Original Article

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Prognostic Significance of Pretreatment Derived Hematological Markers and Serum Biochemical Parameters on the Overall Survival Rate in Individuals Diagnosed with Cervical Cancer Undergoing Curative Surgery

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Abstract

<u>*Objectives:*</u> This study aims to evaluate the prognostic value of pretreatment hematological and biochemical markers, including serum albumin, globulin, and alkaline phosphatase, on overall survival in cervical cancer patients who have undergone curative surgery. <u>*Materials and Methods:*</u> This retrospective cohort study was conducted at Malabar Cancer Centre, Kerala, analyzing data from cervical cancer patients in FIGO stage 1, who underwent surgery between January 2018 and February 2024. Key hematological and biochemical parameters were evaluated, and Kaplan-Meier analysis was performed to assess overall survival, with statistical significance set at $p < 0.05$. <u>*Results:*</u> The study analyzed the overall survival of 35 cervical cancer patients in relation to hematological indices such as LMR, NLR, PLR, MPVP and ALBALKP, along with the impact of co-morbidities and FIGO staging. Statistical analysis revealed no significant differences in survival outcomes across different LMR, NLR, PLR, MPVP and ALBALKP groups ($p > 0.05$). Additionally, FIGO staging showed that most cases were diagnosed in early invasive stages, and co-morbidities like diabetes and hypertension were common among patients. <u>*Conclusion:*</u> Tumor stage and co-morbid conditions significantly influenced survival markers LMR, NLR, PLR, MPVP, and ALBALKP showed no statistically significant association, highlighting the need for further research with larger cohorts to confirm their prognostic value.

Keywords: *Cervical cancer, Lymphocyte Monocyte Ratio, Neutrophil Lymphocyte Ratio, Platelet Lymphocyte Ratio, Albumin Alkaline Phosphatase Ratio, Mean Platelet Volume platelet count ratio, Overall Survival.*

Introduction

Cervical cancer constitutes a substantial share of the overall cancer burden among women worldwide, with the majority of this burden being borne by low- and middle-income countries. Furthermore, within countries with ample resources, marginalized and underserved populations may experience a higher incidence of cervical cancer and face poorer outcomes [1]. A systematic review and meta-analysis conducted in the UK, Finland, USA, Sweden, etc., published 13 years ago revealed an incidence rate (IR) of 56 per 100,000 woman-years for cervical cancer following treatment for cervical intraepithelial neoplasia (CIN). This rate was considered three times higher than the anticipated incidence in the United Kingdom [2]. Definitive concurrent chemo radiotherapy (CCRT)

with a cisplatin-based regimen is the established standard for treating locally advanced cervical cancer (LACC). Nevertheless, approximately one-third of cervical cancer patients encounter recurrence, with the majority experiencing it within two years following the completion of therapy [3]. Hence, precise prognosis prediction plays a crucial role in enhancing the survival prospects of patients who could potentially gain from adjuvant treatment or vigilant monitoring. The acknowledged connection between inflammation and cancer development, along with the assessment of various prognostic markers rooted in systemic inflammation, has been extensively explored for predicting the prognosis of cancer patients [4]. Particularly, alterations in both biochemical and hematological parameters have been identified as adverse prognostic indicators in various cancers, including cervical cancer [5-8].

The primary approach for treating early-stage cervical cancer (International Federation of Gynecology and Obstetrics (FIGO) stage IA2–IIA) involves surgery, radiation, and chemotherapy [9]. A crucial aspect of the surgical treatment is bilateral pelvic lymph node dissection, with or without para-aortic lymph node sampling. Currently, the assessment of cervical cancer progression or recurrence relies mainly on postoperative prognostic factors. To enhance risk stratification for recurrence and guide personalized adjuvant therapy after surgery, there is a notable interest in identifying new prognostic biomarkers. In particular, there is a focus on exploring inflammatory factors as potential biomarkers due to their cost-effectiveness and widespread availability.

