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Association of laboratorial parameters and prognostic factors in uterine corpus cancer

Kaio Raffael Valotta Bezerra[1], Agrimaldo Martins-Filho[1], Marta Carolina Marques Sousa[1], Eddie Fernando Candido Murta[1], Rosekeila Simões Nomelini[1]*

SUMMARY

OBJECTIVE: The aims were to compare the red blood cells, platelet count, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, red cell distribution width, and fasting glucose in peripheral blood of patients with benign and malignant uterine neoplasms and to relate these laboratory parameters with prognostic factors and overall survival in cancer.

METHODS: The results of the laboratory parameters were analyzed using the Mann-Whitney U test. Receiver operating characteristic curves were used to find the cutoff values. Overall survival was estimated using the Kaplan-Meyer method.

RESULTS: Higher values of neutrophil-lymphocyte ratio and fasting glucose were found in cancer patients. Higher platelet-lymphocyte ratio values were associated with other subtypes when compared with endometrioid subtype; higher values of red cell distribution width were found in stage II/IV when compared with stage I; lower hemoglobin values were related to stage II/IV and nonendometrioid histological type. Platelet–lymphocyte ratio <145.56 was associated with longer overall survival.

CONCLUSION: Hemoglobin and platelet–lymphocyte ratio values are prognostic factors in uterine corpus cancer.

KEYWORDS: Uterine neoplasms. Blood platelets. Lymphocytes. Prognosis. Survival.

INTRODUCTION

Cancer progression is influenced by the inflammatory response of the host, with inflammation being an indicator of prognosis, and several prognostic and diagnostic biomarkers have been identified[1]. Laboratory quantification of markers of the systemic inflammatory response, such as hypoalbuminemia, hyperfibrinogenemia, C-reactive protein, absolute leukocyte count, neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR), were introduced as prognostic factors in patients with various types of cancer[2,3].

A study involving two of these inflammatory markers, NLR and PLR, revealed favorable results for these markers, proposing that they can be used as predictors of malignancy for solid tumors originating from various tissues. They could be used as a tool of screening for these tumors, as they are considered low-cost tests and readily available. However, there is a need for more research to assess the value of this finding in establishing scores and indicate the potential predictive value of NLR and PLR markers in gynecological cancers[4].

Endometrial cancer is classified into two subtypes on the basis of histological characteristics, hormone receptor expression, and grade, namely, type I or endometrioid and type II or non-endometrioid tumors[5]. This classification has helped to define the treatment, but the prognostic value remains limited because

[1]Universidade Federal do Triângulo Mineiro, Research Institute of Oncology, Department of Gynecology and Obstetrics – Uberaba (MG), Brazil.
*Corresponding author: rosekeila@terra.com.br

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endometrial cancer comprises a range of neoplasia with distinct genetic polymorphism and molecular features[6-9]. Therefore, the identification of biomarkers that can assist in the selection of patients for surgical treatment and an ideal adjuvant treatment is vital to improve the outcome. The aim of this study was to verify and compare the red blood cells, platelet count, NLR, PLR, red cell distribution width (RDW), and fasting glucose in peripheral blood of patients between benign and malignant uterine neoplasms before surgical treatment and to relate these laboratorial parameters with prognostic factors and overall survival (OS) in patients with primary uterine corpus cancer.

METHODS

A retrospective study was carried out at the Department of Gynecology and Obstetrics. The study sample consisted of 216 women, divided into two groups, namely, uterine corpus cancer (n=92) and leiomyomas (n=124). Patients who were referred to surgical treatment for these neoplasms were assessed. The following parameters were evaluated: age, parity, histological type, staging, red blood cells, neutrophil, lymphocyte and platelet count, RDW, NLR, PLR, fasting glucose, and OS.

The data were analyzed using GraphPad Prism software 6 and MedCalc 19.0.4. The results of laboratory parameters were compared between benign and malignant groups using the Mann-Whitney U test. For parameters that showed statistical significance, a "receiver operating characteristic" (ROC) curve was used to obtain the area under the curve (AUC) and to determine the best cutoff values between uterine corpus cancer and leiomyomas. In uterine corpus cancer, ROC curves were also used to determine the cutoff value between prognostic factors and laboratory parameters. The OS of the groups was estimated by the Kaplan–Meyer method followed by the log-rank test. The level of significance was <0.05.

