Can Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) Score Predict Adrenal Incidentaloma Growth?

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Can Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) Score Predict Adrenal Incidentaloma Growth?

Running title: HALP score in patients with adrenal incidentaloma

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Authors contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by CD and AD. The first draft of the manuscript was written by LO and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

All authors have declared that there is no conflict of interest.

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None

Data Availability Statement

The data underlying this study are patient records from Haydarpasa Numune Hospital Istanbul / Turkiye and contain potentially identifying and sensitive patient information. Therefore, these data are not publicly available due to privacy and ethical restrictions. Access to the de-identified data may be provided upon reasonable request to the corresponding author and with permission from the institutional ethics committee.

Abstract

Objective: The optimal management and follow-up strategies for adrenal incidentalomas (AIs) remain controversial, with conflicting guidelines on routine imaging versus surveillance. This study investigates the prognostic utility of the Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) score, previously validated in malignancies, as a potential predictor of AI growth over a one-year period.

Methods: This retrospective study included 66 female patients (aged 18–80 years) with incidentally detected adrenal masses, who underwent at least two imaging scans within a one-year period. The HALP score at diagnosis and the change in adrenal mass diameter between baseline and follow-up imaging were assessed. Growth of adrenal mass was defined as an increase in diameter ≥3 mm.

Results: Patients with growing AIs exhibited lower baseline HALP scores compared to those with stable lesions ($p = 0.093$). A significant negative correlation was observed between HALP score and diameter change in a subgroup of patients with growth ≥3 mm (Spearman's rho = -0.766, $p = 0.010$). However, HALP score was not a significant predictor of AI growth according to logistic regression analysis ($p > 0.05$).

Conclusion: Although an inverse association exists between the HALP score and AI growth, it lacks sufficient predictive accuracy to serve as a standalone marker for short-term prognosis. Larger-scale, long-term studies are needed to explore its potential role in AI management.

Key words: Adrenal incidentaloma, HALP score, Prognosis

Introduction

Adrenal incidentalomas (AIs) are adrenal masses >1 cm discovered during imaging for unrelated conditions(1). Their detection rate has increased significantly due to advancements in imaging technologies and heightened use during the COVID-19 pandemic. The prevalence of AIs in the general population rose from 0.4% in 1990 to 1.4% in 2022, with rates reaching 3.2% among individuals over 65 years (2). Approximately 8.7% of incidentally discovered adrenal masses are malignant, with adrenocortical carcinoma accounting for 0.3% and the remainder being metastases from other tumors (3). Tumor size is a key predictor of malignancy, with diameters >4 cm and unenhanced Hounsfield units >20 indicating higher risk (4). Additionally, studies have reported a slight positive correlation between the neutrophil-to-lymphocyte ratio and AI size (5), while growth rates differ between benign and malignant tumors, with benign adenomas growing <3 mm/year and malignant tumors >5 mm/year (6).

The Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) score, an index reflecting nutritional status and systemic inflammation, has emerged as a prognostic marker in various malignancies, including gastric, prostate, and renal carcinomas, as well as coronary heart disease (7). However, its role in predicting AI growth remains unexplored. The aim of our study is to investigate the relationship between the HALP score and AI progression over a one-year follow-up period, addressing a critical gap in the literature.

Materials and Methods

Study Design and Ethical Approval

This retrospective cross-sectional study was conducted at the Endocrinology and Metabolic Diseases Outpatient Clinic of Haydarpaşa Numune Hospital, University of Health Sciences, Istanbul, Turkey, between January 1, 2018, and February 20, 2023. The study protocol was approved by the Institution Ethics Committee (Approval No: 2024/8/5; Date: 01.08.2024). Informed consent was waived due to the retrospective nature of the study.

Patients and Sample Size

A total of 1506 patients diagnosed with adrenal incidentalomas (AIs) were screened retrospectively. The required sample size was calculated using G*Power software (version 3.1), assuming a medium effect size (0.6) and 90% power, yielding a minimum of 66 patients. After applying inclusion and exclusion criteria, 66 female patients (aged 18–80 years) with follow-up imaging and laboratory data were included (see Fig. 1 for the patient selection flowchart). Exclusion criteria included male patients, adrenal hyperplasia, cysts, lipomas, renal cell carcinoma metastasis, history of cancer, hormonal activation, recent infection, major trauma, diabetic ketoacidosis, severe liver failure, pregnancy, or an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² (Cockcroft-Gault formula).