There are advantages in cervical cancer treatment so far, even though the outcome is poor. Therefore, it is necessary to find a sensitive and straightforward index for the diagnosis of cervical cancer. The host inflammatory response to cancer is believed to determine disease progression. Current evidence reveals that within a tumor tissue and beside cancer cells, host structures like the extracellular matrix, non-immune cells like fibrous tissue cells, and immune cells—namely white blood cells, mast cells, natural killer cells, and dendritic cells—interact and contribute to a highly immunosuppressive microenvironment [10]. Lymphocytes have an important role in this tumor microenvironment since a progressive increase in tumor-infiltrating lymphocytes is directly correlated with antitumor activity [11]. Many studies were conducted to prove the importance of the lymphocyte-monocyte ratio (LMR) and neutrophil-lymphocyte ratio (NLR) in the progression and immunological response of colorectal cancer [12,13]. Platelet-to-lymphocyte ratio (PLR) as well as platelet count (PC) have been used as useful tests since their value may indicate the immune response in patients with malignancies (10). The mean platelet volume platelet count ratio (MPVP) has been widely studied for the diagnosis of malignant tumors, including hepatocellular carcinoma, pancreatic cancer, and lung cancer. However, only a few studies have reported the impact of derived hematological parameters and biochemical markers in patients with cervical cancer [14]. There have been no reported studies we found on the blood cell parameters derived from cervical cancer patients and their association with overall survival after undergoing curative surgical treatment. The albumin-to-alkaline phosphatase ratio (ALB/ALKP), initially introduced as an indicator for nutritional status and immune response, has recently emerged as a prognostic factor in various cancer types. Despite its recognized significance in cancer prognosis, its efficacy in the context of cervical cancer treatment remains uncertain [15]. The objective of this study was to evaluate the prognostic significance of pretreatment hematological and serum albumin, globulin, and alkaline phosphatase on the overall survival (OS) in cervical cancer patients who underwent surgery.

Methodology

The study was conducted in Malabar cancer centre (MCC) Postgraduate Institute of Oncology Sciences & Research, an autonomous unit under government of Kerala situated in north Kerala, India. MCC is a reference level cancer hospital and the Walk in patients from neighboring states is also getting benefits from this reference level hospital because of its geographical location. This study will be conducted in division of Biochemistry, a medium sized lab with more than 400 samples per day, well equipped with fully automated analyzers under the department of clinical laboratory services and translational research. The study design was Retrospective cohort analysis. The Study period was from 1st January 2018 to 31stDecember 2023. Study was conducted and patients' data retrieved between February 1st 2024 to December 31st 2024. The Study Population was cervical cancer patients undergone surgery, registered in MCC from January1st 2018 to December 31st 2021. Cervical cancer patients undergone surgery from January 2018 to February 1st 2024 with completed data used for the study available in the medical records were included in the study. Patient files with missing data of Complete Blood Count (CBC) and biochemical parameters before treatment was excluded from the study. The data was abstracted from medical records of cervical cancer patients from Malabar Cancer Centre. Principal Investigator and Co-Investigators were responsible for data abstraction. Approximately 50 patients with cervical cancer registered in MCC per year. Thus, data of around 30 patients' undergone surgery were included in the study. The data pertaining to patients was derived from record review of case papers available in the Medical Records Department of MCC. Approval of Institutional Review Board was obtained for conducting this study. While names of patients were referred to compare data across registers, the data abstraction form was containing the name or any other personal identifiers. The following clinical and laboratory parameters available at the time of diagnosis: UHID No., age, CBC values, Albumin, globulin and ALP values were collected. The Lymphocyte monocyte ratio (LMR), neutrophil lymphocyte (NLR) ratio, platelet-to-lymphocyte ratio (PLR), Mean platelet volume and platelet count ratio (MPVP) and albumin ALP ratio (ALBALKP) were calculated. Then the overall survivals of the patients were checked for three year from the initial investigations.

Statistical Analysis

Double data entry was done in EpiData entry (V3.1) by Principal Investigator and Co-Investigators. Both the data bases were compared. All discrepancies in data entry were resolved by referring to the original data abstraction form. This finalized database was securely locked. A duplicate version of the finalized database was used for statistical analysis using EpiData analysis software (version 2.2.2.183, EpiData Association, Odense, Denmark. Quantitative variables were reported as mean ± SD or median (IQR) depending on the normality distribution of data. Qualitative variables were reported in percentage and proportions. Kaplen Meier analysis was done for the overall survival. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 35 cases were included in the study, among which three patients succumbed to the disease. The overall survival of the study population was analyzed in relation to derived hematological parameters, including the LMR, NLR, PLR, MPVP and ALBALKP. The impact of co-morbidities like hyper tension, diabetes mellitus,

cardiovascular disease and FIGO staging in relation to overall survival among cervical cancer cases were also studied. Statistical analysis revealed the association between these hematological indices and survival outcomes.

