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RESEARCH ARTICLE

Association of Aldosterone Excess with Hematological Parameters and Inflammatory Indices in Hypertensive Patients

Hipertansif Hastalarda Aldosteron Fazlalığının Hematolojik Parametreler ve İnflamatuvar İndekslerle İlişkisi

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ABSTRACT

Objective: Despite being one of the most common causes of secondary hypertension, primary aldosteronism (PA) is frequently underdiagnosed. This study aimed to evaluate the associations between biochemical markers used in PA screening (plasma aldosterone concentration [PAC], plasma renin activity [PRA], and aldosterone-to-renin ratio) and routinely measured hematological parameters (leukocyte, neutrophil, lymphocyte, and platelet counts), as well as inflammatory indices derived from these parameters (neutrophil-to-lymphocyte ratio [NLR], platelet-to-lymphocyte ratio [PLR], and the Systemic Immune-Inflammation Index [SII]).

Materials and Methods: This retrospective study analyzed data from 169 hypertensive patients who underwent PA screening between January 2021 and December 2023. Patients were grouped according to PAC cut-off values of ≥15 ng/dL and ≥30 ng/dL. Associations between PAC, PRA, and hematological parameters were assessed using correlation, multivariable linear regression, and receiver operating characteristic (ROC) curve analyses.

Results: Platelet count was significantly higher in patients with PAC ≥15 ng/dL and PAC ≥30 ng/dL ($p = 0.041$ and $p < 0.001$, respectively). In multivariable regression analyses, platelet count ($p = 0.001$), PLR ($p = 0.012$), and SII ($p = 0.044$) remained independently associated with PAC. In ROC analysis, platelet count demonstrated statistically significant discriminative performance for PAC ≥30 ng/dL (AUC = 0.727, $p = 0.001$).

Conclusion: Leukocyte-based hematological parameters and inflammatory indices were not significantly associated with PA screening markers. However, the modest association between platelet count and PAC suggests a potential link with aldosterone activity. Further studies are needed to clarify the clinical relevance of this finding.

Keywords: Hypertension, Neutrophil-to-Lymphocyte Ratio, Systemic Immune-Inflammation Index, Platelet, Platelet-to-Lymphocyte Ratio

ÖZET

Amaç: Primer aldosteronizm (PA), sekonder hipertansiyonun en yaygın nedenlerinden biri olmasına rağmen sıklıkla tanı konulamamaktadır. Bu çalışmada, PA taramasında kullanılan biyokimyasal belirteçler olan plazma aldosteron konsantrasyonu (PAC), plazma renin aktivitesi (PRA) ve aldosteron-renin oranı (ARR) ile hemogram analizinden elde edilen lökosit, nötrofil, lenfosit ve trombosit (PLT) sayıları ve bu parametrelerden türetilen nötrofil/lenfosit oranı (NLR), trombosit/lenfosit oranı (PLR) ve Sistemik İmmün-İnflamasyon İndeksi (SII) gibi göstergeler arasındaki ilişkilerin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu retrospektif çalışmada, Ocak 2021–Aralık 2023 tarihleri arasında PA taraması yapılan 169 hipertansif hastanın verileri analiz edildi. Hastalar PAC eşik değerlerine göre ≥15 ng/dL ve ≥30 ng/dL olmak üzere iki gruba ayrıldı. PAC, PRA ve hematolojik parametreler arasındaki ilişkiler korelasyon analizi, çok değişkenli lineer regresyon ve ROC eğrisi analizi kullanılarak değerlendirildi.

Bulgular: Trombosit sayısı, hem PAC ≥15 ng/dL hem de PAC ≥30 ng/dL gruplarında anlamlı olarak daha yüksek bulundu (sırasıyla $p = 0.041$ ve $p < 0.001$). Çok değişkenli regresyon analizinde PLT ($p = 0.001$), PLR ($p = 0.012$) ve SII ($p = 0.044$) PAC ile bağımsız olarak ilişkili kaldı. ROC analizinde trombosit sayısının PAC ≥30 ng/dL için istatistiksel olarak anlamlı bir ROC paterni gösterdiği saptandı (AUC = 0.727; $p = 0.001$).

Sonuç: Lökosit temelli hematolojik parametreler ve inflamatuvar indeksler PA tarama belirteçleri ile anlamlı ilişki göstermemiştir. Bununla birlikte, trombosit sayısı ile PAC arasındaki mütevazı ilişki, trombosit sayısının aldosteron aktivitesi ile ilişkili olabileceğini düşündürmektedir. Bu bulgunun klinik öneminin netleşmesi için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Hipertansiyon, nötrofil/lenfosit oranı, sistemik immün-inflamasyon indeksi, trombosit, trombosit/lenfosit oranı

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INTRODUCTION

Primary aldosteronism (PA) is the most common cause of secondary hypertension (1). The prevalence of PA in the general hypertensive population is approximately 5.9%, but it may reach up to 20% among patients with resistant hypertension (2). Despite being associated with an increased risk of cardiovascular events and target organ damage, PA often remains an underrecognized cause of hypertension (1,3). Although effective targeted treatment options are available, the complexity of the diagnostic process and the limited applicability of screening algorithms in routine clinical practice result in a high rate of underdiagnosis (4,5). This situation highlights the need for practical, low-cost, and accessible biomarkers that can support early diagnosis and risk stratification in PA.

