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Malignancy In Adrenal Incidentalomas: Are Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio Significant?

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ABSTRACT

The aim of this study was to assess the potential of neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) as diagnostic and prognostic parameters in predicting the malignancy potential of adrenal incidentalomas (AI).
A retrospective analysis was conducted using data from a prospectively maintained database, including 66 patients with AI. The patients were categorized into two groups: Group M (malignancies) and Group B (benign conditions).
Postoperative pathological evaluation revealed adrenocortical cancer in eight patients (12.1%). No statistically significant differences were found between the groups in terms of NLR [Group M: 2.94 ± 1.78, Group B: 2.51 ± 1.08, p = 0.335] and PLR [Group M: 136.90 (98.7-354.05), Group B: 118.39 (28.5-315.32), p = 0.479]. However, analysis of adrenal mass size revealed a statistically significant difference, with Group M having a mean size of 80.5 mm (range: 40-146) and Group B having a mean size of 60.5 mm (range: 40-122) (p = 0.008).
While NLR and PLR showed numerical increases in malignant adrenal masses, their utility in differentiating between benign and malignant masses was not significant. Further investigation of NLR and PLR in larger cohorts of patients with AI is recommended to better understand their diagnostic and prognostic value in this context.

Keywords: Adrenal mass, malignancy, incidentaloma, PLR, NLR

Introduction

Adrenal incidentaloma (AI) refers to an asymptomatic adrenal mass incidentally detected during imaging procedures that were not specifically conducted for suspected adrenal pathology. Typically, masses smaller than 1 cm are not classified as AI. However, for tumors exceeding this size threshold, further diagnostic assessments are recommended to ascertain their hormone activity1. The prevalence of AI has witnessed a notable rise owing to the widespread utilization of high-resolution imaging techniques and improved accessibility. Approximately 2% of the general population is affected by AI, with this figure increasing to 7% among individuals aged 70 and above, while occurrences among those below 40 years of age are rare. Hormone activity is observed in about 10% of AI cases, with adrenocortical cancer (ACC) accounting for approximately 2%2.

In the general population, adrenal masses are typically asymptomatic and benign; however, their comprehensive evaluation is crucial due to the potential for hormone secretion or malignancy. ACC is associated with a grim prognosis, with survival rates of less than 5 years following diagnosis3. Therefore, prompt diagnosis and initiation of treatment are imperative upon detection of an adrenal mass. In our study, our objective was to investigate whether the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), which have been extensively explored as diagnostic and prognostic markers for various diseases in recent years, hold value in the assessment of AIs.

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Material and Methods

The present study involved a retrospective analysis of patients who underwent surgical intervention for adrenal masses at General Surgery Department during the period spanning from 2011 to 2021. Data pertaining to a total of 197 patients were extracted from a meticulously maintained prospective database. Patients presenting with hormonal activity, non-incidental detection of adrenal masses, insufficient diagnostic or follow-up information, and a history of malignancy were excluded from the study to ensure a homogeneous study population.

The patients' data were obtained from clinical follow-up and observation files. Various factors were evaluated, including demographic data, comorbidities, location of the adrenal mass, NLR, PLR, mass size, perioperative and postoperative complications, specimen extraction site, length of hospital stay, and postoperative pathology reports.

Tumor size was measured using preoperative magnetic resonance (MR) or computed tomography (CT) images. NLR and PLR values were calculated based on laboratory measurements obtained upon admission to the hospital.

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) software version 25.0 for Windows. The normality of the data was assessed using the Kolmogorov-Smirnov test and graphical methods. If the data followed a normal distribution, the mean and standard deviation were used for reporting. For non-normally distributed data, the median and range (min-max) were employed. Additionally, numerical values were presented as counts (n) and percentages (%).

The chi-square test was used for comparing two categorical variables, while the independent samples t-test was applied for comparing a categorical variable with a normally distributed numerical variable. The Mann-Whitney U test was used when the numerical variable did not follow a normal distribution. All statistical calculations were two-sided, and a p-value of less than 0.05 was considered statistically significant at a 95% confidence interval.

Results

The data from a total of 197 patients who underwent adrenalectomy for adrenal masses were analyzed, at General Surgery Department. Among these patients, adrenal masses were incidentally detected in 66 cases, accounting for 33.5% of the total.

Among the 66 patients who underwent adrenalectomy for adrenal incidentalomas (AIs), 48 were female (72.7%). The mean age of the patients was 49.59 ± 11.36 years. The majority of the masses were located in the right adrenal gland, with 36 cases (54.5%). Comorbid diseases were absent in 21 patients (31.8%). Postoperative pathological evaluation revealed ACC in eight patients (12.1%). The postoperative pathology results of patients with benign pathology are summarized in Table 1.