**Impact of co morbidities and FIGO staging in overall survival of cervical cancer cases**

The frequency of various co morbidities in patients with cervical cancer was analyzed to assess their impact on overall survival. The co morbidities evaluated included diabetes mellitus, hypertension, cardiovascular disease, and other medical conditions, with their significance tested statistically. Additionally, FIGO staging was examined to determine its potential influence on overall survival. In this study, 55.1% of patients had at least one co morbidity. Among them, diabetes mellitus was the most prevalent, affecting 42.4% of patients, followed by hypertension in 24.2%. Cardiovascular disease was observed in 6.1% of cases, while 15.2% had other co morbid conditions. The distribution of cervical cancer cases according to FIGO staging was analyzed. The majority of patients were diagnosed at Stage IB1 (42.4%), followed by Stage IB2 (30.3%), indicating that a significant proportion of cases were detected in the early invasive stages of the disease. Stage IA1 and IA2 accounted for 18.2% and 9.1% of cases, respectively, representing the earliest forms of micro invasive cervical cancer (**Table 1**).

Table 1: Frequency of FIGO staging in cervical cancer cases

Stage	Frequency	Percentage
I A1	6	18.2
1 A2	3	9.1
1B1	14	42.4
1 B2	10	30.3

Significance of Lymphocyte Monocyte Ratio (LMR) in overall survival of cervical cancer

The study population was categorized into three LMR groups: Low LMR group <2, Intermediate 2–5, and High LMR Group >5. Survival rates were high across all groups, with 87.5% (7 out of 8 cases censored) in the <2 group, 92.3% (12 out of 13 cases censored) in the 2–5 group, and 91.7% (11 out of 12 cases censored) in the >5 group. The Log-Rank test revealed that there is no statistically significant difference in survival among the groups (p = 0.947) (**Figure 1**).
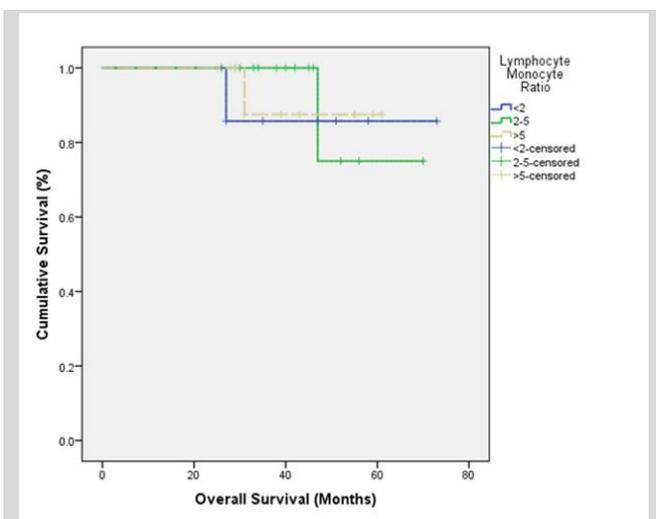
Figure 1: Log rank Test on Lymphocyte Monocyte Ratio (LMR) groups in Overall Survival in Cervical Cancer Patients

Significance of Neutrophil-Lymphocyte Ratio Group (NLR) in overall survival of cervical cancer