Data Collection

The primary outcome was the change in adrenal mass diameter (≥3 mm considered significant growth (8) between baseline and follow-up imaging. Independent variables included age, HALP score, hemoglobin, albumin, lymphocyte, and platelet counts. The HALP score was calculated as follows:

HALP score=hemoglobin (g/L)×albumin (g/L)×lymphocyte count (n/L) / platelet count

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics (Version 21.0, Armonk, NY: IBM Corp.). Normality of continuous variables (age, laboratory parameters, HALP scores, and diameters) was assessed using the Shapiro-Wilk test and graphical methods. Normally distributed variables were expressed as mean ± standard deviation (SD), while non-normally distributed variables (e.g., diameter change) were reported as median (interquartile range, IQR). Between-group comparisons for diameter change were conducted using the Independent-Samples T-test. ANCOVA was used to assess HALP score changes with time as a covariate. The Quade test evaluated diameter change differences. Spearman's correlation coefficient analyzed the relationship between HALP score and diameter changes in subgroups. Logistic regression assessed the predictive value of HALP score on diameter change groups (<3 mm vs. ≥3 mm). A p-value <0.05 was considered statistically significant.

Results

Of the 66 female patients included, the mean age was 57.3 years (SD: 9.83). Baseline characteristics are summarized in Table 1. Patients were divided into two groups based on adrenal mass diameter change: <3 mm (stable group, n = 52) and ≥3 mm (growth group, n = 14). The mean baseline HALP score was 52.63 (SD: 17.53) in the stable group and 52.27 (SD: 12.40) in the growth group, with no statistically significant difference (Independent-Samples T-test, p = 0.093; Table 2).

A subgroup analysis of 10 patients with both an increased HALP score and diameter change ≥3 mm revealed a strong negative correlation (Spearman's rho = -0.766, p = 0.010). In contrast, no significant correlations were observed in other subgroups: increased HALP score with diameter change <3 mm (rho = -0.154, p = 0.472), decreased HALP score with diameter change ≥3 mm (rho = 0.60, p = 0.40), or decreased HALP score with diameter change <3 mm (rho = -0.066, p = 0.740).

Logistic regression analysis evaluating the predictive impact of baseline HALP score, follow-up HALP score, and HALP score change on diameter growth (<3 mm vs. ≥3 mm) showed no significant association (p > 0.05; Table 3).

Discussion

This study evaluated the association between the HALP score and adrenal incidentaloma (AI) growth over a one-year follow-up period. Our findings suggest that while patients with growing AIs (diameter change ≥3 mm) had lower baseline HALP scores compared to those with stable AIs, this difference was not statistically significant ($p = 0.093$). Moreover, logistic regression analysis indicated that the HALP score is not a reliable predictor of short-term AI growth ($p > 0.05$), highlighting its limited prognostic utility in this context.

The HALP score has been established as a prognostic marker in various malignancies, reflecting nutritional status and systemic inflammation (7). For instance, a meta-analysis demonstrated that cancer patients with low pretreatment HALP scores exhibit worse overall survival (9). Similarly, higher HALP scores have been associated with better prognosis and smaller tumor sizes in gastric cancer (10). In contrast, our study found a strong negative correlation between HALP score and diameter change in a subgroup of patients with growing AIs (rho = -0.766, $p = 0.010$), suggesting a potential inverse relationship. However, this finding was limited to a small subgroup ($n = 10$) and requires validation in larger cohorts.

Previous studies on AIs have identified size (>4 cm) and growth rate (>5 mm/year) as key predictors of malignancy (4)(6). Our study aligns with these observations, as benign adenomas in our cohort grew <3 mm/year, consistent with reported rates (6). Additionally, hypercortisolism has been linked to larger non-functioning adrenal tumors and may influence blood parameters such as those in the HALP score (11). Although our patients exhibited similar tumor sizes to those in prior studies, the lack of repeated adrenal hormone assessments limits our ability to evaluate subclinical hypercortisolism as a confounder.

The study has several limitations. First, its retrospective design introduces potential selection bias and confounding factors. Second, the one-year follow-up period may be insufficient

to capture long-term AI progression, particularly given the slow growth rates of benign adenomas. Third, the small sample size (n = 66) and the exclusion of male patients limit the generalizability of our findings. Women were overrepresented in our cohort, possibly due to higher rates of abdominal imaging and follow-up adherence, as noted in prior studies (11). Fourth, the HALP score's prognostic value may be more relevant in malignant diseases than in largely benign conditions like non-functioning AIs. Finally, loss to follow-up and incomplete data from the hospital database reduced the number of eligible patients.

