ORIGINAL RESEARCH PAPER

Volume-8 | Issue-3 | March-2019 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

IS LOCALLY ADVANCED CANCER CERVIX ASSOCIATED WITH HYPOALBUMINEMIA AND INCREASED GRANULOCYTE AND LYMPHOCYTE RATIO?

Biochemistry

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ABSTRACT

Background: With a background of difference in the roles of neutrophils in cancer patients compared to those with no malignancy, note higher incidencef of hypoalbuminemia in critically ill patients with cancer admitted to ICU and paucity of literature establishing their association, in the current setting the study was conducted.

Objective: To determine the association of hypoalbuminemia and increase Granulocyte and Lymphocyte ratio (GLR) with locally advanced cancer cervix.

Materials and Methods: Record based analysis was conducted among 96 locally advanced cancer cervix patients during the study period of 3 years at Kidwai Memorial Institute of Oncology, Bangalore. Granulocyte lymphocyte ratio, hypoalbuminemia and other required data were collected. Correlation of albumin levels and GLR with stages of cancer cervix was determined using Spearman's correlation coefficient (r). Logistic regression was undertaken to assess the various factors associated with hypoalbuminemia and GLR. A P value < 0.05 was considered statistically significant.

Results: The mean age of the study participants was 50 years and majority (57.2%) were in III B stage. With the progression of stages, GLR increased and albumin decreased significantly (P<0.05). Though hypoalbuminemia and raised GLR were not significantly associated and were not independent markers for locally advanced carcinoma cervix of stage ≥ III B, the risk of hypoalbuminemia and raised GLR were 3 times and 1 time higher among those with advanced stage of ≥ III B compared to lower stages of carcinoma cervix respectively (P>0.05).

Conclusion: Hypoalbuminemia and raised GLR were not significantly associated however the proportions are higher among those with advanced stage of cancer cervix. Their roles as independent markers could better be established in higher sample sizes and retrospective or prospective study designs.

KEYWORDS

Cancer cervix, Hypoalbuminemia, Granulocyte lymphocyte ratio.

INTRODUCTION:

Cervical cancer is the fourth most frequent cancer in women worldwide, with an estimated 530,000 new cases representing 7.5% of all female cancer deaths. More than 270,000 deaths of those estimated occur from cervical cancer every year and more than 85% of these occur in less developed regions.[1] It ranks second in India with 1,22,844 new cases with age specific incidence rate of 22 per 100,000 and age specific mortality rate of 12.4 per 100,000.[2]

There are two treatment streams for cervical cancer including surgery with or without adjuvant chemotherapy and primary radiation therapy with or without concurrent chemotherapy. Surgery usually performed for early cervical cancer (IB1 to IIA) and primary radiation therapy considered for locally advanced cervical cancer (IIB to IVA). Standard surgery consisted of type III radical Hysterectomy with bilateral pelvic Lymph Node dissection. In spite of the improvement in cancer care, prognosis of cervical cancer remains poor in India as compared to other Asian countries such as China, Thailand, South Korea and Singapore.[2]

Inflammation and cancer are known to have a strong link. The inflammatory markers like cytokines and chemokines such as granulocyte colony stimulating factor, interleukin-1, interleukin-6 and tumour necrosis factor-α, lead to leucocytosis and neutrophilia. Such changes in systemic inflammatory response to tumour cell manifestation or systemic inflammation can be measured easily by blood parameter examination.3 C-reactive protein (CRP), albumin levels, neutrophil-lymphocyte ratio (NLR) may represent potential prognostic markers in many types of cancer.[4,5] Low serum albumin level correlated with malnutrition and weight loss and is also a risk factor for cancer mortality.[6] Though there are multiple independent prognostic predictors for locally advanced cervical cancer viz.,tumor size, lymph node status, International Federation of Gynaecology and Obstetrics (FIGO) stage, and pre-treatment haemoglobin level, in order to improve the treatment outcome of such patients, search for more prognostic factors are still a necessity.[3]

In addition, the role of hypoalbuminemia or increase Granulocyte and Lymphocyte ratio as prognostic markers in patients with cervical cancer have not been elicited in this part of south India. Hence the current study was taken up with the following objectives to elicit if dysregulated systemic inflammatory response in the form of negative acute phase reactant protein (Hypoalbuminemia) and increase Granulocyte and Lymphocyte ratio (GLR) are associated with locally advanced cancer cervix.