Various studies have shown that a high neutrophil-to-lymphocyte ratio (NLR) is linked to poorer overall survival (OS) in cervical cancer patients. The present study population was stratified into three NLR groups: <1, 1–3, and >3. The survival rates observed were 100% in the <1 group (1 case, fully censored), 94.7% in the 1–3 group (18 out of 19 cases censored), and 84.6% in the >3 group (11 out of 13 cases censored). Statistical analysis using the Log-Rank test demonstrated no significant difference in survival among the groups (p = 0.513) (**Figure 2**). Although the difference between groups with an NLR above 3 and those with an NLR of 1 is not statistically significant, a subtle difference in survival rates is observed, decreasing from 100% to 84.6%, which is a 15 percentage decline.
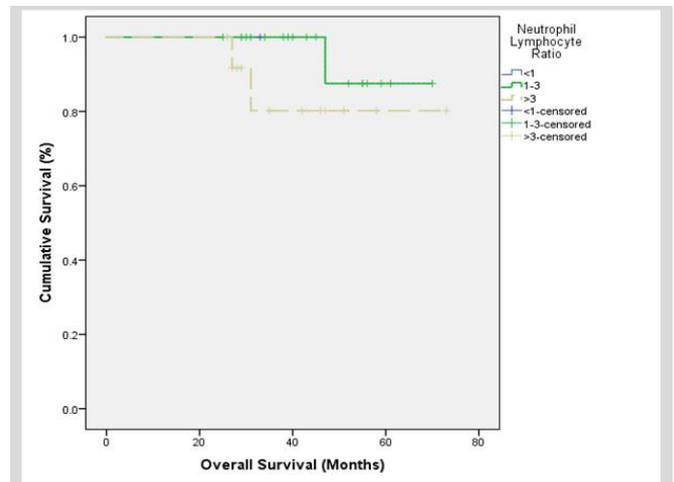
Figure 2: Log rank Test on Neutrophil Lymphocyte Ratio (LMR) groups in Overall Survival in Cervical Cancer Patients showed no significant difference in survival among the groups (p = 0.513)

Significance of Platelet Lymphocyte Ratio (PLR) in overall survival of cervical cancer

The study population was categorized into three PLR groups: <100, 100–300, and >300. The survival rates observed were 100% in the <100 group (all 5 cases censored), 90.0% in the 100–300 group (18 out of 20 cases censored), and 87.5% in the >300 group (7 out of 8 cases censored). Statistical analysis using the Log-Rank test showed no significant difference in survival among the groups (p = 0.665) (**Figure 3**). Even though the results are not statistically significant, a trend of decreasing survival rate is observed, which could be a possible effect of the relatively low sample size.
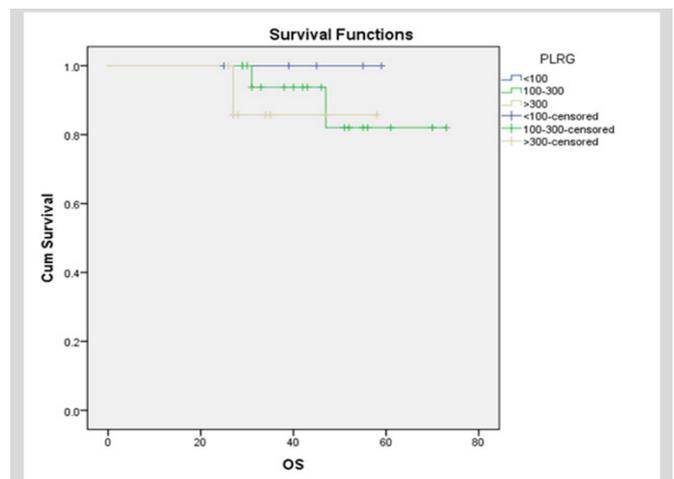
Figure 3: Log rank Test on Platelet Lymphocyte Ratio (PLR) groups in Overall Survival in Cervical Cancer Patients showed no significant difference in survival among the groups (p = 0.665)

**Significance of Mean Platelet Volume platelet count ratio (MPVP) in overall survival of cervical cancer**

All cases analyzed belonged to a single category with MPVP values greater than 0.07. Due to the absence of variability between groups, no comparative statistical analysis could be performed. The overall survival rate was 90.9%, with 30 out of 33 cases being censored during the study period (**Figure 4**).
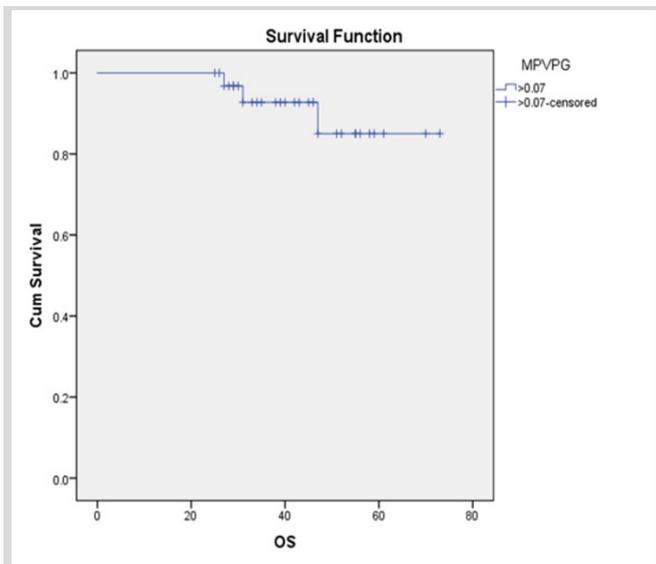
Figure 4: Mean Platelet Volume (MPV) in Overall Survival in Cervical Cancer Patients showed no significant difference in survival among the groups