This study was approved by the Research Ethics Committee of Federal University of Triângulo Mineiro (protocol number 89084018.9.0000.5154).

RESULTS

We evaluated 92 patients with uterine corpus cancer and 124 patients with leiomyomas. In the malignant group, the median age was 64 years (45–88), the median parity was two births (0–12), and 60 (65.2%) of the patients had the endometrioid histological type and 32 (34.8%) were of other subtypes. In relation to the control group (leiomyomas), the median age was 43 years (35–76), and the median parity was two births (0–8).

In the comparison between uterine corpus cancer and leiomyomas, higher values of NLR and fasting glucose were found in cancer patients (p<0.0001 and p=0.0002, respectively) (Figure 1A). There was no statistical significance in the evaluation of the other parameters (i.e., RDW, neutrophil, lymphocyte, and platelet count).

Regarding the ROC curve to verify the cutoff values of NLR in leiomyomas and uterine corpus cancer, the value of 2.852 was found (AUC=0.725 and p<0.001) (Figure 1B).

Evaluating the association of laboratory parameters with prognostic factors in uterine corpus cancer, higher PLR values were associated with other subtypes when compared with endometrioid subtype (p=0.0407), higher RDW values were found in stages II to IV when compared with stage I (p=0.0292), and lower hemoglobin values were related to stages II to IV when compared with stage I and other subtypes (nonendometrioid) and also when compared with endometrioid subtype (p=0.0024 and p=0.006, respectively) (Figure 2).

The ROC curves showed a cutoff value of 145.56 for PLR in relation to the histological type (AUC=0.635 and p=0.037), 11.8 in relation to hemoglobin and histological type (AUC=0.677 and p=0.003), and 12 in relation to hemoglobin and staging (AUC=0.686 and p=0.001) (Figure 3A–C).

Subsequently, survival curves were performed to verify whether there is a relationship between PLR and hemoglobin values and to verify OS of patients with uterine corpus cancer. This relationship was not found with hemoglobin levels. On the other hand, the OS of patients with PLR<145.56 was longer than that in patients with PLR>145.56 (p=0.0005) (Figure 3D).

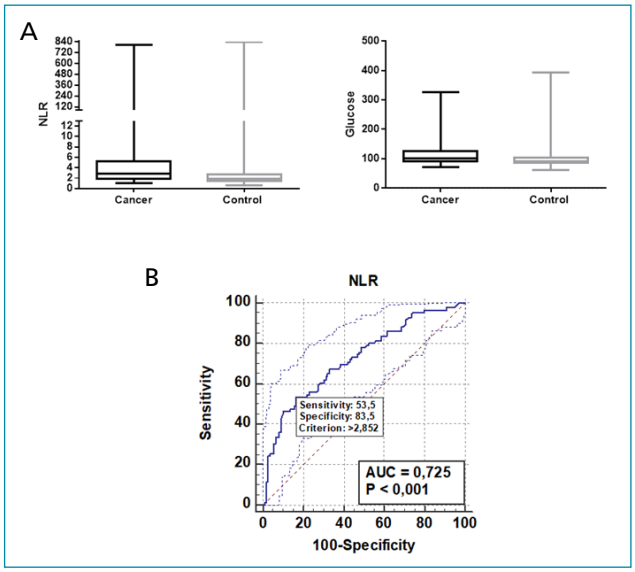

Figure 1. **(A)** Neutrophil–lymphocyte ratio and fasting glucose (g/dL) in uterine corpus cancer and leiomyomas. **(B)** Receiver operating characteristic curve; Neutrophil–lymphocyte ratio in leiomyomas and uterine corpus cancer.

