Original Article

DOI: 10.7860/JCDR/2023/60820.17488

Association of Thrombocytosis and its Prognostic Significance in Cervical Cancer

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ABSTRACT

Introduction: Thrombocytosis is associated with progression of many diseases. There is increasing evidence that tumour cells, platelets, endothelial cells interact with each other leading to spread of tumour cells into the microvasculature which results in poor prognosis due to metastasis. Thrombocytosis is an indirect marker of occult advanced disease.

Aim: To determine thrombocytosis in diagnosed carcinoma cervix patients and its association with stage of cancer cervix and prognosis.

Materials and Methods: This was the retrospective study conducted at Sri Devaraj Urs Medical College, Kolar, Karnataka, India, from April 2021 to May 2022, on medical records of 52 patients who were diagnosed with cancer cervix. The data abstracted from each subject's medical record include the following: age, parity, clinical staging as per International Federation of Gynaecology and Obstetrics (FIGO), size of the lesion, complete blood count and length of the survival. Patients underwent surgery followed by appropriate chemo-radiotherapy or brachytherapy. They were followed-up after treatment every three months for the first two years and every six months for the next three years and annually thereafter. The five-year survival rate of these patients who were on complete follow-up was analysed. The normal platelet count was considered as 4.5×10^9/L. Data was entered into Microsoft excel data sheet and was analysed using Statistical Package for Social Sciences (SPSS) version 22.0.

Results: The mean age of the study population was 50.28 years. Among the 52 patients, 47 (90.03%) were with advanced stages of cancer cervix (stages IIB-IVB) and 5 (9.6%) belonged to early stages of cancer cervix (stages 1B-IIA). Forty patients (76.92%) had a platelet count less than 4.5×10^9/L, out of which 2 patients were in early stage of cervical cancer and 16 patients were with tumour size less than 4 cm. A total of 12 patients had the platelet count more than 4.5 lac. All these 12 patients belonged to advanced stages of cancer cervix (stage IIB-IVB), p-value of 0.001. Among the 12, 11 patients had a tumour size of more than 4 cm, p-value 0.040. The mean five-year survival rate among patients with advanced stages of cancer cervix associated with thrombocytosis was 18%.

Conclusion: The platelet count was found to have strong association with the tumour size, stage of the cervical cancer and five year survival rate thus making thrombocytosis to be a strong prognostic factor in cancer cervix.

Keywords: Cervical carcinoma, Increased platelet count, Survival rate

INTRODUCTION

Cervical carcinoma is the most common gynaecological malignancy in developing countries and the third most widespread malignancy worldwide [1]. It has been estimated that 800,000 new cases of cancer occur every year, according to the Indian Ministry of Health and Family Welfare association [2]. Carcinoma cervix affects about 16 per 10,000 women in a year and kills 9 per 100,000 per year [3]. In India, 1,34,000 were diagnosed to have cervical cancer, of which 72,825 women died due to the same [4].

It is essential to recognise prognostic factors to anticipate treatment outcomes because such predictors aid in clinical management by guiding treatment mode selection, developing appropriate follow-up protocols, and determining prognosis [5]. Proinflammatory cytokine upregulation, such as Interleukin-6, has been linked to cervical cancer development and progression via a variety of mechanisms, including synthesis, activation, and aggregation of platelets [6]. There is mounting evidence that inflammatory cytokines in the tumour microenvironment play an important role in the development of a variety of tumours [7]. Pretreatment thrombocytosis has been linked to a poor prognosis of cervical cancer in several studies as a projection of systemic inflammatory response [8].

The knowledge about relation between the inflammation and the progression of cancer cervix is not well established. Platelets have an important function in haemostasis and vascular integrity. Cytokines that are responsible for thrombopoiesis are elevated in many cancers resulting in thrombocytosis. A retrospective study proved that systemic inflammatory response markers in the blood have relationship with clinico-pathological characteristics of the patient and disease outcome in cancer cervix patients. Patients with more depth of stromal invasion, advanced stage, and tumour size greater than 2 cm have a significantly higher white blood cell count plus monocyte-lymphocyte ratio (NM/L) and platelet-lymphocyte ratio (P/L), which is associated with a poor prognosis [9].