In recent years, basic cellular parameters obtained from hemogram analysis (leukocyte, neutrophil, lymphocyte, and platelet counts) and indices derived from these parameters (neutrophil-to-lymphocyte ratio [NLR], platelet-to-lymphocyte ratio [PLR], and Systemic Immune-Inflammation Index [SII]) have been extensively studied in the diagnostic and prognostic assessment of many systemic diseases, particularly cardiovascular conditions (6,7). Various studies have demonstrated that aldosterone exerts significant effects not only on sodium retention and blood pressure regulation but also on vascular inflammation, endothelial dysfunction, and hemostatic balance (8). These pathophysiological effects may be indirectly reflected in circulating blood elements and inflammatory markers. Considering the impact of glucocorticoids on leukocyte distribution and platelet functions, it can be suggested that aldosterone, another adrenal-derived steroid hormone, may similarly affect the hematological system (9).

In this context, examining the association between hyperaldosteronism due to PA and hematological parameters may help identify complementary biomarkers for screening and risk stratification. However, direct human data regarding the effects of aldosterone on the hematological system remain limited, and current knowledge is largely based on indirect observations and experimental studies (10,11).

In this study, we aimed to evaluate the associations between biochemical markers used in PA screening (plasma aldosterone concentration [PAC], plasma renin activity [PRA], and aldosterone-to-renin ratio [ARR]) and hematological parameters (leukocyte, neutrophil, lymphocyte, and platelet counts), as well as inflammatory indices derived from these parameters (NLR, PLR, and SII) in hypertensive individuals. We also sought to explore their potential value as non-invasive and easily accessible screening tools that may assist in risk stratification for PA, particularly in individuals with elevated PAC levels.

MATERIALS AND METHODS

Study Design and Population

This retrospective study included 169 patients who were referred to the endocrinology outpatient clinic for evaluation of secondary hypertension and underwent screening tests for PA between January 2021 and December 2023. Demographic, clinical, and laboratory data were retrospectively obtained from the electronic health record system of the hospital.

Patient Selection

The inclusion criteria were established indications for PA screening, including resistant hypertension, hypertension accompanied by hypokalemia (even when induced by diuretic use), adrenal incidentaloma, early-onset hypertension, obstructive sleep apnea, and a family history of PA. The exclusion criteria were age under 18, pregnancy, chronic kidney disease, renovascular disease, pheochromocytoma, and other causes of secondary hypertension; conditions that could potentially affect hematological parameters (diabetes mellitus, malignancy, autoimmune or autoinflammatory diseases, hematologic disorders, chronic liver disease, and active/chronic infections); and routine use of drugs known to influence hematological parameters, including acetylsalicylic acid, steroidal and non-steroidal anti-inflammatory agents, or comparable medications.

PA screening was conducted only in patients for whom testing protocols were consistent with current guidelines (12,13). Accordingly, essential criteria for inclusion involved the discontinuation of medications affecting the renin-aldosterone axis (diuretics, beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists) at least two to four weeks before testing in patients on antihypertensive therapy. If necessary, alpha blockers and/or non-dihydropyridine calcium channel blockers, which are known to have minimal effects on ARR, were used. In hypokalemic cases, serum potassium levels were normalized prior to testing. All biochemical measurements were performed in the morning, after at least two hours in the upright position, and under standard laboratory conditions. Patients who did not comply with pre-test preparation or laboratory standards were excluded from the study.

Laboratory Parameters and Subgroup Analysis

In this study, leukocyte, neutrophil, lymphocyte, and platelet counts derived from hemogram analysis were evaluated as basic hematological parameters. The inflammatory markers derived from these values, namely NLR, PLR, and SII, were also analyzed.

NLR, PLR, and SII values were calculated using the following formulas:

- NLR = neutrophil count / lymphocyte count
- PLR = platelet count / lymphocyte count
- SII = (platelet count × neutrophil count) / lymphocyte count (14)

PA screening was conducted in accordance with widely accepted screening principles based on renin suppression and aldosterone elevation. Accordingly, the cut-off values were ≥15 ng/dL for PAC, <1 ng/mL/h for PRA, and >30 for ARR (9,11). In addition, an alternative threshold of PAC ≥30 ng/dL was analyzed to allow for the comparison of individuals with more pronounced aldosterone excess (12,13). Since the primary aim of the study was to evaluate the biological relationships

between screening markers and hematological parameters in hypertensive individuals undergoing PA screening, second-step confirmatory suppression tests recommended in the presence of strong clinical and laboratory suspicion (e.g., the saline infusion test or the captopril challenge test) were beyond the scope of this study and were not evaluated.