Future research should focus on prospective, multicenter studies with larger sample sizes, longer follow-up periods, and inclusion of both genders to better elucidate the HALP score role in AI management. Additionally, incorporating repeated hormonal assessments could clarify the impact of subclinical hypercortisolism on HALP score dynamics.

In summary, this study adds novel information to the medical literature by being the first to explore the HALP score as a potential biomarker for adrenal incidentaloma growth. Although the HALP score did not emerge as a statistically significant predictor, the observed trend toward lower scores in patients with growing lesions suggests a possible link between nutritional-inflammatory status and adrenal tumor behavior. Clinically, these findings indicate that routine laboratory indices, when validated in larger cohorts, could complement imaging-based surveillance strategies and contribute to more individualized follow-up protocols in patients with incidentally discovered adrenal lesions.

Conclusion

This study demonstrates that the HALP score does not reliably predict adrenal incidentaloma (AI) growth over a one-year period, suggesting limited utility as a standalone prognostic marker in the short term. However, its inverse association with AI progression warrants

further exploration. Large-scale, prospective studies with extended follow-up durations are needed to fully elucidate the HALP score's potential role in AI management and its clinical relevance in distinguishing benign versus malignant adrenal masses.

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248 **Table 1.** Demographic, baseline, and follow-up characteristics of study participants and evaluation
249 of differences between groups
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	Post-Follow-Up Maximum Diameter Difference			p
	Total (n:66)	<3mm (n:52)	≥3mm (n:14)	
Age (year)	57.30±9.83	57.89±10.08	55.14±8.83	0.358
Baseline Alb (g/L)	4.30±0.25	4.31±0.22	4.26±0.35	0.570
Follow up Alb (g/L)	4.29±0.36	4.27±0.39	4.37±0.19	0.366
Baseline Hb (g/L)	12.99±1.17	12.97±1.22	13.07±1.00	0.778
Follow-up Hb (g/L)	12.78±1.29	12.68±1.37	13.16±0.87	0.223
Baseline Lym. (…)	2.55±0.82	2.54±0.84	2.57±0.73	0.913
Follow-up Lym. (…)	2.68±0.91	2.62±0.92	2.91±0.86	0.284
Baseline PLT (…)	278.76±76.11	279.20±79.92	277.14±62.44	0.929

Follow up PLT (…)	290.92±75.26	289.48±79.78	296.29±57.55	0.767
Follow-up time(year)	1.17±0.48	1.19±0.50	1.08±0.46	0.434
Baseline.HALP	52.55±16.49	52.63±17.53	52.27±12.40	0.944
Follow-up HALP	52.51±18.36	50.91±18.08	58.46±18.81	0.174
HALP Score Change†	-0.04±15.19	-1.72±15.51	6.19±12.55	0.108†
Baseline Length (mm)	21.06±8.32	21.23±8.41	20.43±8.23	0.751
Follow-up Length (mm)	21.35±8.64	20.11±8.22	25.99±8.88	**0.023**
Diameter Change (mm)#	0.001 (3.0)	0.001 (2.0)	5.00 (3.3)	**<0.001#**

Independent-Samples T Test . †Follow-up HALP Score – Baseline HALP Score. ANCOVA (with follow-up time as covariates) are reported F: 2.661, Adjusted R2: 0.040.# Follow-up diameter-Baseline diameter Quade test (with follow-up time as covariates) are reported F: 17,120 Adjusted R2: 0.199. **Abbreviation**: Alb: Albumin, Hb: Hemoglobin, Lym: Lymphocyte, PLT: Platelets.

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Table 2. Comparison of HALP score increase and decrease groups with diameter change groups

		Post-Follow-Up Maximum Diameter Change		p
		<3mm, %, (n)	≥3mm, %, (n)	
HALP Score Groups	Decreased	42.4 (28)	6.1 (4)	0.093
	Increased	36.4 (24)	15.2 (10)	
Total		78.8 (52)	21.2 (14)	

