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Original Article

The HALP score as a novel predictor of coronary collateral circulation in patients with chronic total occlusion: a retrospective, single-center study

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ABSTRACT

Aims: The hemoglobin, albumin, lymphocyte, and platelet (HALP) score is a composite index reflecting inflammatory, nutritional, and hematological status. While it has prognostic value in cardiovascular diseases, its relationship with the development of coronary collateral circulation (CCC) in patients with chronic total occlusion (CTO) remains unclear. This study aimed to investigate the association between the HALP score and the extent of CCC and to determine its predictive value for poor collateral development in patients with stable CAD and CTO.

Methods: A total of 241 consecutive patients with stable CAD and at least one CTO were retrospectively included. Participants were categorized into good (Rentrop grades 2-3, n=123) and poor CCC (Rentrop grades 0-1, n=118) groups based on blinded angiographic assessment. The HALP score was calculated from admission blood samples. Independent predictors were identified using multivariate logistic regression, and predictive performance was assessed by receiver operating characteristic (ROC) curve analysis.

Results: Patients with good CCC had a significantly higher HALP score than those with poor CCC (p=0.007). The HALP score showed a strong positive correlation with the Rentrop grade (r=0.69, p=0.034). Multivariate analysis confirmed that a lower HALP score was an independent predictor of poor collateral development (OR=0.822, 95% CI: 0.618-0.992, p=0.026), alongside other markers like NLR and NPAR. The ROC analysis demonstrated that a HALP score ≤31.2 predicted poor CCC with 78% sensitivity and 82% specificity (AUC=0.822, 95% CI: 0.760-0.878, p=0.024).

Conclusion: The HALP score is a powerful and independent predictor of well-developed coronary collaterals in patients with stable CAD and CTO. Derived from routine blood tests, it serves as an integrative biomarker for risk stratification, potentially identifying patients who may benefit from more aggressive management strategies.

Keywords: HALP score, chronic total occlusion, coronary collateral circulation

INTRODUCTION

Ischemic heart disease constitutes a predominant global health burden, ranking among the leading causes of morbidity and mortality worldwide. In patients with chronic total occlusion (CTO) of a major coronary artery, the development of coronary collateral circulation (CCC) is a critical compensatory mechanism. Well-developed collaterals function as natural bypass conduits, thereby preserving ventricular function, reducing the extent of infarction and improving clinical outcomes.[1,2]

The formation of CCC represents a sophisticated, dynamic process influenced by inflammation, oxidative stress, and angiogenesis.[3] While conventional risk factors for coronary artery disease (CAD), such as diabetes and hypertension, have been studied in collateral formation, the results have been inconsistent.[4,5] This highlights the need for reliable, easily measurable biomarkers that can predict the extent of collateral development. In recent years, composite indices derived from routine blood tests have gained attention for their ability to reflect the underlying inflammatory and nutritional status of patients with CTO. The neutrophil-to-lymphocyte ratio (NLR), neutrophil percentage-to-albumin ratio (NPAR) and C-reactive protein (CRP) are established markers of systemic inflammation and have been linked to poor collateral development.[6-8]

More recently, the hemoglobin, albumin, lymphocyte, and platelet (HALP) score has emerged as a novel, integrative biomarker. It simultaneously reflects hematological, nutritional, and inflammatory status, where hemoglobin indicates oxygen-carrying capacity, albumin represents nutritional status and anti-inflammatory capacity, lymphocytes reflect immune competence, and platelets are involved in inflammation and thrombosis.[9] A low HALP score has been associated with adverse prognoses in various cardiovascular conditions.[10-16] However, its specific role in predicting the development of CCC in patients with stable CAD and CTO has not been extensively investigated.

Therefore, this study aimed to evaluate the association between the HALP score and the extent of CCC and to determine its potential as an independent predictor of poor collateral development in a well-defined cohort of patients with stable CAD.