Laboratory Analysis

All biochemical analyses were performed in the central laboratory of our hospital. For hemogram analysis, venous blood samples were collected into ethylenediaminetetraacetic acid-containing tubes (Vacutainer, Becton, Dickinson and Company, USA) and analyzed within two hours. Hematological parameters were assessed using a Sysmex XN-10 automated hematology analyzer (Sysmex Inc., Kobe, Japan). All internal and external quality control results remained within acceptable limits throughout the analysis.

PAC was measured using the chemiluminescent immunoassay method with the Diasorin Liaison XL system (DiaSorin®, Italy). PRA was analyzed using the radioimmunoassay method with a gamma counter. For both PAC and PRA measurements, intra- and inter-assay coefficient of variation values were determined to be less than 5%. ARR was calculated by dividing PAC by PRA.

Ethical Approval

The study was conducted in accordance with the tenets of the Declaration of Helsinki, and ethical approval was obtained from the Ethics Committee for Non-Drug and Non-Medical Device Research of a local tertiary care training and research hospital, with the decision dated May 9, 2024, and numbered 2024/012.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics (v. 27.0). The normality of distribution for continuous variables was assessed using the Shapiro-Wilk test. Variables exhibiting a normal distribution were presented as mean ± standard deviation, whereas non-normally distributed data were reported as median (25th–75th percentile). For comparisons between groups, the independent-samples t-test was used for normally distributed variables, while the Mann-Whitney U test was applied for those not normally distributed.

Associations between PAC, PRA, ARR, and hematological/inflammatory parameters were evaluated using Spearman correlation analysis. To identify variables independently associated with PAC levels, univariable and multivariable linear regression analyses were performed. Additionally, the performance of platelet count, PLR, and SII across PAC categories (≥15 ng/dL and ≥30 ng/dL) was evaluated using Receiver Operating Characteristic (ROC) curve analysis, and the area under the curve, optimal cut-off, sensitivity, and specificity values were calculated. A p-value of <0.05 was considered the threshold for statistical significance in all analyses.

RESULTS

The study included 169 patients, with a mean age of 43.60 ± 12.75 years (range, 19–66 years). Of the patients, 114 (67.5%) were women and 55 (32.5%) were men. Table 1 summarizes descriptive statistics regarding demographic characteristics, variables associated with hyperaldosteronism, and hematological and inflammatory parameters. To evaluate associations between PAC levels and hematological and inflammatory parameters, the patients were first grouped based on a PAC cut-off of 15 ng/dL and then analyzed using a 30 ng/dL cut-off.

In the analysis based on the 15 ng/dL cut-off value, platelet count was found to be significantly higher in the group with PAC levels ≥15 ng/dL (p = 0.041). In contrast, no statistically significant differences were observed in leukocyte, neutrophil, and lymphocyte counts or in the remaining hematological and

Table 1. Baseline Demographic Characteristics and Laboratory Parameters of the Sample

Variable	n = 169[1]
Age (years)	43.60 ± 12.75
Sex, n (%)	
Female	114 (67.5%)
Male	55 (32.5%)
PAC (ng/dL)	11.8 (8.215–19.700)
PRA (ng/mL/hour)	2.41 (0.90–5.53)
ARR (ng/dL per ng/mL/h)	5.67 (2.56–12.07)
Glucose (mg/dL)	96.92 ± 11.57
Creatinine (mg/dL)	0.778 ± 0.168
Leukocyte count ($\times 10^3/\mu L$)	7.75 ± 1.79
Neutrophil count ($\times 10^3/\mu L$)	4.29 (3.63–5.52)
Lymphocyte count ($\times 10^3/\mu L$)	2.22 (1.90–2.71)
Platelet count ($\times 10^9/L$)	272 (224.5–320.5)
SII	496.60 (399.50–707.75)
NLR	1.86 (1.53–2.53)
PLR	114.72 (92.27–152.73)

[1]n (%), mean ± standard deviation, median (25th–75th percentile)
Abbreviations: PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone-to-renin ratio; SII, Systemic Immune-Inflammation Index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