Methodology:

This is record based descriptive analysis conducted for a period of 3 years from 1st June 2015 to 30th June 2018. During the study period, a total of 96 newly diagnosed patients with locally advanced carcinoma cervix (FIGO Stages IB2 through IVA) at Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, a Regional Cancer Centre were included.Ethical clearance was obtained from Institutional Ethical Committee. Patients with early cervical cancer (FIGO staging IB1 to IIA), patients who underwent hysterectomy as part of initial treatment; initial radiation therapy / chemotherapy and patients who did not have available pretreatment laboratory data were excluded from the study. Routine baseline biochemistry and haematological investigation were done. The basic data viz., name of the patient, age, stage of cancer was taken from hospital records and also data on blood investigations like total count, granulocytes, lymphocytes, Granulocyte-lymphocyte ratio, Serum Albumin were obtained from laboratory records.

Statistical Analysis: Data were entered in excel and analysed using SPSS version 16.0. Results were presented as proportion, mean ± SD. Categorical variables were analyzed by chi-square test. Correlation of albumin levels and GLR with stages of cancer cervix was determined using spearman's correlation coefficient (r).Logistic regression was

undertaken to assess the various factors associated with hypoalbuminemia and GLR. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were reported. A *P*-value < 0.05 was considered statistically significant.

RESULTS:

The mean age of the study participants was 50 years with a range of 30-70years. Majority (54.1%) of the patients were aged 50 years or younger than that. Highest proportion of patients were in III B stage (57.2%) followed by stage IIB (34.4%) of carcinoma cervix. Nearly 59.0% had grade 2 disease followed by 35% had grade 3. (Table-1)

The mean total leukocyte count was 10806 cells/mm^3 and it ranged from 3200 cells/mm^3 to 28800cells/mm^3. Mean granulocyte and lymphocyte counts were 7.63% and 2.5% respectively. Considering the median of 2.8 for granulocyte lymphocyte ratio (GLR), majority (53.1%) had raised GLR. The mean serum albumin level was 3.9g/dl and nearly 20.0% had hypoalbuminemia. (Table-2)

Though there was no statistical association of hypoalbuminemia and raised GLR with advanced cancer cervix, higher proportion of those with advanced stage (≥ III B Stage) had hypoalbuminemia (≈79.0%) and raised granulocyte lymphocyte ratio (62.7%) (*P*>0.05). (Table-3)

With the progression of stages, GLR increased and albumin decreased significantly (*P*<0.05). (Table 4)(Graph 1)

Though hypoalbuminemia and raised GLR were not significant independent markers for locally advanced carcinoma cervix (≥ III B) staging and histological grading, the risk of hypoalbuminemia and raised GLR were 3 times and 1 time higher among those with advanced stage of ≥ III B compared to lower stages of carcinoma cervix respectively (*P*>0.05). The risk of hypoalbuminemia was also noted to be 1 time higher among those with higher histological grading of 3/4 compared to lower grades of 1/2 (*P*>0.05). Their roles as independent markers could better be established in higher sample sizes and retrospective or prospective study designs.(Tables 5 and 6)

Observing the odds ratio among both hypoalbuminemia and raised GLR, hypoalbuminemia seems to be a better indicator of advanced stage of carcinoma cervix.