METHODS

This study was approved by the Health Sciences Researches Ethics Committee of Yüksek İhtisas University of Health Sciences (Date: 30.10.2025, Decision No: 353). The research protocol adhered strictly to international ethical standards as outlined in the Declaration of Helsinki. In this retrospective study, the cohort consisted of 241 consecutive patients (133 males, 108 females; median age 69 years, range 50-79) who received a diagnosis of stable CAD and were found to have a total occlusion in at least one major epicardial coronary artery during angiography at Ankara Yüksek İhtisas University Hospital between March 2021 and June 2025. We applied the following exclusion criteria: a history of acute or chronic infectious disease, chronic kidney disease (defined by a serum creatinine level >2.0 mg/dl), prior coronary artery bypass graft (CABG) surgery, an acute coronary syndrome event within the preceding three months, significant valvular heart disease, active malignancies, hematologic proliferative disorders, chronic inflammatory or autoimmune conditions (particularly those requiring steroid therapy), active hepatobiliary disease, or symptomatic heart failure with a left ventricular ejection fraction (LVEF) below 50%. We systematically collected demographic and clinical characteristics for all subjects, including age, gender, hypertension status, smoking history, and the presence of diabetes mellitus (DM).

Coronary angiographic procedures were conducted employing the standard Judkins technique. Two independent, experienced interventional cardiologists, who were blinded to all clinical and laboratory information for the patients, evaluated the images. The degree of CCC was scored according to the established Cohen-Rentrop classification system: grade 0 indicated no filling of collateral vessels; grade 1 denoted collateral filling of side branches without opacification of the epicardial artery; grade 2 represented partial opacification of the epicardial artery; and grade 3 signified complete filling of the epicardial artery via collateral channels. For the purpose of statistical analysis, patients were stratified into two groups: a "poor CCC" group (encompassing grades 0 and 1) and a "good CCC" group (encompassing grades 2 and 3).[17] In patients with collateral vessels supplying multiple occluded arteries, the vessel demonstrating the most robust antegrade or retrograde collateral flow was used for the final classification.

Peripheral venous blood samples were drawn at the time of hospital admission and subsequently processed within a 30-minute window. A fully automated hematology analyzer was used to determine complete blood count parameters. Standard serum biochemical assays, including measurements of creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and the full lipid profile, were performed using an automated clinical chemistry analyzer. We quantified serum albumin concentration via the bromocresol green (BCG) dye-binding method, a conventional and widely utilized technique in clinical laboratories. The HALP index was derived from the following calculation: Hemoglobin (g/L)×albumin (g/L)×lymphocyte count (10^9/L)/platelet count (10^9/L). The relationship between the HALP score and CCC status was then examined as a primary objective of this study.[18]

To ensure the reliability of the angiographic assessments, we evaluated interobserver and intra-observer variability. For this, data from 20 randomly chosen subjects from each group were re-evaluated independently by the two original cardiologists, who remained blinded to their own previous assessments and to each other's findings. The calculated interobserver variability was 2.8%, and the intraobserver variability was 2.7%.

Statistical Analysis

All statistical computations were performed with the IBM SPSS Statistics software, version 20.0 (IBM Corp., Armonk, NY, USA). Data conforming to a normal distribution are summarized as mean±standard deviation, whereas non-normally distributed data are reported as median values along with their minimum and maximum ranges. The Kolmogorov-Smirnov test was employed to verify the normality of the data distribution. For comparative analyses between the two independent groups, the Independent Samples t-test was used for normally distributed continuous variables, and the Mann-Whitney U test was applied for their non-normal counterparts. Categorical variables are presented as number (percentage) and were compared using the Pearson's Chi-square test, with Fisher's exact test or continuity correction applied where appropriate.

A post hoc power analysis was conducted using G*power 3.1 software to determine the statistical power of our study for detecting the difference in HALP scores between good and poor collateral circulation groups. Based on the observed effect size (Cohen's d=1.71), which represents a very large difference between groups, with sample sizes of 118 patients in the poor collateral group and 123 patients in the good collateral group, and setting the alpha error probability at 0.05, the analysis revealed a statistical power of 100%. This indicates that our study had more than adequate power to detect the significant difference in HALP scores observed between the two groups, substantially reducing the likelihood of a type II error.

To identify independent predictors of poor collateral circulation (CCC), we initially conducted univariate binary logistic regression analyses. Variables that demonstrated a significance level of $p<0.05$, or showed a trend towards significance ($p<0.10$), in the univariate analysis were subsequently entered into a multiple binary logistic regression model using the 'enter' method. The results are presented as odds ratios (OR) with their corresponding 95% confidence intervals (CI) and p-values. Furthermore, a receiver operating characteristic (ROC) curve analysis was utilized to establish the optimal discriminatory cutoff value for the HALP score in predicting poor CCC. The area under the curve (AUC), its 95% CI, and the p-value are reported. The consistency of measurements was assessed using the intraclass correlation coefficient (ICC) along with its 95% CI.

