Diagnostic Value of Neutrophil Leukocyte Ratio and Platelet Lymphocyte Ratio to Differentiate Adnexal Masses as Benign or Malignant in the Preoperative Period

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Summary
Aims and Objectives: To assess the diagnostic accuracy of neutrophil leukocyte ratio (NLR), platelet lymphocyte ratio (PLR) and CA125 individually and in combination with each other to help differentiate between malignant and benign adnexal masses preoperatively.
Material and Methods: This is a retrospective analytical study with a sample size of 166 conducted from January 2018 to February 2021 at the Regional Cancer Centre. The records of all women presenting to our institute were screened based on the inclusion criteria and consecutive cases of 166 women with adnexal masses with a complete blood count (CBC) and CA125 done preoperatively were included. NLR and PLR were calculated and their cut-offs were measured using the receiver operating characteristic (ROC) curve. The diagnostic efficacy of these markers was measured by using the statistical results of specificity, sensitivity, negative predictive value and positive predictive value.
Results: As per our study, CA125 was the most sensitive (67.57%) in distinguishing malignant from benign adnexal masses. The best positive predictive value is indicated by PLR and CA125≥35 together (62.75%) whereas the best negative predictive value is seen with NLR and CA125<35 (78.95). As per the statistics, the diagnostic accuracy of NLR and CA125<35 is better (63.01%) than the other parameters.
Conclusion: Although in our study NLR and CA125<35 had the best negative predictive value, specificity and diagnostic accuracy out of all the parameters considered, these values are only fairly significant and their clinical significance needs to be studied further.

Introduction

Adnexal masses can be functional or neoplastic. Neoplastic tumors can be benign or malignant. During the reproductive years, the ovarian masses are most commonly benign but the possibility of malignancy must be considered.[1]

Out of all the gynaecologic malignancies, ovarian cancer has the highest mortality rate because more than two-thirds of patients have advanced disease at presentation.[2]

Adnexal masses are frequently detected on imaging exams such as transvaginal ultrasonography. The nature of these masses is diagnostically challenging. The diagnostic accuracy of serum biomarkers like cancer antigen 125 (CA125) alone has been evaluated and established. Different approaches incorporating other factors like imaging, menopausal status and other biomarkers are available, such as the risk of malignancy index (RMI), the risk of ovarian malignancy algorithm (ROMA), and OVA1. In spite of these, there is a dearth of simpler and more accessible tools which can be widely used in a population with adnexal masses.[3]

Infiltrating cancers can provoke an extensive chronic inflammatory reaction. Inflammatory cells also modify the tumor cells and the local microenvironment. This enables many of the hallmarks of cancer either by direct interactions between inflammatory and tumor cells or through indirect effects on other stromal cells, particularly cancer-associated fibroblasts and endothelial cells.[4]

Systemic inflammatory response (SIR) mediators compromise immune function, which increases the concentrations of the white blood cells, polymorphonuclear leucocytes, and thrombocytes. As a result, preoperative inflammatory markers, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been suggested to be useful for distinguishing benign from malignant ovarian tumors. NLR and PLR are non-invasive and can be measured by a simple CBC which is an easily available and cost-effective investigation.[5]

This study was performed to establish NLR and PLR with CA125 as a diagnostic marker to preoperatively distinguish adnexal masses as benign or malignant.

Materials and Method

The present retrospective study was conducted at the Gynaecological Oncology Department of the Gujarat Cancer and Research Institute, Ahmedabad. The sample size was 166 cases evaluated from January 2018 to February 2021.