Significance of Albumin alkaline phosphatase ratio (ALBALKP) in overall survival of cervical cancer

The ALBALKP is emerging as a potential prognostic marker in cervical cancer, particularly in assessing overall survival (OS). In the present study the survival distributions for different levels of ALBALKP were assessed using the Log-Rank (Mantel-Cox) test. The analysis yielded a chi-square value of 0.361 with a significance level (p-value) of 0.548. These results indicate that there was no statistically significant difference in survival distributions between the groups, suggesting that ALBALKP levels did not have a notable impact on survival outcomes in this study (**Figure 5**).
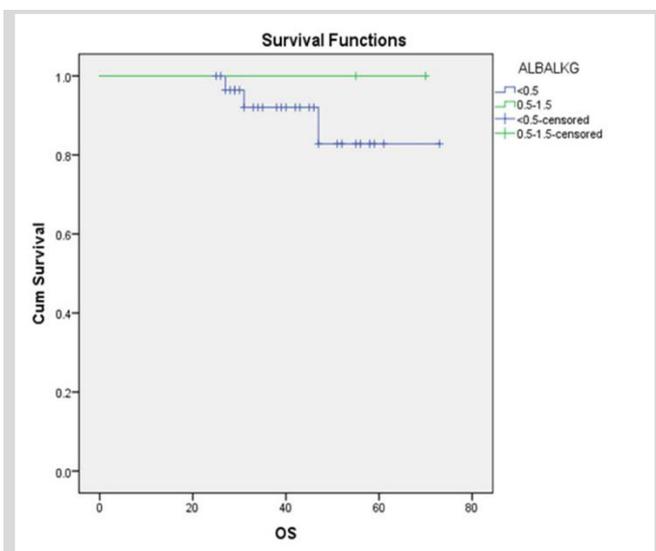
Figure 5: Albumin alkaline phosphatase ratio in Overall Survival in Cervical Cancer Patients showed no significant difference in survival among the groups

Discussion

The prognosis and survival of cervical cancer patients are largely determined by the tumor stage and grade at diagnosis, along with the efficacy of contemporary treatment strategies. Effective management requires accurate staging and a multidisciplinary approach involving surgery, radiation therapy, and chemotherapy. In developed countries, disease control is achieved in up to 95% of early-stage cases and around 85% of advanced-stage cases within three years of initiating treatment [16]. The primary treatment for early-stage cervical cancer (FIGO stage IA-IB1) typically involves radical hysterectomy with lymph node dissection and/or radiation therapy, with or without chemotherapy [17,18]. For patients with early-stage cervical cancer, surgery followed by adjuvant therapy is preferred to maintain a consistent treatment approach among study participants. A cone biopsy is considered sufficient for stage IA1 disease. However, for patients with stage IA1 with lympho vascular space invasion or stage IA2 disease, a cone biopsy with negative surgical margins and pelvic lymph node dissection is recommended [16]. This study aims to evaluate the prognostic significance of pre-treatment hematological markers and serum biochemical parameters on overall survival in cervical cancer patients undergoing curative surgery. We included newly diagnosed cases of cervical cancer at FIGO stage I, who underwent surgery followed by adjuvant therapy. The purpose of selecting this group was to obtain identical cases, as treatment patterns would otherwise vary among patients. Since this represents the primary stage of the disease, overall survival rates were high, with only a few reported deaths. However, there are no prior studies assessing the impact of these pre-treatment markers on survival outcomes in this patient group.