RESULTS

The final study population comprised 241 individuals diagnosed with stable CAD, stratified into a poor CCC group (n=118) and a good CCC group (n=123). The baseline demographic, clinical, and coronary angiographic characteristics of the patients are detailed in **Table 1**. The two groups were well-matched, showing no statistically significant differences in terms of age, sex, prevalence of hypertension or DM, smoking status, the anatomical location of the occluded vessel, or the number of diseased vessels.

Table 1. Baseline characteristics and coronary angiographic findings

Variable	All (n=241)	Poor CCC (n=118)	Good CCC (n=123)	p value
Age, years	69 (50-79)	70 (58-82)	73 (49-80)	0.688
Gender, male (%)	133 (55)	65 (55)	68 (55)	0.864
Hypertension, n (%)	140 (58)	65 (55)	75 (61)	0.122
Diabetes, n (%)	190 (79)	89 (75)	101 (82)	0.114
Smoking, n (%)	130 (54)	71 (60)	59 (48)	0.066
1 vessel disease, n (%)	89 (37)	44 (37)	45 (37)	0.888
2 vessel disease, n (%)	62 (26)	33 (28)	29 (24)	0.246
3 vessel disease, n (%)	90 (37)	40 (34)	50 (41)	0.122
Occluded LAD, n (%)	91 (38)	40 (34)	51 (41)	0.244
Occluded Cx, n (%)	58 (24)	28 (24)	30 (24)	0.784
Occluded RCA, n (%)	92 (38)	45 (38)	47 (38)	0.884

CCC: Coronary collateral circulation, Cx: Circumflex artery, LAD: Left anterior descending artery, RCA: Right coronary artery

As shown in **Table 2**, the comparative analysis of laboratory parameters revealed that fasting blood glucose, creatinine, ALT, AST, total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride levels were comparable between the poor and good CCC groups. However, significant differences were observed in several inflammatory and hematological markers. Specifically, the poor CCC group exhibited significantly elevated levels of white blood cell count (p=0.046), neutrophil count (p=0.038), NLR, (p=0.021), CRP, (p=0.033), and NPAR, (p=0.018). Conversely, the HALP score was found to be significantly higher in the good CCC group compared to the poor CCC group (p=0.007). Correlation analysis further demonstrated a significant positive relationship between the HALP score and the Rentrop collateral grade (r=0.69, p=0.034), as illustrated in **Figure 1**.

In the univariate binary logistic regression analysis; WBC, hemoglobin, platelet, neutrophil, lymphocyte count, CRP, albumin, NLR, NPAR, and HALP were evaluated. Variables with p<0.10 were included in the multiple binary logistic regression analysis. We acknowledge the potential for collinearity when including both NPAR and its component, albumin, neutrophile (in NLR) in the same multivariate model. To rigorously address this statistical concern, we have revised our analytical approach: in all multivariate models featuring NPAR, albumin and NLR was systematically excluded (in model 1 and 2). Furthermore, to provide a meaningful clinical context for the predictive utility of NPAR, we performed a comparative ROC analysis that included the NLR, a well-established inflammatory marker. This direct comparison allows for a clearer evaluation of NPAR's discriminant power relative to a standard benchmark. Multiple logistic regression analysis identified that a lower HALP score (OR=0.822, 95% CI: 0.618-0.992, p=0.026), higher NPAR (OR=0.766, 95% CI:0.525-0.982, p=0.026), higher NLR (OR=0.704, 95% CI:0.440-0.900, p=0.036), higher CRP (OR=0.678, 95% CI: 0.404-0.890, p=0.022), increased neutrophil count (OR=0.636, 95% CI:0.410-0.884, p=0.028) and lower lymphocyte count (OR=0.602, 95% CI:0.388-0.862, p=0.042) were independent predictors of poor CCC (**Table 3**).