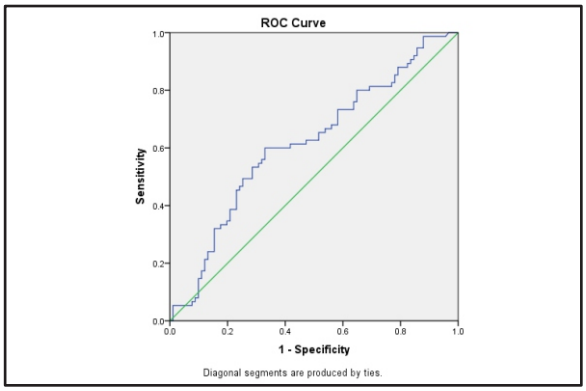

Figure1: ROC curve for NLR [For NLR, the best cut off based on the receiver operating characteristic (ROC) analysis was 3.09 [Area under curve=0.615 (0.529 to 0.702), p value=0.012]

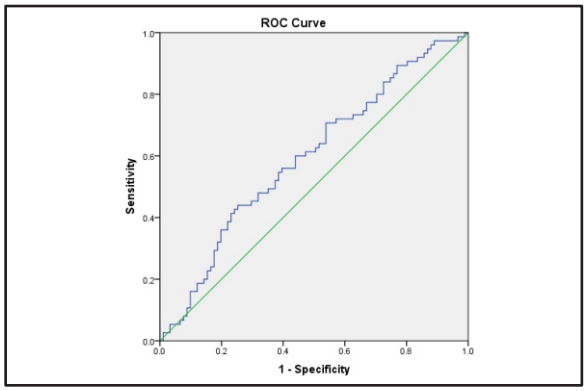

Figure 2: ROC curve for PLR [For PLR, the best cut off based on the above receiver operating characteristic (ROC) analysis was 203.68 [Area under curve=0.595 (0.509 to 0.682), p value=0.044].

Table 1: Sensitivity, specificity, negative predictive value, positive predictive value and diagnostic accuracy measured of NLR, PLR, CA125 and combination of these parameters

Parameter	Sensitivity (lower and upper 95% confidence interval)	Specificity (lower and upper 95% confidence interval)	Positive predictive value (lower and upper 95% confidence interval)	Negative predictive value (lower and upper 95% confidence interval)	Diagnostic accuracy
NLR≥3.09	61.33 (50.02 - 71.54)	58.24 (47.98 - 67.84)	54.76 (44.14– 64.96)	64.63 (53.84– 74.11)	59.64 (52.04 – 66.8)
PLR≥203.68	60.00 (48.69 - 70.34)	53.85 (43.66 - 63.72)	51.72 (41.37– 61.93)	62.03 (51 – 71.93)	56.63 (49.02 – 63.93)
CA125 (cut-off 35 U/mL)	67.57 (56.27 - 77.14)	53.85 (43.66 - 63.72)	54.35 (44.2 – 64.15)	67.12 (55.73 – 76.81)	60 (52.38 – 67.17)
NLR and CA125<35	66.67 (46.71 - 82.03)	61.22 (47.25 - 73.57)	45.71 (30.47– 61.81)	78.95 (63.65 – 88.93)	63.01 (51.55 – 73.18)
NLR and CA125≥35	58 (44.23 - 70.63)	54.76 (39.95 - 68.78)	60.42 (46.31– 72.98)	52.27 (37.94 – 66.25)	56.22 (46.33 – 66.19)
PLR and CA125<35	50 (31.43 - 68.57)	53.06 (39.38 - 66.30)	34.29 (20.83– 50.85)	68.42 (52.54 – 80.92)	52.05 (40.78 – 63.12)
PLR and CA125≥35	66.30 (50.14 - 75.86)	54.76 (39.95 - 68.78)	62.75 (49.02– 74.68)	56.10 (41.04 – 70.11)	59.78 (49.57 – 69.22)

All the women who had preoperative ultrasonography showing adnexal masses, CA125 and a CBC within one month of surgery and whose final histopathology showed ovarian pathology were included in the study. Those cases who were already operated outside or had received preoperative chemotherapy were excluded from the study. Fungal and tubercular infections causing adnexal masses were also excluded to remove bias as they also cause an increase in leucocytes and would distort the outcome of the study. On retrospective examination of the histopathological results, out of 166 cases studied, 91 were benign and 75 were either borderline or malignant. All borderline and malignant cases were considered together as a single category.

The CBC, CA125 reports and the final histopathological reports were reviewed retrospectively. The data of neutrophils, lymphocytes, absolute neutrophil count, absolute lymphocyte count and thrombocyte count were collected from CBC reports. NLR and PLR were calculated from these values.

