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# Blood count and fasting blood glucose level in the assessment of prognosis and survival in advanced cervical cancer

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## SUMMARY

**OBJECTIVE:** The objective of this study was to verify whether the parameters of the blood count and the fasting glucose level before treatment are related to prognosis and survival in cervical cancer (IIB–IVB staging).

**METHODS:** Patients with cervical cancer (stages IIB–IVB) were evaluated (n=80). Age, parity, staging, histological grade, histological type, hemoglobin, red blood cells, hematocrit, neutrophil, lymphocyte and platelet counts, red blood cell distribution width, neutrophil–lymphocyte ratio, platelet–lymphocyte ratio, fasting glucose levels, overall survival, and disease-free survival were evaluated. The results of laboratory parameters were compared using the Mann–Whitney U test. Receiver operating characteristic curve was used to obtain the area under the curve and determine the best cutoff values for each parameter. Survival was verified by using the Kaplan–Meier method, followed by the log-rank test. The level of significance was ≤0.05.

**RESULTS:** Regarding staging, lower hemoglobin values (p=0.0013), red blood cells (p=0.009), hematocrit (p=0.0016), higher leukocytes (p=0.0432), neutrophils (p=0.0176), platelets (p=0.0140), red blood cell distribution width (RDW) (p=0.0073), neutrophil–lymphocyte ratio (p=0.0039), platelet–lymphocyte ratio (p=0.0006), and fasting glucose level (p=0.0278) were found in IIIA–IVB compared with IIB staging. Shorter disease-free survival was associated with hemoglobin ≤12.3 g/dl (p=0.0491), hematocrit ≤38.5% (p=0.05), neutrophil–lymphocyte ratio >2.9 (p=0.0478), and platelet–lymphocyte ratio >184.9 (p=0.0207). Shorter overall survival was associated with hemoglobin ≤12.3 g/dl (p=0.0131), hematocrit ≤38.5% (p=0.0376), neutrophil–lymphocyte ratio >2.9 (p=0.0258), and platelet–lymphocyte ratio >184.9 (p=0.0038).

**CONCLUSION:** The analysis of these low-cost and easily accessible parameters could be a way to monitor patients in order to predict treatment failures and act as early as possible.

**KEYWORDS:** Uterine cervical neoplasms. Blood cell count. Glucose. Prognosis. Survival.

## INTRODUCTION

Among the types of cancer with the highest incidence globally, cervical cancer occupies the eighth position in the world ranking. When analyzing only among the female population, it is the fourth type of cancer with the highest incidence and mortality[1]. In Brazil, cervical cancer remains the third position among the types of cancer with the highest incidence in the country, excluding the cases of nonmelanoma skin cancer[2]. One of the main factors related to the prognosis of cervical cancer is the staging, and detection through prevention programs is essential to increase survival[3].

Recent studies have shown that the systemic inflammatory response is related to factors of progression and prognosis in cervical cancer. Neutrophils and platelets are responsible for providing the bioactive substances necessary for molecules in neoplastic progression[4]. These bioactive agents are factors of angiogenic, epithelial, and stromal growth, as well as matrix remodeling enzymes. In addition, the imbalance in the innate and adaptive immune system will lead to lymphocytopenia and a compromised T-lymphocytic response. Consequently, the host's immune system response will not be fully effective[5].

The decrease in hemoglobin levels may occur with the progression of the disease. The values of the neutrophil–lymphocyte ratio (NLR) and the platelet–lymphocyte ratio (PLR) also have a potential use to be predictors of invasive cervical cancer, whose values tend to increase considerably in severe cases[6]. The value of NLR was also associated with the response to the chemoradiotherapy, and patients with higher NLR had a worse response[7].

Another change is related to the pretreatment fasting blood glucose level. The existence of an association between diabetes mellitus and gynecological cancer has been demonstrated[8]. Thus, the presence of pretreatment diabetes mellitus could be a parameter associated with worse prognosis and patient survival.

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The objective of this study was to verify whether the parameters of the blood count and the fasting glucose level before treatment in patients with cervical cancer in stages >IIB are prognostic and are related to survival.