Table 2. Comparison of laboratory parameters between poor and good CCC groups

Variable	Poor CCC (n=118)	Good CCC (n=123)	p
Glucose, mg/dl, mean±SD	130 (73-386)	121 (72-274)	0.076
AST, IU/L, mean±SD	26±4.6	32±6.4	0.122
ALT, IU/L, mean±SD	36±6.6	38±6.1	0.746
Creatinine, mg/dl, mean±SD	0.94±0.36	0.98±0.22	0.877
Total cholesterol, mg/dl, mean±SD	214±28.6	176±17.7	0.444
LDL-C, mg/dl, mean±SD	130±34.4	118±30.2	0.646
HDL-C, mg/dl, mean±SD	30.8±9.4	33.1±8.8	0.622
Triglyceride, mg/dl, mean±SD	144±23.3	132±16.6	0.566
WBC, $\times10^3$/mm^3, mean±SD	9.2±2.4	8.5±2.3	0.046
Neutrophils, 10^9/L, median (min-max)	4.90 (3.62–7.51)	4.32 (3.53–5.61)	0.038
Lymphocytes, 10^9/L, median (min-max)	1.06 (0.80–1.32)	2.20 (1.86–2.60)	0.042
Hemoglobin, g/dl, median (min-max)	12.1 (10.7-13.9)	12.8 (10.8-14.6)	0.082
Platelet count, $\times10^3$/mm^3, mean±SD	269±31.2	246±27.7	0.078
Albumin, g/dl, mean±SD	3.79±0.98	4.45±1.66	0.086
CRP, mg/dl, median (min-max)	2.9 (0.9-5.5)	1.7 (1.1-4.1)	0.033
NLR, mean±SD	3.85±1.5	2.42±1.4	0.021
NPAR, mean±SD	19.8±3.1	11.1±2.7	0.018
HALP, mean±SD	17.4±4.6	49.7±26.1	0.007

SD: Standard deviation, Min: Minimum, Max: Maximum, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CCC: Coronary collateral circulation, CRP: C-reactive protein, HALP: Hemoglobin, albumin, lymphocyte, and platelet, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, NLR: Neutrophil-to-lymphocyte ratio, NPAR: Neutrophil percentage-to-albumin ratio, WBC: White blood cells

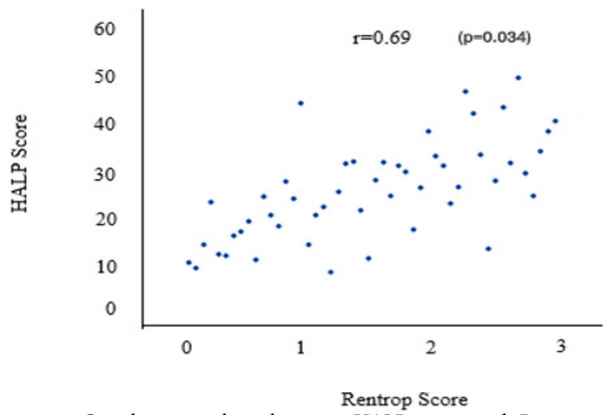

Figure 1. Correlation analysis between HALP score and Rentrop score (p=0.034)
HALP: Hemoglobin, albumin, lymphocyte, and platelet

Table 3. Results of multivariate logistic regression

Variable	Univariate OR (95% CI)	p	Multivariate (model 1) OR (95% CI)	p	Multivariate (model 2) OR (95% CI)	p
Hemoglobin	0.788 (0.412-1.372)	0.664	0.766 (0.408-1.262)	0.774	0.766 (0.408-1.262)	0.774
Albumin	0.684 (0.312-1.174)	0.786	0.588 (0.266-1.079)	0.555	-	-
WBC	0.744 (0.402-0.972)	0.044	0.788 (0.412-1.372)	0.664	0.788 (0.412-1.372)	0.664
Platelet	0.777 (0.532-1.066)	0.264	0.642 (0.478-1.166)	0.334	0.642 (0.478-1.166)	0.334
NPAR	0.714 (0.576-0.882)	0.033	-	-	0.766 (0.525-0.982)	0.026
Lymphocyte	0.598 (0.312-0.742)	0.034	0.602 (0.388-0.862)	0.042	0.602 (0.388-0.862)	0.042
Neutrophil	0.694 (0.404-1.962)	0.038	0.636 (0.410-0.884)	0.028	0.636 (0.410-0.884)	0.028
NLR	0.708 (0.444-0.908)	0.044	0.704 (0.440-0.900)	0.036	-	-
CRP	0.688 (0.398-0.906)	0.032	0.678 (0.404-0.890)	0.022	0.678 (0.404-0.890)	0.022
HALP	0.748 (0.410-0.972)	0.036	0.766 (0.525-0.982)	0.026	0.822 (0.618-0.992)	0.026