Cervical cancer prognosis is influenced by several factors, including tumor stage at diagnosis and the presence of co-morbid conditions [19]. So, in the present study, we assessed the impact of co-morbidities and FIGO staging on the overall survival of cervical cancer patients undergoing curative treatment. The presence of co-morbidities was observed in more than half of the patients (55.1%), with diabetes mellitus being the most prevalent (42.4%), followed by hypertension (24.2%) and cardiovascular disease (6.1%). Other medical conditions were present in 15.2% of cases. These findings align with previous studies that have reported a significant association between chronic metabolic disorders and cancer outcomes, potentially due to altered immune responses, systemic inflammation, and impaired treatment tolerance. Among these, diabetes mellitus is known to contribute to poorer cancer prognosis due to hyperglycemia-induced tumor progression and reduced therapeutic efficacy. Similarly, hypertension and cardiovascular disease can influence treatment decisions and increase the risk of complications, thereby affecting survival rates.

FIGO staging remains a crucial determinant of cervical cancer outcomes. In this study, the patients were diagnosed at Stage IB1 (42.4%) and IB2 (30.3%), suggesting that a significant proportion of cases were identified in early invasive stages. The presence of micro invasive cervical cancer (Stage IA1 and IA2) was relatively lower, accounting for 18.2% and 9.1% of cases, respectively. These findings highlight the importance of early detection, as patients diagnosed at earlier stages typically have a better prognosis and higher survival rates. The combined impact of FIGO staging and co-morbidities on survival outcomes needs further investigation. While early-stage diagnosis improves prognosis, the presence of co-morbidities may serve as an independent risk factor, potentially reducing overall survival despite curative treatment. Future studies with larger cohorts and longer follow-up periods are

necessary to establish definitive correlations and optimize treatment strategies for patients with multiple co-morbidities.

There is no significant difference in different LMR groups to the OS in cervical cancer patients undergoing curative surgery in this cohort. Small sample size could limit statistical power, making it difficult to detect subtle survival differences. LMR which is calculated by lymphocytes and monocytes, represents the antitumor immunity and tumor burden [20]. High survival rates across all groups may indicate that surgical treatment was effective, reducing the impact of LMR on prognosis.

The prognostic significance of NLR in the overall survival of cervical cancer patients was examined, and the findings suggest that while an elevated NLR may be associated with reduced survival rates, the difference is not statistically significant within this cohort. A larger cohort may be needed to detect a significant association. A high proportion of censored cases, particularly in the NLR 1–3 and >3 groups, may have influenced survival estimates and statistical outcomes. Higher NLR is often linked to systemic inflammation and poor prognosis in various cancers, its impact in cervical cancer may be modulated by other factors, such as tumor stage, treatment response, and immune system dynamics. The median NLR and PLR were significantly higher in the advance stage compared with early stage. A strong positive correlation was found between the staging of cervical cancer and NLR [21]. A p-value of 0.513 indicates that the observed differences in survival could be due to random chance rather than a true effect of NLR on survival outcomes. Although the difference between groups with an NLR above 3 and those with an NLR of 1 is not statistically significant, a subtle difference in survival rates is observed, decreasing from 100% to 84.6%, which is a 15 percentage decline. This trend suggests that further investigation with a larger sample size could be valuable.

The prognostic significance of the PLR in the overall survival of cervical cancer patients by categorizing them into three groups: PLR <100, PLR 100–300, and PLR >300. The observed survival rates were 100%, 90.0%, and 87.5%, respectively. Although a trend of slightly lower survival was noted in the higher PLR group, statistical analysis using the Log-Rank test revealed no significant difference in survival among the groups (p = 0.665). Lack of Statistical Significance – The p-value of 0.665 suggests that the observed differences in survival across PLR groups could be due to random variation rather than a true prognostic impact of PLR. This indicates that PLR alone may not be a strong independent predictor of survival in this cohort. The small sample size, particularly in the <100 PLR group limits the statistical power of the study. PLR is considered a marker of systemic inflammation, with elevated PLR often associated with poorer prognosis in various cancers. However, in cervical cancer, the interplay of inflammation, immune response, and tumor progression may be more complex, and other factors such as treatment response, tumor stage, and patient co morbidities may modulate survival outcomes [21].