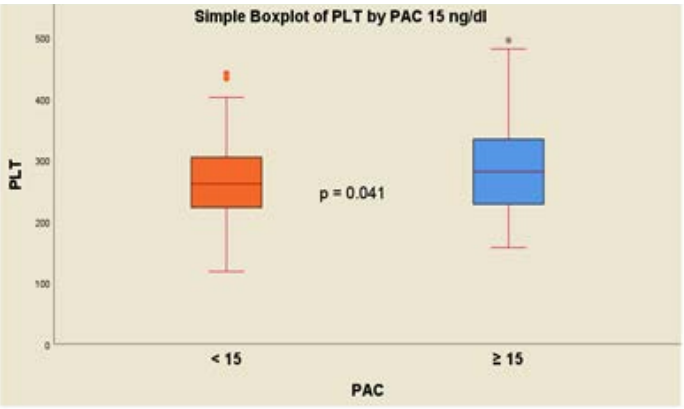

Figure 1. Boxplot graph showing the distribution of platelet count (PLT) in the group with plasma aldosterone concentration (PAC) ≥15 ng/dL

Table 2. Hematological and Inflammatory Parameters by PAC (<15 vs. ≥15 ng/dL)

Variable	PAC <15 ng/dL (n = 108[1])	PAC ≥15 ng/dL (n = 61[1])	p[2]
LEU (×10³/μL)	7.72 ± 1.88	7.78 ± 1.64	0.837
NEU (×10³/μL)	4.16 (3.47–5.00)	4.75 (3.80–5.62)	0.370
LYM (×10³/μL)	2.24 (1.89–3.07)	2.19 (1.72–2.98)	0.935
PLT (×10³/μL)	261 (221–305)	281 (215–323)	0.041
NLR	1.82 (1.39–2.37)	2.04 (1.51–2.71)	0.436
PLR	110.5 (92.3–144.5)	118.7 (97.5–160.0)	0.138
SII	479.9 (366.8–608.2)	538.8 (405.5–710.4)	0.094

[1]Presented as n (%), mean ± standard deviation, or median (25th–75th percentile), [2]Mann-Whitney U test or independent-samples t-test
Abbreviations: PAC, plasma aldosterone concentration; PRA, plasma renin activity; SD, standard deviation; LEU, leukocyte count; NEU, neutrophil count; LYM, lymphocyte count; PLT, platelet count; SII, Systemic Immune-Inflammation Index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Table 3. Hematological and Inflammatory Parameters by PAC (<30 vs. ≥30 ng/dL)

Variable	PAC <30 ng/dL (n = 147[1])	PAC ≥30 ng/dL (n = 22[1])	p[2]
LEU (×10³/μL)	7.71 ± 1.78	8.00 ± 1.91	0.474
NEU (×10³/μL)	4.26 (3.61–5.55)	4.72 (3.66–5.47)	0.573
LYM (×10³/μL)	2.21 (1.87–2.70)	2.24 (1.99–2.81)	0.489
PLT(×10³/μL)	263.00 (223.00–302.50)	335.00 (270.25–393.00)	<0.001
NLR	1.85 (1.53–2.48)	2.05 (1.35–2.63)	0.870
PLR	112.27 (92.00–146.91)	147.73 (93.12–205.14)	0.114
SII	488.23 (380.42–643.85)	595.51 (415.28–951.64)	0.086

[1]Presented as n (%), mean ± standard deviation, or median (25th–75th percentile), [2]Mann–Whitney U test or independent-samples t-test
Abbreviations: PAC, plasma aldosterone concentration; PRA, plasma renin activity; LEU, leukocyte count; NEU, neutrophil count; LYM, lymphocyte count; PLT, platelet count; SII, Systemic Immune-Inflammation Index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

inflammatory parameters (NLR, PLR, and SII) (Table 2). In the comparison based on the 30 ng/dL cut-off, platelet count was statistically significantly elevated in patients with PAC levels ≥30 ng/dL ($p < 0.001$). Although NLR, PLR, and SII showed a trend toward higher values in the elevated PAC group, the differences did not reach statistical significance (Table 3). Boxplot graphs illustrating the distribution of platelet count in groups with PAC levels ≥15 ng/dL and ≥30 ng/dL are presented in Figures 1 and 2, respectively.

In the analysis stratified by PRA levels, no statistically significant differences were observed in hematological and inflammatory parameters between the <1 ng/mL/h (n = 46) and ≥1 ng/mL/h (n = 123) groups ($p > 0.05$). Similarly, there were no statistically significant differences in these parameters between patients with ARR <30 (n = 149) and those with ARR ≥30 (n = 20) ($p > 0.05$). When comparing the subgroup of patients meeting both criteria (PRA <1 ng/mL/h and PAC ≥15 ng/dL) (n = 15) with those not meeting these criteria (n = 154), there were no statistically significant differences in any of the evaluated parameters ($p > 0.05$). The median NLR value was found to be higher in patients with PAC ≥15 ng/dL [2.22 (1.81–2.96)], with this difference approaching statistical significance ($p = 0.080$).