The patients were categorized into two groups: malign (Group M) and benign (Group B). There was no significant difference in age between the two groups (49.63 ± 13.98 years for Group M and 49.59 ± 11.10 years for Group B, $p = 0.094$). No difference was detected between the two groups in terms of the rate of comorbidities ($p = 0.239$), side ($p = 0.630$) and gender ($p = 0.878$). The mean NLR value in Group M was 2.94 ± 1.78, while it was 2.51 ± 1.08 in Group B. However, there was no statistically significant difference in NLR between the two groups ($p = 0.335$). Similarly, there was no significant difference in PLR values between the groups [136.90 (98.7-354.05) for Group M and 118.39 (28.5-315.32) for Group B, $p = 0.479$]. On the other hand, the size of the adrenal masses differed significantly between the groups, with a mean size of 80.5 mm (40-146) in Group M and 60.5 mm (40-122) in Group B. Adrenal masses were larger in patients with statistically malignant masses ($p = 0.008$). Detailed characteristics of Groups M and B are summarized in Table 2.

NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio

In the subanalysis of Group M, the mean follow-up period for the patients was 63.3 (7-119) months. During the follow-up period, metastases were observed in three patients, with metastatic sites including the liver (p1), lung (p2), and lung with multiple bones (p3).

Discussion

Adrenal tumors frequently come to light incidentally during cross-sectional abdominal imaging conducted for purposes unrelated to adrenal masses. The initial inquiry revolves around ruling out malignancy, followed by a meticulous assessment of adrenal hormones. Surgical intervention is warranted in cases of evident hormone secretion, such as primary aldosteronism, adrenal Cushing's syndrome, or pheochromocytoma. However, the management of subclinical hormone secretion remains a subject of ongoing debate in the field.

Certain researchers posit that adrenal incidentalomas (AI) should not be categorized as such if the imaging study was conducted during the evaluation of a

Table 1: Postoperative Pathology Results of Benign Adrenal Incidentalomas

Pathologicalresults	Patients (n)	%
Nonfunctional adenoma	44	67
Pheochromocytoma	6	9
Adrenal cyst	4	6
Myelolipoma	2	3
Ganglioneuroma	1	1,5
Corticalhyperplasia	1	1,5

Table 2: Comparative Characteristics of Groups M and B

	Grup M (n=8)	Grup B (n=58)	p
Age (year)	49.63±13.98	49.59±11.10	0.994
NLR	2.94±1.78	2.51±1.08	0.335
PLR	136.9 (98,70-354,05)	118.39 (28.5-315.32)	0.479
Tumor size (mm)	60.5 (40-146)	40.5(40-122)	0.008

known non-adrenal malignancy. Consequently, given the primary purpose of imaging for malignancy screening, the presence of an adrenal mass is more likely to signify metastasis. Recent studies have indicated a prevalence of metastasis in AI cases, ranging at approximately 7.5%, and have further suggested that the likelihood of malignancy increases by 22-fold when AI is detected during cancer staging4. During patient selection for our study, we specifically excluded individuals with a history of malignancy to mitigate the risk of AI representing a metastatic mass. Among patients who underwent adrenalectomy for AI, malignancy was identified in 12.1% of cases. This rate aligns with the range reported in the existing literature (0.7-15%) (1). Numerous studies have demonstrated a higher prevalence of adrenal incidentalomas (AIs) in women, while the risk of malignancy associated with AIs appears to be greater in men5,6. In our comprehensive study group, comprising individuals with AI, 72.7% were women. Moreover, among those who were diagnosed with malignancy, 75% were women.

Thorough evaluation of preoperative clinical findings, blood values, and imaging is essential to exclude malignancy following the detection of an adrenal mass. Nonetheless, the definitive diagnosis relies on pathological examination following adrenalectomy. The European Network for the Study of Adrenal Tumors recommends the assessment of basal cortisol, ACTH, dehydroepiandrostenedione sulfate, 17-hydroxyprogesterone, testosterone, androstenedione, estradiol, as well as the dexamethasone suppression test and urinary free cortisol, when there is suspicion of adrenal carcinoma7. However, none of these tests alone are adequate to differentiate ACC from adrenal adenoma. This underscores the necessity for novel parameters that can aid in further investigation and facilitate prompt diagnosis. It should be noted that ACC carries a dismal prognosis, with a life expectancy of less than 5 years from the time of diagnosis8.

ACC has traditionally been regarded as non-functional. Nevertheless, research has demonstrated that certain ACCs are capable of secreting urinary steroid metabolites. Consequently, there has been recent utilization of metabolic analysis of steroids in urine for this purpose9. However, a comprehensive examination of the literature reveals the necessity for prospective studies involving a substantial patient population in order for this test to become integrated into routine clinical practice9.