Regarding the prognostic significance of MPVP in the overall survival of cervical cancer patients, the overall survival rate observed was 90.9%, with 30 out of 33 cases being censored during the study period. Statistical tests such as the Log-Rank test could not be applied to assess differences in survival outcomes based on MPVP levels. Higher MPV levels have been linked to tumor progression in some malignancies, but its specific role in cervical cancer remains unclear. A broader study with a more diverse cohort is needed to explore its potential prognostic value. Earlier it was reported that MPVP could serve as a novel independent prognostic factor for patients with resectable cervical cancer and may provide a more reliable prediction of survival outcomes in cervical cancer patients following radical surgery [22].

Albumin and alkaline phosphatase have been studied as prognostic biomarkers in several cancers, including cervical cancer. Albumin is often a marker of nutritional status and systemic inflammation, while alkaline phosphatase reflects liver function and bone metabolism [23]. A lower ALBALKP ratio has been linked to poorer survival in some cancers, suggesting a potential role in tumor progression and systemic deterioration [24]. However, in this study, the lack of significant association implies that ALBALKP might not be a strong independent predictor of survival in cervical cancer patients. The analysis of survival distributions for different levels of the Albumin-Alkaline Phosphatase (ALBALKP) ratio using the Log-Rank (Mantel-Cox) test yielded a chi-square value of 0.361 with a p-value of 0.548 suggests that there is no statistically significant difference in overall survival based on ALBALKP levels in cervical cancer patients in this study. This indicates that variations in ALBALKP levels do not show significant impact on survival outcomes in this study. The study might have had a limited sample size, reducing the ability to detect subtle differences. Cervical cancer has multiple subtypes and stages, and other factors (such as treatment modality and immune response) might have a stronger impact on survival than ALBALKP alone. Further studies with larger sample sizes and prospective designs may clarify its prognostic significance.

Conclusion

This study evaluated the prognostic significance of pre-treatment hematological markers and serum biochemical parameters on overall survival in cervical cancer patients undergoing curative surgery at FIGO Stage I. While tumor stage and co-morbid conditions significantly influenced survival, markers such as the LMR, NLR, PLR, and MPVP showed no statistically significant association with survival outcomes probably due to the small sample size. Higher NLR and PLR levels were observed in advanced stages, suggesting a potential role in disease progression, though further studies are needed to confirm their prognostic impact. Similarly, the ALBALKP ratio did not demonstrate a significant correlation with survival, indicating that other clinical factors may have a stronger influence on prognosis. Future research with larger cohorts and longer follow-up periods is necessary to validate these findings and optimize treatment strategies for cervical cancer patients with multiple co-morbidities.

List of abbreviations

LMR: Lymphocyte–Monocyte Ratio
NLR: Neutrophil–Lymphocyte Ratio
PLR: Platelet–Lymphocyte Ratio
MPVP: Mean Platelet Volume–Platelet Count Ratio
ALB/ALKP: Albumin–Alkaline Phosphatase Ratio
FIGO: International Federation of Gynecology and Obstetrics
OS: Overall Survival

Declarations

Ethical Approval and Consent to participate

The study was reviewed and approved by the Institutional Ethics Committee (IEC) through the Expedited Review process, as documented in the IEC approval letter. The committee evaluated the study protocol and granted ethical clearance for the conduct of the study. As per the IEC approval, the study complied with institutional and ethical guidelines. Requirements regarding informed consent were addressed in accordance with the committee's decision

outlined in the approval certificate. As this was a retrospective analysis based on existing medical records, the requirement for informed consent was waived by the Institutional Ethics Committee.

Author contributions

Conceptualization: E.R.S., K.E.G and K.S; Methodology: N.D, D.S.A.K.; Data analysis: M.M and K.S; Writing–original draft preparation: E.R.S.; Writing – review and editing: E.R.S, M.M; Supervision: K.S. and D.S.A.K.

Acknowledgements

Authors are thankful to Dr. Sangeetha K Nayanar, HOD, Department of clinical laboratory services and translational medicine, Dr. Ashitha R. G., Assistant Professor, Division of Gynec and Breast Oncology, Malabar Cancer Centre (Postgraduate Institute of Oncology Sciences and Research) who provided valuable suggestions throughout the research.

Financial disclosure

There was no funding utilized for this study.

Conflict of interest

There was no conflict of interest declared

Consent for Publication

Not applicable. This study is a retrospective analysis of anonymized patient data, and no identifiable individual information is included.

Availability of Supporting Data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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