## METHODS

A retrospective study was carried out at the Department of Gynecology and Obstetrics (Oncology Research Institute – IPON) at the Federal University of Triângulo Mineiro (UFTM). Patients who underwent chemoradiotherapy treatment for cervical cancer (stages IIB–IVB; FIGO) were evaluated (n=80). The following medical record data were evaluated: age, parity, histological type, staging, neutrophil, lymphocyte and platelet counts, RDW, NLR, PLR, fasting glucose levels, number of deaths, overall survival (OS), and disease-free survival (DFS).

The inclusion criterion was patients with cervical cancer stages IIB–IVB. Exclusion criteria were immunosuppressive diseases and pregnancy. The prognostic factors evaluated were staging, histological grade, and histological type. DFS and OS were also assessed. The study was approved by the Research Ethics Committee of UFTM.

The data were analyzed using the GraphPad Prism 6 and MedCalc 19.0.4 software. The results of laboratory parameters were compared using the Mann–Whitney U test. For statistically significant parameters, a receiver operating characteristic (ROC) curve was used to obtain the area under the curve (AUC) and determine the best cutoff values for each parameter. Survival was verified by using the Kaplan–Meier method, followed by the log-rank test. The level of significance was ≤0.05.

## RESULTS

The median age was 56 years (45–85), and the median parity was four births (0–14). The most frequent histological type was squamous cell carcinoma (86.25%), followed by adenocarcinoma (11.25%). Other histological types appeared in only 2.5% of cases. Regarding staging, 30 patients had stage IIB, and 50 patients had stages IIIA–IVB. The median, minimum, and maximum values of the laboratory parameters evaluated in stage IIB compared with stages IIIB–IVB are described in Table 1.

Regarding staging, lower hemoglobin values (p=0.001; medians 10.5 vs. 12.6), red blood cells (p=0.0014; medians 3.8 vs. 4.75), and hematocrit (p=0.0011; medians 33.6 vs. 37.65) were more associated with stages ≥IIIA–IVB than in stage IIB. On the leukogram, absolute values of leukocytes (p=0.0245; medians 9,280 vs. 7,655) and neutrophils (p=0.0088; medians 6,206 vs. 4,877) were higher in IIIA–IVB staging than in IIB staging.

When the platelets were evaluated, their absolute value was higher in IIIA–IVB staging than in IIB staging (p=0.0120; medians 324,000 vs. 258,000).

Evaluating RDW, NLR, and PLR, their values were higher in IIIA–IVB staging than in IIB staging (p=0.0047; medians 14.6 vs. 13.5; p=0.0022; medians 3.6 vs. 2.3; and p=0.0007; medians 191.1 vs. 127.6, respectively). Regarding fasting blood glucose level, their values were higher in IIIA–IVB staging than in IIB staging (p=0.0263; medians 102.8 vs. 94.65). There was no statistical significance when assessing the grade of differentiation and histological type.

Subsequently, ROC curves were constructed to verify the cutoff values. According to the cutoff values found, the

**Table 1.** Values of the laboratory parameters evaluated in stage IIB compared with stages IIIB–IVB (median, minimum, and maximum values).

| | Stage IIB (n=30) | Stages IIIA–IVB (n=50) |
|---|---|---|
| Hemoglobin (g/dl)* | 12.6 (7.6–16.6) | 10.5 (6–15.2) |
| Red blood cells (× $10^6$/$mm^3$)** | 4.75 (2.9–5.5) | 3.8 (2.13–5.36) |
| Hematocrit (%)*** | 37.65 (23.2–47) | 33.6 (18.3–46.6) |
| Leukocit (/$mm^3$)$^+$ | 7,655 (4,750–16300) | 9,280 (4,500–24,360) |
| Neutrophil (/$mm^3$)$^{++}$ | 4,877 (1,494–12,877) | 6,206 (2,475–18,026) |
| Lymphocytes (/$mm^3$) | 1,970 (1,179–3,927) | 1,844 (115–3,167) |
| Platelets (×$10^3$/$mm^3$)$^{+++}$ | 258 (165–449) | 324 (157–702) |
| RDW$^{\#}$ | 13.5 (12.2–19.6) | 14.6 (12.3–21.4) |
| NLR$^{\#\#}$ | 2.3 (0.6–6.7) | 3.6 (1.2–92.6) |
| PLR$^{\#\#\#}$ | 127.6 (68.1–317) | 191.1 (77.1–1,852.2) |
| Fasting glucose level (mg/dl)$^{\#\#\#\#}$ | 94.65 (72.3–161) | 102.8 (74.4–170.2) |

Mann–Whitney test. *p=0.001; **p=0.0014; ***p=0.0011; $^+$0.0245; $^{++}$p=0.0088; $^{+++}$p=0.0120; $^{\#}$p=0.0047; $^{\#\#}$p=0.0022; $^{\#\#\#}$p=0.0007; $^{\#\#\#\#}$p=0.0263.