DISCUSSION:

The tumour microenvironment and in particular, the inflammatory response play an important role in cancer development and progression and may be associated with systemic inflammation. Measurable parameters in blood that reflect the systemic inflammatory response are elevated C-reactive protein, hypoalbuminemia, increased levels of some cytokines, and increased levels of leucocytes and their subtypes. Biochemical markers of inflammatory response have been incorporated in prognostic scores for several types of cancer.[7]

In the present study, we studied the association of inflammatory response i.e., hypoalbuminemia and increased Granulocyte to lymphocyte ratio in different stages of locally advanced cancer cervix.

The mean age of the study participants in the current study was 50.10±10.64yrs with a range of 30-70years, which is comparable to the findings of Lee YY*et al*.,[8] with a median age of 50 yrs (21-85yrs)and Singh S *et al*., who reported a median age of 52 years (25-92 yrs).[9]In the present study, highest proportion of patients were in III B stage (57.2%) followed by stage IIB (34.4%) which is similar to findings of Singh S *et al*.,who also noted majority of the study subjects in stageIII B (33.7%) at the time of diagnosis followed by stage IIB(22.7).[9]

In this study, the mean total leukocyte count was 10806 cells/mm^3(3200 cells/mm^3 to 28800 cells/mm^3). Mean granulocyte and lymphocyte counts were 7.63% and 2.5% respectively. Chun S *et al*., in his study noted a mean WBC count of 6161.2 ± 1561.6cells/mm^3, mean absolute neutrophil, monocyte and eosinophil count of 3601.6 ± 1308.4, 386.8 ± 135.2 and 120.9 ± 100.3 cells/mm^{3}respectively, mean lymphocyte count of 2045.1 ± 560.7cells/mm^3.Considering the median of 2.8 for granulocyte lymphocyte ratio (GLR), majority (53.1%) had raised GLR which is in contrast to the findings of Chun S *et al*., who considered a cut-off of Neutrophil-Lymphocyte Ratio(NLR) as 2.1, majority (72.6%) had NLR-low.The difference may be due to difference in the cut off values and also staging in which patients are included.[10]

In a study by Nyarota K *et al*., in Zimbabwe has shown 28% of patients having hypoalbuminaemia which is slightly higher than our study (20.0%).[11] In the current study, we noted that though hypoalbuminemia was not a significant independent marker, advanced stage of ≥ III B had 3 times and higher grades of 3/4 had 1-time higher risk of hypoalbuminemia compared to lower stages and grades of carcinoma cervix respectively (*P*>0.05). With the progression of stages, albumin decreased significantly (*P*<0.05).Seebacher V*et al*.,in his study observed that,pre-treatment serum albumin levels were inversely proportionally associated with FIGO tumor stage and histological grade. On multivariable analysis pre-treatment serum albumin levels (*P*<0.05) was independently associated with disease-free and progression-free survival, respectively.[12]Zheng RR *et al*., studied the role of hypoalbuminemia in disease outcome and concluded that decreased serum albumin were associated with shorter overall survival and disease free survival in operable cervical cancer patients.[13]

Though raised GLR was also not a significant independent marker, higher proportion of those with advanced stage (≥ III B Stage) had raised granulocyte lymphocyte ratio (62.7%) (*P*>0.05).Lee YY *et al*.,in his study noted that when the cohort was divided according to the median value of NLR as 1.9, patients with higher NLRs (≥1.9) demonstrated poorer prognoses than participants with lower NLRs which is similar to our study. In comparative analysis of two groups based on the median level of NLR, the higher NLR group (≥1.9) had more advanced stage disease.[8]

Huang QT*et al*., in his study demonstrated significant correlation of Neutrophil-to-Lymphocyte Ratio with advanced FIGO stage (OR 2.12, 95% CI 1.28–3.49) which is similar to the current study findings which showed with the progression of disease staging, GLR increased.[14]

In this study, we observed that among both hypoalbuminemia and raised GLR, hypoalbuminemia seems to be a better indicator of advanced stage of carcinoma cervix which is not been studied in any other studies.

Limitations of this study are inherent to its small sample size and record based. Outcome was not studied because of lack of data.Further studies with higher sample sizes and prospective study addressing the confounders are recommended to establish association.