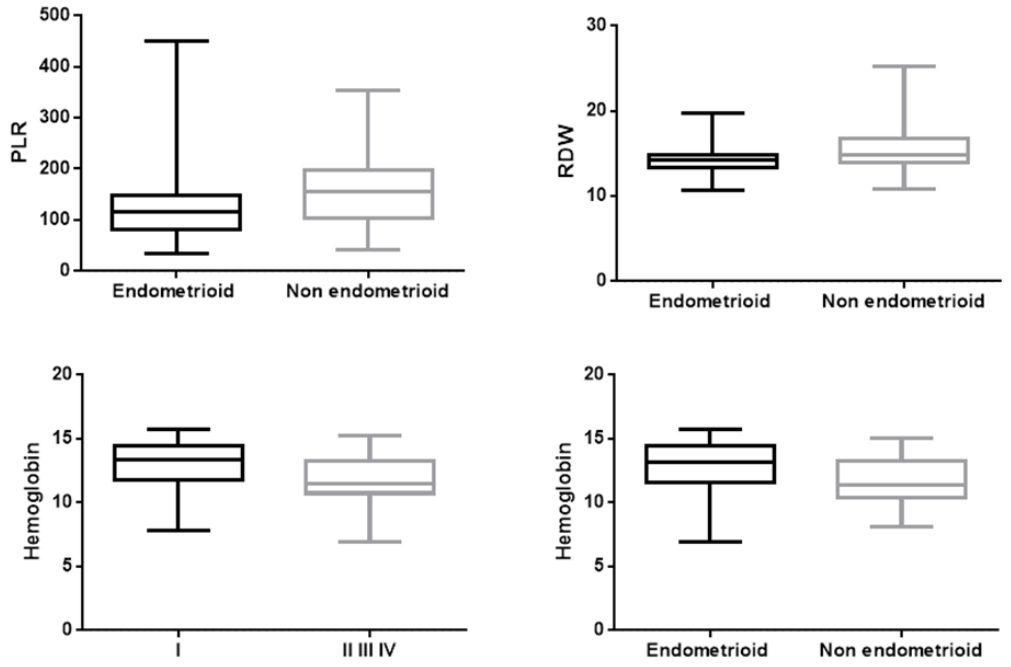

Figure 2. Laboratory parameters and prognostic factors in uterine corpus cancer.