Kaplan–Meier curves were constructed to assess DFS and OS. Shorter DFS was associated with hemoglobin ≤12.3 g/dl (p=0.0491), NLR >2.9 (p=0.0478), and PLR >184.9 (p=0.0207). The parameters of hematocrit ≤38.5% (p=0.05) and red blood cells ≤4.38 million/mm$^3$ were shown at the significance threshold (p=0.0603) (Figure 1).

Shorter OS was associated with hemoglobin ≤12.3 g/dl (p=0.0163), hematocrit ≤38.5% (p=0.0451), NLR >2.9 (p=0.0305), and PLR >184.9 (p=0.0031). The parameter of red blood cells ≤4.38 million/mm$^3$ was shown at the significance threshold (p=0.0689) (Figure 2).

## DISCUSSION

The relationship between anemia and prognosis has been demonstrated in several types of gynecological tumors[9-12]. In ovarian cancer, higher levels of platelets were found in advanced disease, since hemoglobin levels were higher in stages I/II[12]. In our study, lower hemoglobin values, red blood cells, and hematocrit were more associated with staging ≥IIIA–IVB than in IIB staging. Higher hemoglobin values before treatment for uterine cervical cancer were associated with longer DFS, but were not associated with OS in multivariate analysis[10]. We found an association of lower hemoglobin levels with both DFS and OS.

Leukocytosis, neutrophilia, thrombocytosis and lymphocytosis, as well as PLR and NRL are related to prognosis, stage of the disease, and response to the treatment of cervical cancer. Neutrophils secrete vascular endothelial growth factor, interleukin (IL)-18, and metalloproteinases, thus contributing to tumor growth, vascularization and metastasis. Neutrophilia can then promote tumor metabolism by secreting several proliferative factors[13]. One study analyzed blood count parameters in 110 patients with preneoplastic diseases and cervical cancer, and found significantly higher values of neutrophils in these patients[14].

In contrast, lymphocytes exert antitumor effects by inhibiting the proliferation and migration of tumor cells, promoting apoptosis and mediating cytotoxicity. Patients with lymphopenia imply immunosuppression and worse survival. Therefore, NLR may reflect a balance in the host's antitumor immunity[13]. The increase in neutrophils may also be related to neoplastic progression and may suppress lymphocyte antineoplastic properties. Patients with invasive cervical cancer have higher NLR and PLR compared with patients with preneoplastic lesions of the cervix. Significant correlations were also found between the PLR value and depth of stromal infiltration, tumor size, and lymph node metastases. The decrease in the number of lymphocytes has