Hematological and inflammatory parameters were also compared using the Mann-Whitney U test between the high-risk patient group meeting all biochemical criteria suggestive of PA (PAC ≥15 ng/dL, PRA <1 ng/mL/h, and ARR >30; n = 9) and those not meeting these criteria (n = 160). No statistically significant differences were observed for leukocyte count ($p = 0.721$), neutrophil count ($p = 0.944$), lymphocyte count ($p = 0.209$), platelet count ($p = 0.641$), NLR ($p = 0.307$), PLR ($p = 0.193$), or SII ($p = 0.462$).

Associations between screening markers and hematological and inflammatory parameters were assessed using Spearman correlation analysis (n = 169). A weak but statistically significant positive correlation was observed between PAC and platelet count (rho = 0.176; $p = 0.022$) (Figure 3). However, there were no statistically significant correlations between PAC and the

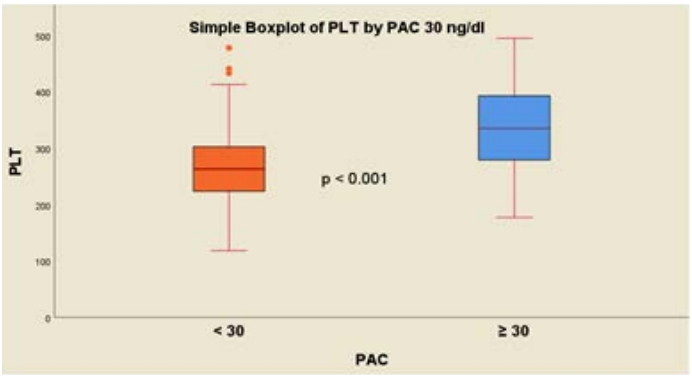

Figure 2. Boxplot graph showing the distribution of platelet count (PLT) in the group with plasma aldosterone concentration (PAC) ≥30 ng/dL

Table 4. Univariable Linear Regression Analyses of Variables Associated with Plasma Aldosterone Concentration

	Unstandardized Coefficients		Standardized Coefficients	95% CI		
Variable	**B**	**Std. Error**	**β**	**Lower Bound**	**Upper Bound**	**p**
Age (years)	-0.185	0.100	-0.143	-0.382	0.011	0.064
Sex (Female)	4.040	2.709	0.115	-1.309	9.389	0.138
Glucose (mg/dL)	-0.034	0.111	-0.024	-0.254	0.185	0.758
Creatinine (mg/dL)	-3.260	7.641	-0.033	-18.346	11.827	0.670
LEU (10^3/μL)	0.175	0.716	0.019	-1.237	1.588	0.807
NEU (10^3/μL)	0.419	0.917	0.035	-1.392	2.230	0.648
LYM (10^3/μL)	-0.340	1.783	-0.015	-3.861	3.181	0.849
PLT (10^3/μL)	0.068	0.018	0.286	0.033	0.102	<0.001
PLR	0.082	0.027	0.229	0.029	0.136	0.003
NLR	0.491	1.483	0.026	-2.437	3.419	0.741
SII	0.009	0.004	0.165	0.001	0.017	0.032

Abbreviations:
PAC, plasma aldosterone concentration; LEU, leukocyte count; NEU, neutrophil count; LYM, lymphocyte count; PLT, platelet count; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, Systemic Immune-Inflammation Index; CI, confidence interval; B, unstandardized coefficient; β (beta), standardized coefficient.

remaining parameters and indices (p > 0.05). In addition, PRA and ARR had no statistically significant correlations with any of the evaluated variables (p > 0.05). Univariable linear regression analyses were conducted to assess the associations between PAC levels and clinical, biochemical, and hematological parameters (n = 169). These analyses revealed that platelet count, PLR, and SII were positively associated with PAC (p < 0.05), with the strongest association observed for platelet count. The results of all univariable regression analyses are summarized in Table 4.

To determine factors independently associated with PAC levels, three separate multivariable linear regression models were constructed (Table 5). Since platelet count is a component of PLR and SII, these indices were analyzed in separate models to avoid multicollinearity and clarify their individual associations. All models included age, sex, glucose, and creatinine as covariates. In Model 1, neutrophil, lymphocyte, and platelet counts were added to the covariates, and only platelet count was found to be a statistically significant predictor of PAC levels (B = 0.068, p = 0.001). In Model 2, PLR was included instead of the individual hematological components and was also significantly associated with PAC levels (B = 0.071, p = 0.012); however, this model demonstrated a lower explanatory power than Model 1 (R^2 = 0.084, p = 0.028). In Model 3, SII and age emerged as statistically significant predictors (B = 0.008, p = 0.044 and B = -0.217, p = 0.045, respectively), although this model had the lowest explanatory power among the three.

ROC analyses were performed to evaluate how platelet count, PLR, and SII performed across different PAC categories (≥15 ng/dL and ≥30 ng/dL), and the area under the curve, optimal cut-off, sensitivity, and specificity values were calculated for each parameter. The corresponding results are presented in Table 6 and Figure 4.