Data collection, compilation and analysis was done by EPI info (version 7.2). The qualitative variables were expressed as percentages. The quantitative variables were categorized and expressed as percentages or terms of mean and standard deviations. The chi-square test was used to interpret the difference between the two proportions. The student t-test was used to evaluate the difference between the two means. The diagnostic performance of the data was measured in terms of sensitivity, specificity, positive predictive value, negative value and diagnostic accuracy. We used receiver operating characteristic (ROC) curves to determine the best cut-off. The analysis was 2-tailed. The significance level was set at 0.05. Based on Youden's index the best cut-off for NLR was 3.09 [Area under curve=0.615 (0.529 to 0.702), p value=0.012] and for PLR was 203.68 [Area under curve=0.595 (0.509 to 0.682), p value=0.044](Figure 1 and Figure 2). The cut-off for CA125 is 35 U/mL.

Result

A total of 166 women with ultrasound showing adnexal masses were enrolled. The patient distribution as per their final histopathological reports showed that 91 cases (54.82%) were benign whereas 75 cases (45.18%) were either borderline or malignant. All borderline and malignant cases were considered together as a single category.

The sensitivity of CA125 (67.57%) is better than NLR (61.33%) or PLR (60%) whereas the specificity was better when NLR was considered with CA125<35 (61.22%). This indicates that CA125 is a better marker than NLR or PLR alone or even if considered together with CA125, to distinguish malignant from benign ovarian masses preoperatively. But if CA125 is less than 35 IU/ml and NLR < 3.09, then the chances of the ovarian mass being benign are more. The best positive predictive value is indicated by PLR and CA125≥35 together (62.75%) whereas the best negative predictive value is seen with NLR and CA125<35 (78.95%). Therefore, if CA125 is more than 35 and PLR ≥ 203.68, the ovarian mass is likely to be malignant. If NLR<3.09 and CA125<35, the ovarian mass is more likely to be benign. As per the statistics, the diagnostic accuracy of NLR and CA125<35 is better (63.01%) than the other parameters (Table-1).

Discussion

The carcinogenesis of different types of tumors, including ovarian cancer (OC), has been associated with chronic inflammation. There are multiple mechanisms involving inhibition of apoptosis, angiogenesis, non-repair or deliberate DNA damage, and overexpression of cytokines and inflammatory mediators which advance this process. In addition, SIR mediators weaken the immune system. This causes an increase in the concentrations of leukocytes, neutrophils, platelets, C-reactive protein (CRP) and fibrinogen, and decreased levels of albumin and lymphocytes.[3] The majority of adnexal masses are benign and only ~20% are malignant. Hence the identification of novel markers in the preoperative period to determine the nature of the suspected adnexal masses has become essential.[7]

In the present study, we evaluated and compared CBC parameters alone and in combination with the CA125 levels and their diagnostic accuracy in 166 women with various types of ovarian tumors. We showed that the NLR, the PLR or their association with CA125 could not present a superior performance in the prediction of malignancy in the preoperative setting which was also proved by Yoshida et al,[3] but opposed to Khatib et al and Cramer et al, whose studies prove the contrary to be true.[5,6] Although in our study NLR and CA125<35 had the best negative predictive value, specificity and diagnostic accuracy out of all the parameters considered, these values are only fairly significant. This parameter may be useful to distinguish benign from malignant ovarian masses, but its clinical significance needs to be studied further.

NLR and PLR in our study show better sensitivity than specificity as compared to the study by Yoshida et al whose results had better specificity than sensitivity.[3] According to present study, NLR and PLR alone are only fairly significant to indicate preoperatively whether the adnexal mass is malignant.

Conclusion

Given the discrepancies in the results of various studies and the non-uniformity in the cut-off values for NLR and PLR, more studies need to be conducted to determine the cut-offs and also their clinical significance. Our study showed better statistical significance of NLR in combination with CA125 rather than with NLR alone. Hence, the significance of NLR and PLR with other sociodemographic factors as well as other biomarkers needs to be studied to further evaluate their significance to distinguish adnexal masses preoperatively to help make suitable therapeutic decisions.

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