A meta-analysis concluded that clinico-pathological factors such as age, cell type, depth of tumour invasion, the FIGO stage, haemoglobin level, histological grade, leukocytosis, lymph node involvement, lympho-vascular space invasion, neutrophil-to-lymphocyte ratio, parametrial invasion, platelet-to-lymphocyte ratio, resection margin, squamous cell carcinoma antigen level, thrombocytosis, tumour grade, tumour size, and tumour volume has prognostic influence on overall survival and disease free survival in cancer cervix patients [10]. Hence, the aim of this study was to determine thrombocytosis in diagnosed carcinoma cervix patients and its association with stage of cancer cervix and prognosis in cancer cervix patients.

MATERIALS AND METHODS

A retrospective study was conducted at the Sri Devaraj Urs Medical College, Kolar, Karnataka from April 2021 to May 2022. The

Institutional Ethics Committee approval was obtained (DMC/KLR/IEC/117/2022-23).

Inclusion criteria: Histopathologically proven carcinoma cervix patients as primary disease with complete medical records.

Exclusion criteria: Recurrent carcinoma cervix and other gynaecological malignancies, patients whose required medical records were inadequate, those patients who discontinued the treatment or lost follow-up post-treatment were excluded from the study.

Sample size calculation: was done by using the proportion of late stage cancer cervix in cancer cervical patients was 84% from the study conducted by Rathod A et al., using the formula [1]:

$$\frac{Z^2_{(1-\alpha/2)}P(1-P)}{d^2}$$

$Z_{(1-\alpha/2)}$ is standard normal variate, at 5% type 1 error (p-value <0.05)=1.96.

As in majority of studies, p-values are considered significant below 0.05 hence 1.96 is used in formula.

P=Expected proportion [1], d=Absolute error or precision, P=84% or 0.84, q=16% or 0.16, d=10% or 0.10.

Using the above values at 95% Confidence level a sample size of 52 subjects with cancer cervix needed to be included in the study.

Study Procedure

The medical records of 102 patients were retrospectively reviewed and included. The data abstracted from each subject's medical record included the following: age, parity, clinical staging as per FIGO, size of the lesion, complete blood count and length of the survival. Based upon the inclusion and exclusion criteria, 52 patients were selected for the study.

Patients with early stage of cancer cervix (stage IA-IIA) underwent surgery followed by chemoradiation or brachytherapy. Patients with advanced stage of cancer cervix (stage IIB-IVB) underwent chemoradiation or brachytherapy. The surgery done was radical hysterectomy with bilateral pelvic lymph node dissection for early stage cancer cervix patients. In advanced stage disease, the drugs used for chemotherapy were Cisplatin and Paclitaxel. The radiotherapy given was external beam radiation of 50 Gy per day for five days in a week for five weeks. Postchemoradiation, depending on the regression or progression of the disease, intracavitary brachytherapy was given to the patients of advanced stage cancer cervix. For early stage disease, the need for chemoradiation or brachytherapy, postsurgery, was decided upon individual approach. In the institute, the study was conducted, after completion of the treatment, patients were followed-up every three months for first two years, six months for the next three years and annually thereafter. The five-year survival rate of these patients who were on complete follow-up was analysed.

Thrombocytosis was considered as platelet count of more than 4.5×10^9/L. The study evaluated the association between platelet count with stage of cancer cervix, tumour size and five-year survival rate and to see if platelet count has an influence in all these factors.