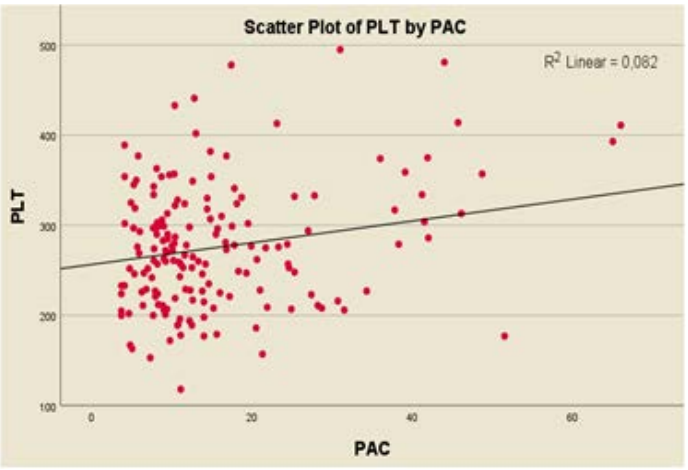

Figure 3. Scatter plot graph showing the association between plasma aldosterone concentration (PAC) and platelet count (PLT)

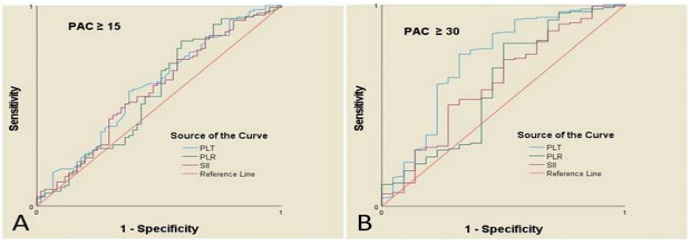

Figure 4. Receiver operating characteristic (ROC) curves of platelet count (PLT), platelet-to-lymphocyte ratio (PLR), and Systemic Immune-Inflammation Index (SII), demonstrating their statistical performance across plasma aldosterone concentration (PAC) categories:
A) PAC ≥15 ng/dL,
B) PAC ≥30 ng/dL.

Table 5. Comparison of multivariable linear regression models assessing factors associated with plasma aldosterone concentration

Model	Independent Predictor(s) and p-values	Model	
		R^2	p
Model 1 (PLT)*	Platelet count (p = 0.001)	0.115	0.006
Model 2 (PLR)*	PLR (p = 0.012)	0.084	0.028
Model 3 (SII)*	SII (p = 0.044), Age (p = 0.045)	0.068	0.044

*Note:
Model 1 includes age, sex, glucose, creatinine, neutrophil count, lymphocyte count, and platelet count.
Model 2 includes: age, sex, glucose, creatinine, neutrophil count, and PLR.
Model 3 includes: age, sex, glucose, creatinine, and SII.
Abbreviations: PLR, platelet-to-lymphocyte ratio; SII, Systemic Immune-Inflammation Index

Table 6. ROC analysis of PLT, PLR, and SII for PAC thresholds ≥15 and ≥30 ng/dL

Variable	PAC (ng/dL)	AUC	p	95% CI	Optimal Cut-off	Sensitivity (%)	Specificity (%)
PLT	≥15	0.595	0.041	0.504–0.686	273.000	62.3	57.4
	≥30	0.727	0.001	0.595–0.858	304.000	68.2	75.5
PLR	≥15	0.569	0.138	0.474–0.664	151.630	41.0	82.4
	≥30	0.605	0.114	0.460–0.749	154.320	50.0	81.0
SII	≥15	0.578	0.094	0.486–0.669	602.970	42.6	73.1
	≥30	0.614	0.086	0.479–0.748	488.900	72.7	50.3

Abbreviations: PAC, plasma aldosterone concentration; PLT: platelet count; PLR: platelet-to-lymphocyte ratio; SII: Systemic Immune-Inflammation Index; AUC: area under the curve; CI: confidence interval.

DISCUSSION

This study evaluated the associations between PA screening markers, hematological parameters, and inflammatory indices in 169 hypertensive individuals. The potential contribution of these parameters to the screening process was also assessed. A particularly strong and consistent positive correlation was observed between platelet count and PAC. Subgroup analyses using PAC cut-offs of ≥15 ng/dL and ≥30 ng/dL revealed a statistically significant increase in platelet count with higher PAC levels. Univariable regression analyses indicated positive associations of PAC with platelet count, PLR, and SII. In multivariable models, platelet count remained the strongest independent marker, while PLR and SII retained weaker but significant associations. In contrast, no significant differences were observed between PAC and other hematological parameters. Furthermore, none of the hematological parameters or inflammatory indices had significant correlations with PRA or ARR. In ROC analysis, the discriminative performance of platelet count, PLR, and SII for PAC ≥15 ng/dL was low but showed improvement at PAC ≥30 ng/dL.