In a separate investigated study, the sensitivity of FDG PET/CT in the assessment of adrenal masses for detecting ACC was determined to be 86.7%, with a specificity of 86.1%10. Nonetheless, performing PET/CT examinations for all adrenal masses is not deemed cost-effective. Rather, this diagnostic modality may be considered for patients with a heightened risk of malignancy in the preoperative period.

Conventional imaging modalities can effectively identify adrenal masses that exhibit radiological features indicative of potential malignancy. Nevertheless, the diagnosis of such masses, particularly those smaller than 4 cm, presents challenges. In cases where imaging findings suggest malignancy or functional adrenal tumors, regardless of the size of the mass, surgical intervention is recommended. The risk of ACC is directly correlated with tumor size: masses larger than 4 cm demonstrate a sensitivity of 97% and a specificity of 52%, while

masses larger than 6 cm exhibit a sensitivity of 91% and a specificity of 80%11. Consequently, tumor size serves as an additional indication for surgical intervention12. The findings of our study further support the accuracy of these established principles.

NLR and PLR, the primary focus of this study, have been extensively investigated due to their ease of measurement. These ratios serve as valuable indicators not only for acute viral or bacterial infections but also as markers to assess the systemic response, as demonstrated by several studies13.

Numerous studies have provided evidence supporting the use of systemic inflammatory markers for prognostic evaluation in various malignancies14-18. Moreover, the value of NLR as a predictor of disease activity and prognosis extends beyond malignant conditions, encompassing cardiovascular and autoimmune diseases. Elevated NLR has emerged as a significant prognostic indicator in both malignant and inflammatory processes19.

Bagante et al.20 demonstrated a relationship between systemic inflammatory markers and ACC. They reported that NLR and PLR were valuable indicators for assessing recurrence or disease-free survival in ACC. Similarly, Mechteld C de Jong et al. conducted a study on ACC and found that preoperative elevated NLR and PLR were associated with reduced overall survival, while high PLR was also linked to shorter disease-free survival21. In contrast to our findings, a study published in 2021 reported a correlation between NLR and tumor size. However, our study did not find any significant correlation between NLR or PLR and tumor size22.

Several limitations were encountered in this study that should be acknowledged. Firstly, the retrospective nature of the study design may have introduced inherent biases and limitations. The study relied on data collected retrospectively, and the time intervals between radiological imaging, laboratory results, and surgical intervention varied among patients, ranging from approximately 1 to 4 weeks. This variation in timing could have impacted the accuracy and reliability of interpreting the effect of NLR and PLR on survival outcomes. A prospective study design with standardized timing of assessments would have provided more robust and accurate results.

Another limitation stems from the fact that only patients who underwent surgery were included in the analysis, while the data of patients with AIs who were managed conservatively without surgical intervention could not be accessed and evaluated. This introduces a potential selection bias, as patients who underwent surgery may have had different clinical characteristics or disease progression compared to those managed non-surgically. Consequently, the generalizability of the findings to the broader population of patients with AIs may be limited.

Moreover, the small sample size of the study may have affected the statistical power and precision of the results. In addition, one of the limitations of the study is that the number of patients is not close to each other between the two groups. The numerical differences in NLR and PLR between the malignant and non-malignant groups observed in the analysis did not reach statistical significance, likely due to the limited number of patients included in the study. A larger sample size would be necessary to detect more subtle differences and provide more conclusive evidence regarding the prognostic value of NLR and PLR in predicting malignancy.

In conclusion, the retrospective design, variability in timing of assessments, limited inclusion of surgically treated patients, and small sample size represent important limitations of this study. These limitations should be taken into account when interpreting the results and generalizing them to clinical practice. Further prospective studies with larger patient populations are needed to confirm the prognostic value of NLR and PLR in predicting malignancy in patients with adrenal tumors.

ACC is a malignancy characterized by a poor prognosis, underscoring the importance of promptly evaluating incidentally detected adrenal masses and providing appropriate treatment. The availability of additional parameters beyond imaging could expedite the diagnostic process for clinicians. In this regard, NLR and PLR have been considered as biomarkers that offer quick and easy evaluation. However, our findings indicate that although NLR and PLR levels tend to be elevated in malignant masses, their utility in differentiating benign adrenal masses from ACC remains inconclusive. Radiological imaging and tumor characteristics continue to be the primary factors for diagnosing malignancy. Nevertheless, further investigation of NLR and PLR in large patient populations with adrenal incidentalomas is warranted. These investigations would contribute to a more comprehensive understanding of the potential role of NLR and PLR in the evaluation and management of adrenal masses.

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