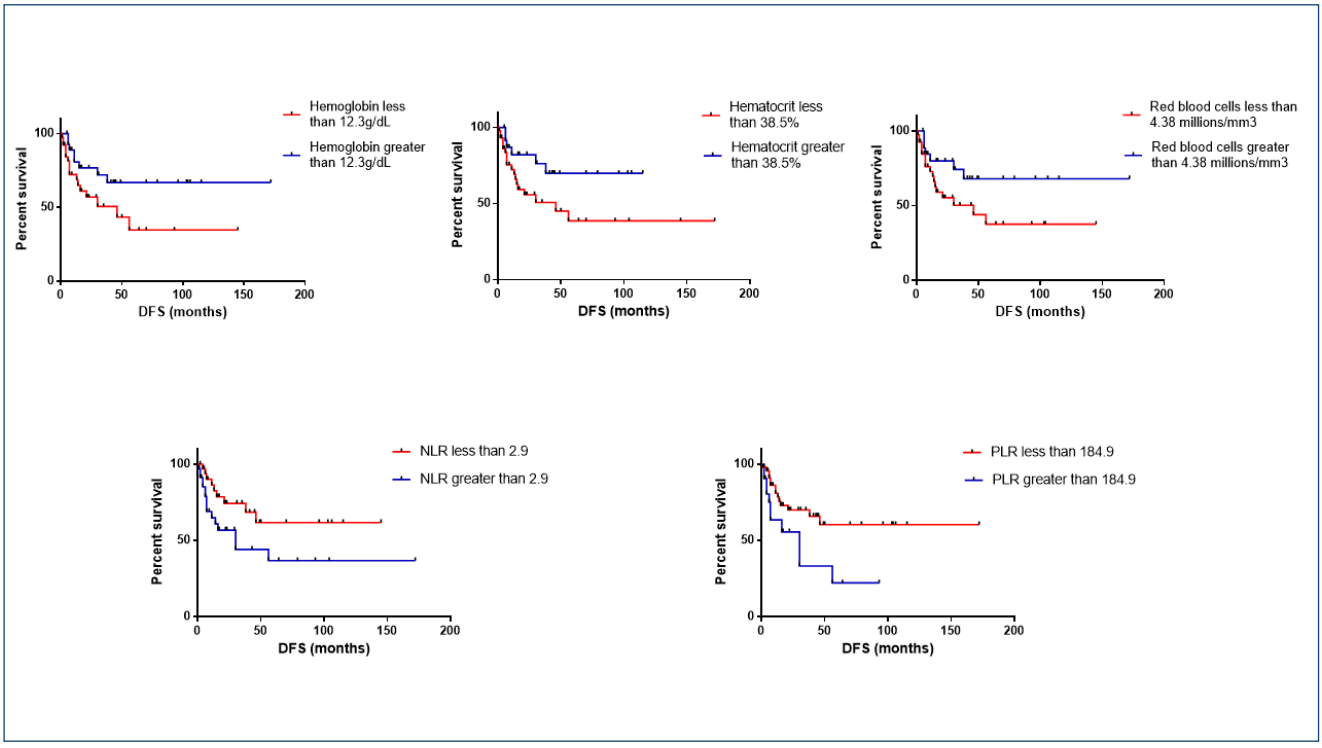


**Figure 1.** Disease-free survival: hemoglobin (p=0.0491), hematocrit (p=0.05), red blood cells (p=0.0603), neutrophil–lymphocyte ratio (p=0.0478), and platelet–lymphocyte ratio (p=0.0207).