Overall, hemogram-derived inflammatory indices showed no significant association with aldosterone excess, except for a modest correlation with platelet count. The absence of significant associations between PAC and leukocyte, neutrophil, and lymphocyte counts or NLR suggests that these markers offer limited value in reflecting biological variability in aldosterone levels. The weak associations observed for PLR and SII appear to stem from the contribution of platelet count in the calculation of these indices. Moreover, the lack of significant associations between PRA and hematological parameters or inflammatory indices indicates that these indices also provide limited information regarding renin suppression. The low sensitivity and specificity of platelet count in the PAC ≥15 ng/dL category suggest that its contribution at this level is limited. In contrast, the improved discriminative performance of platelet count at PAC ≥30 ng/dL suggests that this parameter may provide supportive information in identifying individuals with more pronounced aldosterone elevation when planning PA screening. Although this finding does not indicate diagnostic utility, it suggests a modest association and underscores the need for further research to identify hypertensive patients who may have underlying hyperaldosteronism.

Current guidelines recommend ARR as the first-line screening test in high-risk patients in the presence of suppressed renin and elevated aldosterone levels. However, PA frequently remains undiagnosed in clinical practice due to suboptimal guideline implementation, variability in ARR cut-off values, and challenges in test standardization. Furthermore, PAC levels can be influenced by various external factors, such as medications, posture, and sodium intake, further reducing the diagnostic reliability of the test (12,13). Given these limitations, there has been growing research interest in complementary biomarkers that may allow PA to be identified more easily and reliably. Accordingly, various inflammatory markers such as high-sensitivity C-reactive protein, serum amyloid A, homocysteine, plasminogen activator inhibitor-1, and malondialdehyde have been investigated. Hemogram-derived inflammatory indices have also been explored as potential tools to differentiate hyperaldosteronism from other forms of hypertension (10). However, none of these parameters have yet been validated for routine clinical use.

The established association between hematological parameters and cardiovascular disease supports their

consideration as potential biomarkers in PA, a condition in which similar pathophysiological mechanisms are implicated. One such marker, NLR, reflects systemic inflammation and is one of the most commonly associated inflammatory indices in cardiovascular diseases. Large-scale studies in recent years have shown that NLR is an independent prognostic marker in predicting both all-cause and cardiovascular mortality (15). Nevertheless, data regarding the relationship between NLR and PA remain limited, and findings in the literature are largely heterogeneous. Some studies have reported lymphopenia and increased NLR in patients with PA, suggesting that this increase may be associated with major cardiovascular events and may serve as an independent risk marker for long-term prognosis (16,17). In contrast, in our study, lymphocyte count, neutrophil count, and NLR were not significantly associated with PAC or PRA. This finding is consistent with a multicenter study by Libianto et al., in which NLR levels did not significantly differ between patients with PA and hypertensive controls (10).

SII and PLR are derived inflammatory indices derived from blood cell counts: SII incorporates neutrophils, platelets, and lymphocytes, whereas PLR uses only platelets and lymphocytes. There is strong evidence in the literature linking high SII levels with mortality and disease severity (18–20). While PLR is also recognized as an inflammation marker (21), evidence for its relationship with PA remains limited. In our study, despite increased PAC levels, SII and PLR exhibited only a limited and statistically non-significant upward trend, and correlation analyses failed to demonstrate significant associations between these indices and PAC. However, in multivariable regression analyses, both PLR and SII were significantly associated with PAC. To isolate the individual effect of each index and avoid model multicollinearity, we analyzed platelet count, PLR, and SII in separate multivariable models. The decreasing statistical strength from platelet count to PLR and SII suggests that the associations observed for these indices may primarily reflect the influence of platelet count within their calculations. Supporting this, no similar pattern was observed for NLR, which does not include platelets in its composition. This indicates that the associations detected for PLR and SII may reflect platelet-dependent contributions rather than independent marker characteristics and that the specificity of these indices may therefore be limited. Considering this potential contribution, the association between platelet count and PAC was evaluated separately in our study, and a modest but statistically significant result was obtained.

Aldosterone affects more than vascular dysfunction and inflammation. It may also promote thrombosis through alterations in coagulation, impaired fibrinolysis, and endothelial dysfunction (22). These prothrombotic effects are associated with increased oxidative stress, production of reactive oxygen species, and reduced bioavailability of nitric oxide (23). Experimental animal models and in vitro studies have shown that aldosterone can affect platelet function and increase platelet accumulation in regions prone to endothelial injury (24-26). Moreover, chronic hyperaldosteronism has been reported to facilitate platelet aggregation and increase thrombotic susceptibility by disrupting the nitric oxide/cyclic guanosine monophosphate signaling pathway (27). The presence of mineralocorticoid receptors on platelet membranes further supports the possibility that aldosterone may exert direct effects on these cells (28). Evidence for the direct effects of aldosterone on platelets in human studies is limited. Existing knowledge consists primarily of indirect findings, such as changes in platelet function observed after treatment with renin-angiotensin-aldosterone system inhibitors (29,30).

