 47.1% had foul-smelling vaginal discharge, 20.0% had leukorrhea, and 15.7% complained of post-menopausal bleeding and irregular per-vaginal bleeding.

Table 1: Distribution of the respondents according to their demographic characteristics (n=70).

Demographic characteristics	N	%
Age (in years)		
30-44	33	47.1
45-59	29	41.4
≥60	8	11.4
Mean±SD	45.37±9.54	
Marital status		
Married	60	85.7
Widowed	9	12.9
Divorced/separated	1	1.4
Occupation		
Housewife	59	84.3
Service holder	7	10.0
Household worker	4	5.7
Presenting complaints		
Post-coital bleeding	37	52.9
Foul-smelling vaginal discharge	33	47.1
Post-menopausal bleeding	11	15.7
Leucorrhea	14	20.0
Irregular per-vaginal bleeding	11	15.7

Table 2: Distribution of mean±SD of pretreatment AFR in different stages of cervical cancer among the respondents (n=70).

FIGO stages	Frequency	AFR (mean±SD)	P value
Stage I	31	10.69±1.63	
Stage II	16	10.56±1.31	0.006ᵈ
Stage III	20	9.63±0.97	
Stage IV	3	8.41±0.33	

d=statistically significant.

Table 2 illustrates pretreatment AFR in different stages of cervical cancer among the respondents. There were significant differences in the mean±SD of albumin to fibrinogen ratio between different stages of cervical cancer (p<0.05).

Table 3: Categorization of the respondents according to mean±SD albumin to fibrinogen ratio by advanced and early-stage group (group A =35, group B =35).

Parameter	Group A (stage IIB-IV)	Group B (stage IA-IIA)	P value
Albumin to fibrinogen ratio (Mean±SD)	9.77±1.21	10.74±1.54	0.005ᵇ

Group A: advanced stage (inoperable cases) of cervical cancer; group B: early stage (operable cases) of cervical cancer; b=statistically significant.

Table 3 shows the mean±SD of albumin-to-fibrinogen ratio by advanced and early-stage groups. A statistically significant difference was observed between group A and group B patients based on their albumin-to-fibrinogen ratio (p=0.005).
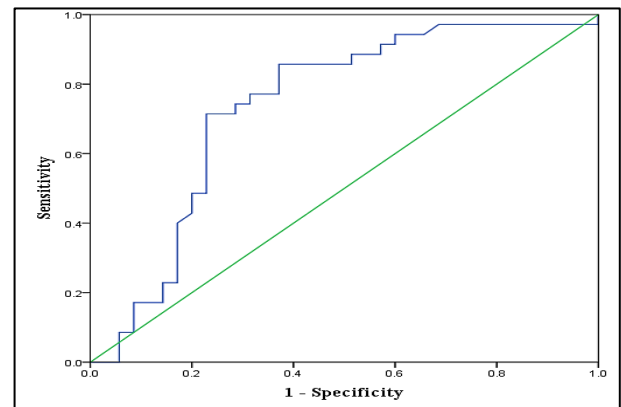

Figure 1: Receiver operating characteristic curve (ROC) of albumin to fibrinogen ratio (AFR) for prediction of advanced-stage cervical cancer.

The ROC for the AFR for the prediction of advanced-stage cervical cancer is shown in Figure 1. The area under the curve was 0.736 (0.613-0.860), with a standard error of 0.063 and a significance level of 0.001, categorizing it as a fair test for the prediction of cervical cancer. The accuracy of a test was assessed by the area under the ROC curve, where 0.90-1 was considered excellent, 0.80-0.90 good, 0.70-0.80 fair, 0.60-0.70 poor, and 0.50-0.60 as a failed test.[17]

ROC curve was constructed by using albumin to fibrinogen ratio, which is depicted in Table 4, giving a cut-off value of 10.7, with 85.7% sensitivity and 62.9% specificity for the prediction of advanced-stage cervical cancer.

Table 4: Different sensitivity and specificity at different scores according to the albumin to fibrinogen ratio (coordinates of the ROC).

AFR	Sensitivity	Specificity	Youden index sensitivity + specificity -1
10.415	0.771	0.686	0.457
10.52	0.771	0.657	0.428
10.58	0.771	0.629	0.400
10.615	0.800	0.629	0.429
10.64	0.829	0.629	0.458
10.7	0.857	0.629	0.486
10.775	0.857	0.600	0.457
10.83	0.857	0.571	0.428
10.89	0.857	0.543	0.400
10.985	0.857	0.514	0.371
11.08	0.857	0.486	0.343

Table 5: Diagnostic efficacy of the AFR for prediction of advanced-stage cervical cancer (n=70).