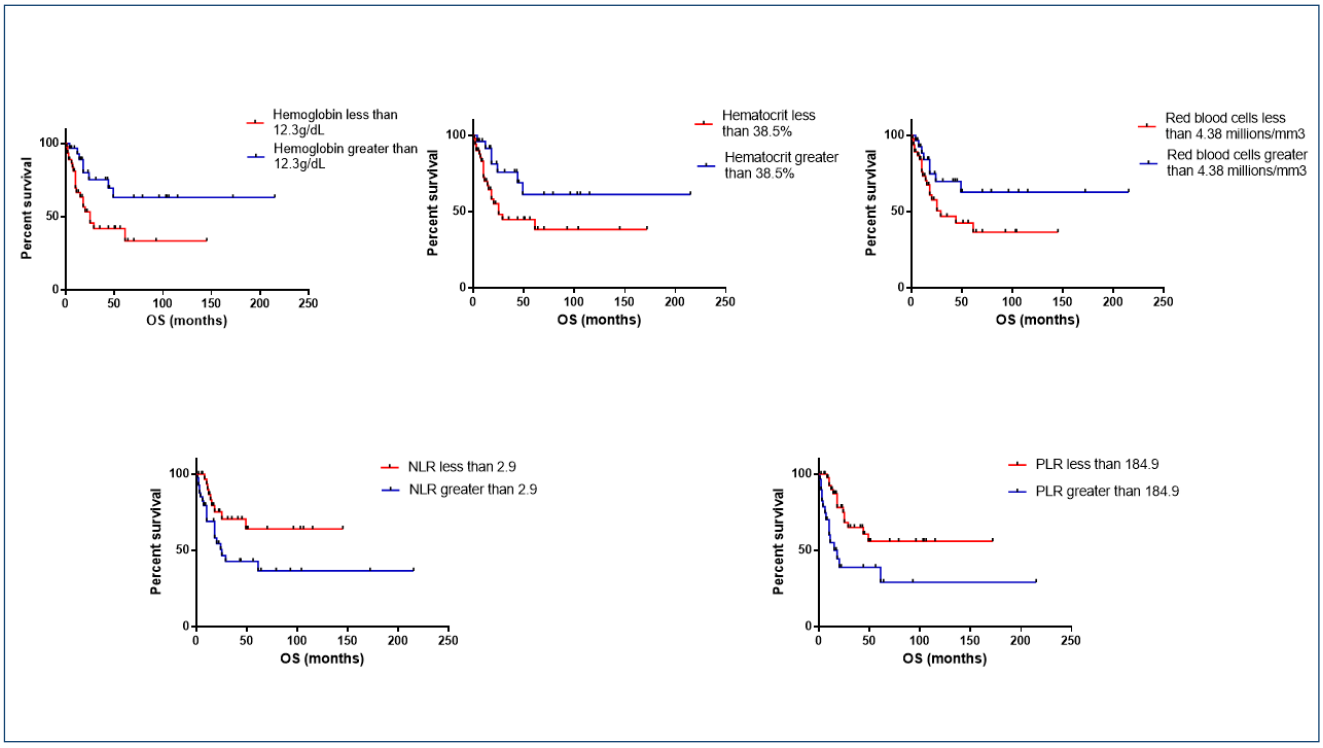


**Figure 2.** Overall survival: hemoglobin (p=0.0163), hematocrit (p=0.0451), red blood cells (p=0.0689), neutrophil–lymphocyte ratio (p=0.0305), and platelet–lymphocyte ratio (p=0.0031).

been demonstrated in more advanced stages of the disease[14]. Our study shows a significant association between NLR, disease staging, and patient survival. Higher NLR values were associated with more advanced disease staging and lower DFS and OS.

Platelet count is another marker of host systemic inflammation. Certain pro-inflammatory cytokines, such as IL-1, IL-3, and IL-6, stimulate thrombopoiesis in cancer patients. Platelets have also been implicated in processes that lead to angiogenesis in tumors by releasing vascular endothelial growth factor and other proangiogenic factors, including urokinase-type plasminogen activator. PLR may then be high in more advanced stages of cervical cancer[13]. Thrombocytosis may be associated with shorter survival and more advanced staging[6,15]. In our study, we found that PLR values >184.9×10³/mm³ are associated with shorter OS and DFS.

Regarding glucose, a study showed that patients with fasting glucose level ≥102 mg/dl in the pretreatment with chemoradiotherapy had a shorter survival compared with patients with fasting glucose level <102 mg/dl[16]. A retrospective study investigated the impact of glycemic control on survival and response to neoadjuvant chemotherapy in advanced cervical cancer and found that poor glycemic control was considered an independent predictor of survival and response to chemotherapy[17]. Our results demonstrated that fasting glucose values were higher in IIIA–IVB staging than in IIB staging, but no association was found with survival.

Increased RDW can be associated with several types of cancer[18-20]. In the literature, we found only one study that demonstrated a correlation between RDW and invasion of cervical cancer[21], and two studies that evaluated RDW in cervical cancer, but found no association with prognostic factors[22,23]. To the best of our knowledge, no study in the literature demonstrated the association of this parameter with cervical cancer staging. In our study, RDW values were higher in IIIA–IVB staging than in IIB staging.

## CONCLUSIONS

The study of systemic laboratory parameters may lead to new discoveries of prognostic factors in patients with cervical cancer who have no surgical indication, and may better guide the oncologist for more aggressive chemotherapy and radiotherapy treatments in those patients with worse prognostic factors. These parameters can be obtained with simple blood tests (complete blood count and fasting glucose level), using low-cost and easily accessible methods.

## AUTHORS' CONTRIBUITIONS

**SDSM:** Data curation, Methodology, Writing – original draft. **SSO:** Investigation, Methodology, Writing – original draft. **EFCM:** Conceptualization, Formal Analysis, Supervision, Validation, Writing – review & editing. **RN:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project Administration, Writing – review & editing, and guarantor.

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