The limited sensitivity and specificity of the PAC ≥15 ng/dL cut-off used in PA screening indicate that platelet count alone is not sufficient for diagnostic identification of aldosterone excess, although it may still reflect associated biological changes. Nevertheless, it is notable that the increase in platelet count becomes more apparent when PAC levels rise substantially. Particularly, the elevated platelet count observed at PAC ≥30 ng/dL may provide an indirect indication of hematological changes accompanying aldosterone excess. In current guidelines, PAC ≥30 ng/dL is considered a strong criterion for suspicion of PA when accompanied by appropriate clinical and laboratory findings, and it may even support surgical decision-making without adrenal venous sampling in some younger patients (13). The finding in this study that platelet count > 304,000/mm^3 had 68.2% sensitivity and 75.5% specificity in individuals exceeding PAC ≥30 ng/dL suggests that this parameter may provide modest complementary support in screening at higher PAC levels. Further research is needed to clarify the clinical relevance of this observation.

Due to the study methodology, the associations between first-stage PA screening criteria and hematological parameters were evaluated. Since confirmatory suppression tests were not performed, a definitive PA diagnosis could not be established, and comparisons between PA and essential hypertension were therefore not possible. Nonetheless, a small subgroup within our data who met first-stage criteria and could be considered at high risk for PA was examined separately. However, no statistically significant difference was detected in platelet count in this subgroup. A limited number of studies in the literature similarly report that platelet levels do not differ significantly between patients with PA and those with essential hypertension (10,31). The absence of an observed association between platelet count and PRA or ARR in our study is also consistent with these findings. At the same time, subgroup analyses showed that platelet count tended to increase with higher PAC levels, and this association remained independent in multivariable models, suggesting that although platelet count lacks diagnostic utility, it may still provide limited but clinically relevant supplementary information regarding biological variability in aldosterone levels.

According to current hypertension guidelines, mineralocorticoid receptor antagonists are recommended as the first-line treatment in patients with PA who are not suitable candidates for surgery. Despite this, platelet count is not yet considered in the selection of antihypertensive agents or in decisions regarding the initiation of antiplatelet therapy (32,33).

Medications acting on the renin-angiotensin-aldosterone system, especially angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists, not only suppress aldosterone secretion but also have regulatory effects on platelet function (29,30,34). These pharmacological observations support a possible pathophysiological link between aldosterone and platelet levels. In our study, the parallel trend between platelet count and changes in PAC levels provides an additional finding consistent with this possible link; however, it does not allow for any diagnostic or prognostic interpretation. Therefore, there is a need for larger studies including functional platelet parameters and long-term outcome data to determine the clinical relevance of platelets.

Study limitations

One major strength of this study is the simultaneous evaluation of both basic biochemical tests (PAC, PRA, and ARR) and various hematological parameters in a screening population composed of hypertensive individuals undergoing PA screening. However, the study also has several limitations. Specifically, it has a single-center, retrospective design, which may lead to selection bias and limits causal inference. In addition, second-stage confirmatory tests (e.g., the saline suppression test and the captopril challenge test) were not performed; therefore, patients with PA subtypes confirmed through adrenal venous sampling could not be included. Thus, it was not possible to evaluate potentially more pronounced differences in hematological parameters among patients with true PA. The lack of a significant difference in platelet count in the subgroup with simultaneous renin suppression and aldosterone elevation can be attributed to the limited sample size, preventing definitive conclusions.

As another limitation, the cut-off value determined for platelet count (304,000/mm^3) falls within the normal reference range, which necessitates cautious interpretation of this finding in a clinical context. Moreover, as the study evaluated associations only, the results cannot be interpreted as indicating causality. The low R^2 values in regression models indicate that most of the variation in PAC remains unexplained and that the effects of unmeasured confounders (particularly body mass index and smoking) may be substantial. Failure to control for these variables is another factor limiting the generalizability of the results. Lastly, as the study did not allow subgroup analyses based on hypertension stages or complications, a more detailed assessment of the relationship between hematological markers and disease severity could not be undertaken.

CONCLUSION

In this study, with the exception of platelet count, which had a modest association with aldosterone levels, none of the remaining hematological parameters or inflammatory indices derived from these parameters had significant associations with biochemical tests used in PA screening. The association between platelet count and PAC was consistently observed across multiple analytical approaches and was more pronounced in subgroups with markedly elevated PAC levels. Although these findings do not support platelet count as a diagnostic marker for PA, they suggest that it may provide modest supplementary information on hematological changes accompanying aldosterone excess. Larger, prospective studies including patients with confirmed PA are needed to clarify the clinical validity and potential applications of this observation.

DECLARATIONS

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