Diagnostic accuracy	AFR	95% CI (lower-upper)
Sensitivity (%)	85.71	69.74 to 95.19
Specificity (%)	62.86	44.92 to 78.53
PPV (%)	69.77	59.50 to 78.38
NPV (%)	81.48	65.27 to 91.15
Accuracy	74.29	62.44 to 83.99

Table 5 shows the diagnostic accuracy of the albumin to fibrinogen ratio for the detection of advanced-stage cervical cancer, where the AFR<10.7 results had 85.71% sensitivity and 62.86% specificity. Positive and negative predictive value for AFR was 69.77% and 81.48% respectively.

DISCUSSION

In the present study, 47.1% of the patients were within the 30-44 years age group and the mean age was 45.37±9.54 years. The majority of the patients (85.7%) were married, and 84.3% were housewives. A similar study by Khanam et al, showed comparable findings, reporting 96.3% housewife, 0.2% labor, 2.3% service, 0.6% businessman, and 0.6% teaching.[18]

In this study, the most common cervical cancer-related symptoms were postcoital bleeding (52.9%), foul-smelling vaginal discharge (47.1%), and leucorrhea (20%). These results are consistent with previous studies that have highlighted the diverse and often nonspecific symptoms associated with cervical cancer and highlight the need for effective screening and early detection programs to address this significant health problem. Aminimoghaddam et al enumerated that the most common symptoms in early-stage cancer were abnormal vaginal bleeding, postcoital bleeding, and vaginal discharge. In advanced stages of the

disease, it presents with pelvic or lower back pain, and urinary and bowel involvement symptoms.[19]

In the present study, a comprehensive evaluation of histopathological findings revealed that of the 70 subjects, 35 were diagnosed with early-stage cervical cancer, while the remaining 35 were in advanced stages of the disease.

In the present study, there were notable differences in the mean±SD of the albumin-to-fibrinogen ratio (AFR) among different stages of cervical cancer (p<0.05). Stage IV cancer exhibited the lowest AFR mean of 8.41±0.33, while stage I had the highest mean AFR at 10.69±1.63. Furthermore, the average AFR was significantly lower among respondents in group A compared to group B (9.77±1.21 versus 10.74±1.54; p value =0.005). AFR had a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 85.71% 62.86% 69.77% 81.48%, and 74.29% for the prediction of cervical cancer.

Only a few studies were conducted previously on this subject which indicated that AFR is a valuable prognostic marker for assessing disease severity and informing clinical decisions in cervical cancer patients.

Huang et al showed that the AFR levels of patients with cervical cancer were significantly lower than those of patients with CIN and control subjects. AFR was negatively associated with tumor stage, histological type, lymph node metastasis, distant metastasis, depth of stromal infiltration, tumor size, and tumor stage, but it was not associated with the blood group. They found that AFR has a 90.85% specificity and a 76.61% sensitivity. Furthermore, the NPV was 77.8% and the PPV was 89.3%.[20]

Sun et al in their meta-analysis found that a low AFR correlated with increased risk of cancer mortality and recurrence. They recommended that AFR may be a promising prognostic marker for cancers.[21] Zhang and Xiao conducted a comprehensive meta-analysis encompassing various cancer types, including cervical cancer. They reported that a lower AFR was associated with advanced stages of cervical cancer, indicating its potential diagnostic significance.[5] In contrast, An et al in their study indicated that elevated preoperative FAR might be a novel prognostic factor for cervical cancer patients with stage IB-IIA. They demonstrated that the pretreatment fibrinogen-to-albumin ratio was an effective predictor for overall survival in cervical cancer patients with a cut-off value of 7.75 and an area under the curve (AUC) of 0.707 (p<0.001).[22]

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

In our study, we found that the albumin to fibrinogen ratio (AFR) varies with different stages of cervical cancer. The more the stages the less the ratio. Considering the cut-off value of 10.7, a pretreatment value of less than it can significantly detect the more advanced stage of cervical cancer. Therefore, the albumin-to-fibrinogen ratio (AFR) emerges as a promising prognostic marker to differentiate between advanced and early-stage cases and could aid in clinical decision-making.

So 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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