CONCLUSION:

- With the progression of cancer cervix stages, GLR increased and albumin decreased significantly.
- Higher proportion of the study subjects with advanced stage (≥ III B Stage) of disease had hypoalbuminemia and raised granulocyte lymphocyte ratio compared to lower stages of the disease.

Table 1: Distribution of the study participants based on age, staging and grading of carcinoma cervix

Particulars	n (%)
Age in years (Mean±SD)	50.10±10.64
30-40 yrs	20 (20.8)
41-50 yrs	32 (33.3)
51-60 yrs	26 (27.1)
61-70 yrs	18 (18.8)
Stage	
II A	01 (1.1)
II B	33 (34.4)
III A	03 (3.1)
III B	55 (57.2)
IV A	03 (3.1)
IV B	01 (1.1)
Grades	
Grade 1	04 (4.1)
Grade 2	57 (59.4)
Grade 3	34 (35.4)
Grade 4	01 (1.1)

Table 2: Means of blood parameters among the study participants

Blood Parameters	Mean ± SD
Total Count (cells/ mm^3)	10806±4433 (3200 – 28800)
Granulocyte	7.63%±3.84%
Lymphocyte	2.50%±0.96%
G/L ratio¥	2.8 (1.10 – 8.90)

<2.8 ♣	45 (46.9)
≥2.8 ♣	51 (53.1)
Albumin levels (g/dl)	3.90±0.61
Hypoalbuminemia♣	19 (19.8)

¥ - Median (Range); ♣- frequency (%)

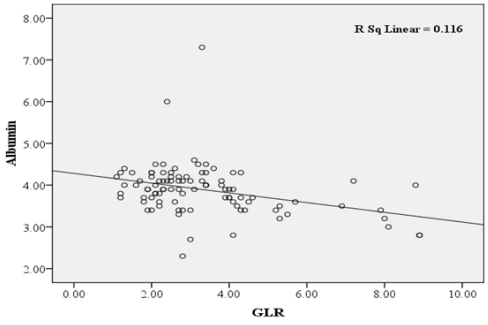
Table 3: Means of blood parameters among the study participants

Particulars	< III B Stage	≥ III B Stage	χ2 – value (P-value)
Hypoalbuminemia			
Present	33 (21.1%)	44 (78.9%)	3.06 (0.08)
Absent	04 (42.9%)	15 (57.1%)	
Granulocyte /Lymphocyte ratio			
<2.8	18 (40.0%)	27 (60.0%)	0.08 (0.78)
≥2.8	19 (37.3%)	32 (62.7%)	

Table 4: Correlation of staging, granulocyte lymphocyte ratio and albumin levels

Variables	GLR	Albumin
Staging	r = 0.22 P = 0.03*	r = - 0.25 P= 0.01*
Albumin	r = - 0.34 P= 0.001*	-

* indicates significant correlation at P<0.05



Graph 1: Correlation between granulocyte lymphocyte ratio and albumin levels

Table 5: Logistic regression of various factors with hypoalbuminemia

Particulars	Hypoalbuminemia		OR (95% C.I)	P-value
	Present	Absent		
Age in years				
≤50	13 (25.0%)	39 (75.0%)	1	0.14
>50	06 (31.6%)	38 (86.4%)	0.44 (0.15 – 1.32)	
Staging				
< III B Stage	04 (10.8%)	33 (89.2%)	1	0.07
≥ III B Stage	15 (25.4%)	44 (74.6%)	2.97 (0.89 – 9.91)	
Grading				
Grade 1/2	12 (19.7%)	49 (80.3%)	1	0.87
Grade 3/4	07 (20.0%)	28 (80.0%)	1.09 (0.37 – 3.25)	