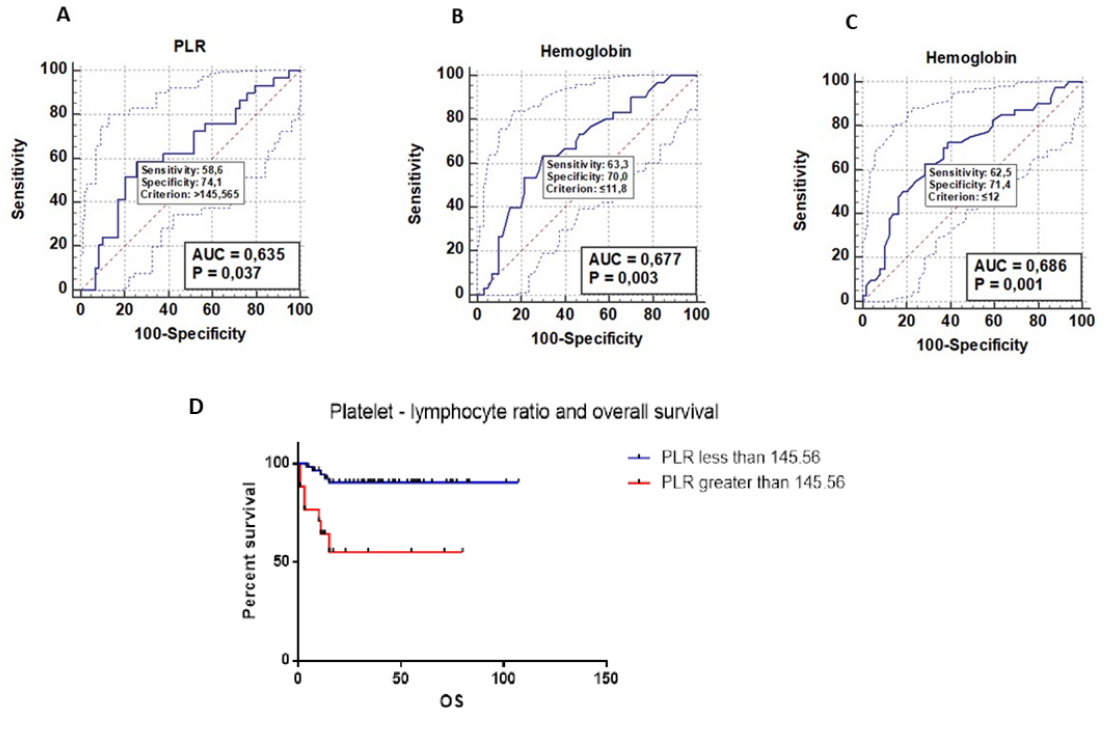

Figure 3. Receiver operating characteristic and survival curves: (A) Receiver operating characteristic curve, platelet–lymphocyte ratio and histological type (endometrioid *versus* other subtypes). (B) Receiver operating characteristic curve, hemoglobin and histological type (endometrioid *versus* other subtypes). (C) Receiver operating characteristic curve, hemoglobin and staging (I *versus* II–IV). (D) Overall survival and platelet-lymphocyte ratio.

DISCUSSION

Studies have demonstrated the relationship between inflammatory response markers and prognosis in endometrial cancer[10-13]. A study demonstrated that platelet volume and platelet distribution width might have a predictive value in the discrimination of benign and malign endometrium diseases[11]. In the comparison between uterine corpus cancer and leiomyomas, the cancer patients had higher values of NLR. Regarding the ROC curve to verify the cutoff values of NLR in leiomyomas and uterine corpus cancer, the value of 2.852 was found.

A study involving 763 patients with endometrial carcinoma showed a cutoff value of 3 for NLR; the sensitivity and specificity were found to be 68 and 69%, respectively, to predict lymph node metastasis[14]. Another study that applied cutoff values of 2.4 for NLR and 240 for PLR had independent prognostic significance[15]. A meta-analysis of 23 studies, including 6,869 patients, showed that PLR is related to a worse prognosis in ovarian tumors but not in endometrial tumors[12]. A higher pretreatment NLR was demonstrated as a predictor of lymph node metastasis in endometrial cancer[16]. A study found that patients with high baseline NLR (≥4.1) had more baseline distant metastases than patients with low baseline NLR (<4.1), and patients with high baseline PLR (≥0.3) had more distant metastases than patients with low baseline PLR (<0.3)[17]. The clinicopathological data and five year follow-up data were obtained for a retrospective series of 605 surgically treated endometrial cancer patients. By applying cutoff values of ≥2.4 (NLR) and ≥240 (PLR), NLR and PLR had independent prognostic significance[18]. Patients with elevated PLR had a high risk of decreased OS and unfavorable disease-free survival[13]. Another study demonstrated that the median OS in patients with a PLR of <300 was 37.4 months (95%CI 26.1–48.7), and it was 14.5 months (95%CI 11.7–17.2) in those with a PLR of >300. PLR, but not NLR, retained its significance as a prognostic marker on the multivariate Cox's regression analysis, along with staging (p<0.001) and residual disease (p=0.015)[10]. By evaluating the association of laboratory parameters with prognostic factors in uterine cancer, our study demonstrated that higher PLR values were associated with a nonendometrioid subtype when compared with endometrioid subtype (which has a better prognosis). A study demonstrated that the combination of NLR, PLR, and monocyte-lymphocyte ratio is a superior prognostic factor of endometrial cancer[19]. A meta-analysis demonstrated that elevated NLR and PLR values during pretreatment are biomarkers of poor prognosis in patients with endometrial cancer[20]. No significant association between NLR and prognostic factors was found. On the other hand, ROC curves showed a cutoff value of 145.56 for PLR in relation to the histological type. Moreover, OS of patients with a PLR<145.56 was longer than that in patients with a PLR>145.56.

Metabolic syndrome can be related to a high risk for mortality from cancer, including endometrial cancer, and leads to an unfavorable prognosis for patients with endometrial adenocarcinoma[21,22]. Our study did not assess all parameters of the metabolic syndrome, but it found that in the comparison between uterine corpus cancer and leiomyomas, cancer patients had higher values of fasting glucose when compared with the control group.