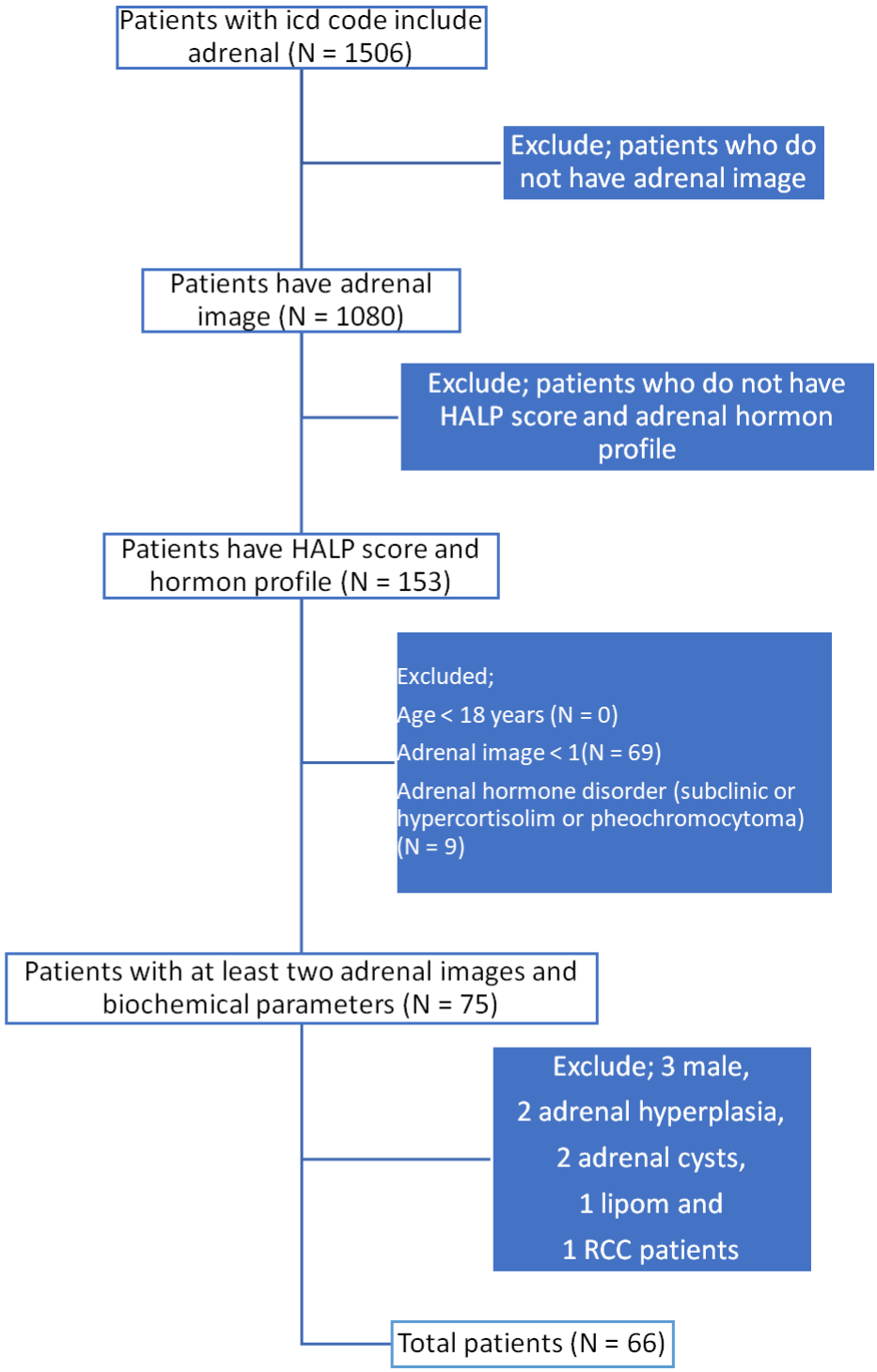
Chi-square test

Table 3. Logistic Regression Analysis of the Effect of HALP Scores on Diameter Change Groups (<3 mm and ≥3 mm).

Model	B	ε	p	ß	95% C.I.for EXP(B)	
					Lower	Upper
Baseline.HALP	-0.018	0.034	0.608	0.983	0.918	1.051
Follow-up HALP	0.026	0.032	0.410	1.026	0.965	1.092
HALP Score Group*	-0.538	0.942	0.568	0.584	0.092	3.699
Constant	-1.585	1.277	0.215	0.205		

Dependent variable: diameter change groups (<3 mm and ≥3 mm), Hosmer and Lemeshow Test: 0.361, Nagelkerke R^2: 0.083., ***** Decreased and Increased Follow-Up HALP Score Groups**,**

Abbreviations: ε: Standard error



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282 **Abbreviations**: RCC: Renal cell carcinoma, DST: Dexamethasone

283 **Figure 1**. Selection of participants and exclusion status

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