STATISTICAL ANALYSIS

Data was entered into Microsoft excel data sheet and was analysed using Statistical Package for Social Sciences (SPSS) version 22.0 (IBM SPSS Statistics, Somers NY, USA). Categorical data was represented in the form of frequencies and proportions. Chi-square test or Fischer's-exact test was used as test of significance for qualitative data. Microsoft (MS) Excel and MS word was used to obtain various types of graphs. The p-value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

RESULTS

Total of 52 diagnosed cancer cervix patients have been included in this study. The majority were between 51-60 years of age. The mean age of the study population was 50.28 years. A total of 47 patients (90.03%) were with advanced stages of cancer cervix (stages IIB-IVB) and 5 patients (9.6%) belonged to early stages of cancer cervix (stages 1B-IIA).

Forty patients had platelet count less than 4.5×10^9/L and 12 had platelet count more than 4.5×10^9/L. A majority (35) had tumour size ≥4 cm [Table/Fig-1]. All the 12 patients (100%) with increased platelet count belonged to advanced stages of cancer cervix (stage IIB-IVB). There was a statistically significant difference found between increased platelet counts and staging [Table/Fig-2].

Demographic details	N (%)
Age (years)	
31-40	8 (15.4)
41-50	20 (38.5)
51-60	21 (40.4)
>60	3 (5.8)
Mean±SD, (years)	50.28±9.14
Parity	
0	1 (1.9)
1	5 (9.6)
2	19 (36.5)
3	11 (21.2)
4 and above	16 (30.8)
Stage of cervical cancer	
3B	17 (32.7)
3C	2 (3.8)
4A	11 (21.2)
4B	3 (5.8)
Platelet count	
$<4.5\times10^9$/L	40 (77%)
$>4.5\times10^9$/L	12 (23%)
Size of the tumour	
<4 cm	17 (32.7)
≥4 cm	35 (67.3)

[Table/Fig-1]: Demographic data, clinical and laboratory investigation data of the participants; (Stage of Cervical cancer denotes advanced stage patients, hence N=33).

Stage	$<4.5\times10^9$/L, N (%)	$<4.5\times10^9$/L, N (%)	p-value
IB	2 (100.0%)	0	0.001
2A	3 (100.0%)	0	
2B	12 (100.0%)	0	
3A	2 (100.0%)	0	
3B	15 (88.2%)	2 (3.8%)	
3C	1 (50%)	1 (50%)	
4A	5 (45.5%)	6 (54.5%)	
4B	0	3 (100%)	

[Table/Fig-2]: Distribution of subjects according to platelet count and cancer staging.

In patients with platelet count of more than 4.5×10^9/L, only one had tumour size less than 4 cm and rest of the 11 patients had tumour size of more than 4 cm. There was a statistically significant difference found between platelet and tumour size [Table/Fig-3]. There was no

statistically significant difference found between parity and staging [Table/Fig-4]. Among the 12 patients with thrombocytosis, only two patients survived for more than 5 years, rest of the 10 patients survived less than 5 years [Table/Fig-5].

Tumour size	<4.5×10^9/L N (%)	>4.5×10^9/L N (%)	p-value
<4 cm	16 (94.1%)	1 (5.9%)	0.040
>4 cm	24 (68.57%)	11 (31.43%)	

[Table/Fig-3]: Distribution of subjects according to platelet and tumour size.

Stage	1 N (%)	2 N (%)	3 N (%)	4 and above N (%)	p-value
IB	0	0	0	2 (100.0%)	0.781
2A	1 (33.3%)	2 (66.7%)	0	0	
2B	1 (8.3%)	5 (41.7%)	1 8.3%	4 (33.3%)	
3A	0	0	1 50.0%	1 (50.0%)	
3B	1 (5.9%)	8 (47.1%)	5 29.4%	3 (17.6%)	
3C	0	1 (50.0%)	1 50.0%	0	
4A	2 (18.2%)	2 (18.2%)	2 18.2%	5 (45.5%)	
4B	0	1 (33.3%)	1 33.3%	1 (33.3%)	

[Table/Fig-4]: Distribution of subjects according to parity and staging.