A study demonstrated that the frequency of preoperative anemia was 27.7%. Patients whose disease progressed to more advanced stages and those who presented with an unfavorable differentiation grade, myometrial invasion ≥50%, lymphovascular invasion, or tumor recurrence had significantly lower preoperative hemoglobin levels when compared with patients who did not present with anemia in the preoperative period. This study indicated that patients with preoperative anemia had significantly lower recurrence-free survival rates after five years and significantly lower OS rates when compared with patients without preoperative anemia, demonstrating that the preoperative hemoglobin rate is a prognostic factor with an important clinical significance[23]. By evaluating the association of laboratory parameters with prognostic factors in uterine cancer, lower hemoglobin values were related to stages II to IV when compared with stage I and nonendometrioid histological type and also when compared with endometrioid subtype. The ROC curves showed a cutoff value of 11.8 in relation to hemoglobin and histological type and 12 in relation to hemoglobin and staging. Thus, anemia was related to factors with a worse prognosis (histological type and staging). No relation was found with OS.

RDW is another blood count parameter that can be used in the management of endometrial diseases. In one study, the group with endometrial cancer had significantly higher levels of RDW compared with the benign group[24]. Other study demonstrated that combination of RDW, mean platelet volume, and CA125 can improve the differential diagnosis of endometrial cancer and endometrial hyperplasia[25]. In our study, the higher PLR values were associated with a nonendometrioid subtype when compared with endometrioid subtype. Higher values of RDW were found in stages II–IV when compared with stage I, and lower hemoglobin values were related to stages II–IV when compared with stage I and nonendometrioid histological type and also when compared with endometrioid subtype.

The identification of new cancer biomarkers in peripheral blood samples is promising due to the ease of sampling, and analysis methods are readily available. However, few blood-based biomarkers are validated and clinically used. Currently, surgical treatment decisions for endometrial cancer are based on a preoperative histopathological assessment of the tumor

biopsy in combination with the preoperative ultrasound image available. However, these preoperative data are often inconsistent with the postoperative data[26], indicating the need for the emergence of alternatives that increase the accuracy of the prognosis and diagnosis of this disease without adversely affecting the patients.

The limitations of this study are the heterogeneity of the histological subtypes studied and the lack of evaluation of the influence of molecular profile on the prognosis of uterine body cancer. On the other hand, our study reinforces the importance of investigating new prognostic markers in this cancer, which are easy to collect and inexpensive. New studies associating molecular profiles, gene polymorphisms, and laboratory parameters in uterine body cancer may lead to a better elucidation of prognostic factors in uterine body cancer.

Several prognostic biomarkers could be used in the management of uterine cancer. The group of malignant uterine tumors observed an increase in NLR and blood glucose levels, as well as an increase in RDW and PLR. In this group, the increase in PLR was observed in nonendometrioid tumors when compared with endometrioid subtype (which has a better prognosis). In nonendometrial tumors, a decrease in hemoglobin rates was also observed. In this study, it was observed that the increase in the OS rate of patients with malignant tumors was directly related to the decrease in PLR, indicating that this parameter is strongly linked to OS.

The identification of new cancer biomarkers in peripheral blood samples is promising due to the ease of sampling and low cost, and these methods of analysis are readily available. However, few blood biomarkers are validated in clinical use. The adoption of these practices in clinical conduct can better guide the oncologist in performing less aggressive surgeries and adjuvant treatments in patients whose laboratory parameters suggest prognostic factors that are more favorable.

CONCLUSIONS

The values of NLR and fasting glucose were higher in uterine cancer than in leiomyomas. In uterine corpus cancer, PLR was higher in nonendometrioid tumors, RDW was higher in II–IV stages, and hemoglobin was lower in II–IV stages and nonendometrioid tumors. RPL<145.56 was associated with longer OS.

AUTHORS' CONTRIBUTIONS

KRVB: Data curation, Methodology, Writing – original draft. **AMF:** Investigation, Methodology, Writing – original draft. **MCMS:** Data curation, Methodology, Writing – original draft. **EFCM:** Conceptualization, Formal Analysis, Supervision, Validation, Writing – review & editing. **RSN:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Writing – review & editing.

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