Table 6: Logistic regression of various factors with GLR

Particulars	GLR (Median - 2.8)		OR (95% C.I)	P-value
	Raised (≥2.8)	Not raised (<2.8)		
Age in years				
≤50	22 (42.3%)	30 (57.7%)	1	0.36
>50	23 (52.3%)	21 (47.7%)	0.68 (0.30 – 1.55)	
Staging				
< III B Stage	18 (48.6%)	19 (51.4%)	1	0.72
≥ III B Stage	27 (45.8%)	32 (54.2%)	1.16 (0.51 – 2.67)	
Grading				
Grade 1/2	27 (44.3%)	34 (55.7%)	1	0.56
Grade 3/4	18 (51.4%)	17 (48.6%)	0.78 (0.33 – 1.81)	

REFERENCES:

1. http://www.who.int/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer
2. Jain A, Bobdey S, Sathwara J, Ganesh B, Saoba S, Khan A. Role of monocyte and lymphocyte counts in prognosis of cervical cancer. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2017 Feb 23;5(7):2243-9.
3. Wang YY, Bai ZL, He JL, Yang Y, Zhao R, Hai P, Zhe H. Prognostic value of neutrophil-related factors in locally advanced cervical squamous cell carcinoma patients treated with cisplatin-based concurrent chemoradiotherapy. Disease markers. 2016;2016.
4. Badora-Rybicka A, Nowara E, Starzyczny-Słota D. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio before chemotherapy as potential prognostic factors in patients with newly diagnosed epithelial ovarian cancer. ESMO open. 2016 Mar 1;1(2): e000039.
5. Jomrich G, Paireder M, Gleiss A, Kristo I, Harpain L, Schoppmann SF. Comparison of Inflammation-Based Prognostic Scores in a Cohort of Patients with Resectable Esophageal Cancer. Gastroenterology research and practice. 2017;2017.
6. He X, Li JP, Liu XH, Zhang JP, Zeng QY, Chen H, Chen SL. Prognostic value of C-reactive protein/albumin ratio in predicting overall survival of Chinese cervical cancer patients overall survival: comparison among various inflammation based factors. Journal of Cancer. 2018;9(10):1877.
7. Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, Leibowitz-Amit R, Sonpavde G, Knox JJ, Tran B, Tannock IF. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. JNCI: Journal of the National Cancer Institute. 2014 Jun 1;106(6).
8. Lee YY, Choi CH, Kim HJ, Kim TJ, Lee JW, Lee JH, Bae DS, Kim BG. Pretreatment neutrophil: lymphocyte ratio as a prognostic factor in cervical carcinoma. Anticancer research. 2012 Apr 1;32(4):1555-61.
9. Singh S, Himler J, Nagel CI, Resnick K. The prognostic value of baseline lymphocyte, neutrophil, and monocyte counts in locally advanced cervical carcinoma treated with radiation. Obstetrics and gynecology international. 2017;2017.
10. Chun S, Shin K, Kim KH, Kim HY, Eo W, Lee JY, Namkung J, Kwon SH, Koh SB, Kim HB. The Neutrophil-Lymphocyte Ratio Predicts Recurrence of Cervical Intraepithelial Neoplasia. Journal of Cancer. 2017;8(12):2205.
11. Nyarota K, Zhou DT. Albumin and Total Protein in Cancer Patients at Radiotherapy Clinic, Zimbabwe.
12. Seebacher V, Grimm C, Reinthaller A, Heinze G, Tempfer C, Hefler L, Polterauer S. The value of serum albumin as a novel independent marker for prognosis in patients with endometrial cancer. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2013 Nov 1;171(1):101-6.
13. Zheng RR, Huang M, Jin C, Wang HC, Yu JT, Zeng LC, Zheng FY, Lin F. Cervical cancer systemic inflammation score: a novel predictor of prognosis. Oncotarget. 2016 Mar 22;7(12):15230.
14. Huang QT, Man QQ, Hu J, Yang YL, Zhang YM, Wang W, Zhong M, Yu YH. Prognostic significance of neutrophil-to-lymphocyte ratio in cervical cancer: A systematic review and meta-analysis of observational studies. Oncotarget. 2017 Mar 7;8(10):16755.