Variables	<4.5×10^9/L N (%)	>4.5×10^9/L N (%)	p-value
No	10 (25%)	10 (83.33%)	<0.002
Yes	30 (75%)	2 (16.66%)	

[Table/Fig-5]: Distribution of subjects according thrombocytosis and five-year survival post-treatment.
Yes: patients survived for five years and more No: patients survived less than five years

DISCUSSION

The association between platelet count and malignancy was initially reported by Levin J and Conley L in 1964 [9]. Yu M et al., proved that pretreatment thrombocytosis was a prognostic indicator in gynaecological malignancies [8]. Cheng J et al., discovered that cervical cancer patients with a pretreatment elevated platelet count are more likely to present with advanced clinical staging, lymph node metastasis, and a bigger tumour size, all of which are signifiers of a poor prognosis and aggressive behaviour of disease [11].

In this study, according to FIGO staging, cancer cervix patients were from stage I-IV. Among the 52 patients, 47 (90.03%) were with advanced stages of cancer cervix (stages IIB-IVB) and 5 patients (9.6%) belonged to early stages of cancer cervix (stages 1B-IIA). Among the 52 cancer cervix patients in this study 17 (32.7%) patients had tumour size of less than 4 cm and 35 patients (67.3%) had tumour size of more than or equal to 4 cm.

Stone RL et al., observed in his study that in ovarian cancer, thrombocytosis can be a part of paraneoplastic syndrome because tumour derived Interleukin-6 can itself cause increased thrombopoiesis resulting in thrombocytosis and tumour progression [12]. Non white race, larger lesion size (greater than 4 cm), platelet count greater than 300,000/microL, and the presence of nodal metastases were factors related to poor prognosis [13].

As per World Health Organisation, thrombocytosis is defined as platelet count equal to or more than 450×10^9/L. In this study the same value was taken and compared with the stage of cancer cervix at diagnosis and with tumour size. In this study, 13 patients with advanced stages of cancer cervix had thrombocytosis. Eleven patients (31.43%) had larger tumour size along with thrombocytosis. Platelet count before chemotherapy above the median value of 272,000/L was associated with a trend for shorter recurrence-free survival and a significantly shorter overall survival when compared to a lower platelet count, according to Gadducci A et al., [14].

As per American Cancer Society, the five year survival rate for cancer cervix patients with localised disease is 92%, regional disease is 58% and with metastatic disease is 18% [15]. In the current study, among the 12 patients with thrombocytosis, only two survived for more than five years. Overall, stage, lymph node positivity, lymph-vascular space invasion, parametrial and/or surgical margin status, and platelet count before treatment are predictive factors of health outcome in cervical cancer. The strengths in this study to our knowledge are that it is a comprehensive study on the association of platelet count and survival in cancer cervix patients. Platelet count is a common and simple measure that can be easily collected in a routine complete blood count with which the prognosis of a cancer cervix patient can be analysed.

Limitation(s)

Long-term follow-up is required for advanced stages of cancer cervix cases. The sample size was limited in this study.

CONCLUSION(S)

From the study, the authors conclude that those patients who had increased platelet count (thrombocytosis) were presented in advanced stages of cancer cervix and most of them had a tumour size of more than 4 cm. Out of those 12 patients, only two of them survived for more than five years. The retrospective analysis from this study shows that the platelet count has a strong association with the tumour size, stage of the cervical cancer and five year survival rate. Hence, elevated platelet count can be considered as one of the bad prognostic factor in patients with cancer cervix.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Oct 29, 2022
- Manual Googling: Nov 22, 2022
- iThenticate Software: Dec 30, 2022 (23%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Oct 18, 2022**
Date of Peer Review: **Nov 26, 2022**
Date of Acceptance: **Jan 18, 2023**
Date of Publishing: **Feb 01, 2023**