CCC: Coronary collateral circulation, CI: Confidence interval, CRP: C-reactive protein, HALP: Hemoglobin, albumin, lymphocyte, and platelet, NLR: Neutrophil-to-lymphocyte ratio, NPAR: Neutrophil percentage-to-albumin ratio, OR: Odds ratio, WBC: White blood cell

ROC analysis revealed that HALP score had an optimal cutoff value of ≤31.2 for predicting poor CCC, with 78% sensitivity and 82% specificity. The AUC was 0.822 (p=0.024, 95% CI: 0.760-0.878) comparable with the other independent parameters (**Figure 2**).

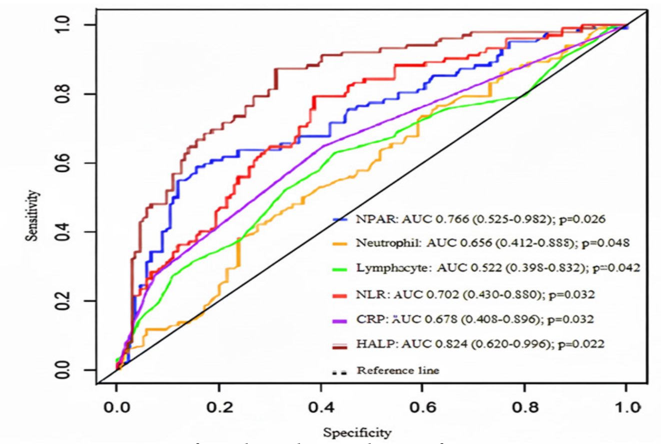

Figure 2. ROC curves for independent predictors of poor CCC
AUC: Area under the curve, CCC: Coronary collateral circulation, CRP: C-reactive protein, HALP: Hemoglobin, albumin, lymphocyte, and platelet, NLR: Neutrophil-to-lymphocyte ratio, NPAR: Neutrophil percentage-to-albumin ratio, ROC: Receiver operating characteristic

DISCUSSION

In this study, we identified the HALP score as a significant and independent predictor of well-developed CCC in patients with stable CAD and at least one CTO. Our results demonstrate that patients with good CCC had a significantly higher HALP score, and a strong positive correlation was observed between the HALP score and the Rentrop collateral grade. Multivariate logistic regression analysis confirmed that a lower HALP score was independently associated with a higher likelihood of poor collateral development, alongside other inflammatory markers such as NPAR, NLR, and CRP. Furthermore, the HALP score showed a robust predictive performance with an AUC of 0.822, suggesting its potential utility as a clinical biomarker. To the best of our knowledge, this is the pioneering study to identify the HALP score as a novel, significant, and independent predictor of well-developed CCC in this specific patient population.

When contextualized within the existing literature on inflammatory biomarkers and collateral circulation, our findings for HALP show both convergence and distinct advantages. The negative correlation between NLR and collateral development observed in our study is strongly supported by previous research. High NLR was founded to be independently associated with poor collateral circulation in CTO patients, with similar predictive performance (AUC: 0.71 in their cohort vs. 0.704 in our study).[7,19] The relationship between PLR and collateral circulation has been more variable across studies. While we found PLR to be significant in univariate analysis but not in multivariate models.[20] The principal advantage of the HALP score over these established markers lies in its multidimensional nature. While NLR and PLR primarily reflect the systemic inflammatory state, HALP integrates information about inflammation (through lymphocytes), nutritional status and antioxidant capacity (through albumin), oxygen-carrying capacity (through hemoglobin), and thrombotic tendency (through platelets). This comprehensive profile likely explains why HALP maintained stronger independent predictive value in our multivariate models compared to NLR or PLR alone.

The development of CCC is a complex, adaptive response to chronic myocardial ischemia, orchestrated by a balance between pro-angiogenic and inflammatory pathways.[1] Our findings of significantly higher NLR, CRP, and neutrophil counts in the poor CCC group strongly reinforce the well-established concept that a heightened systemic inflammatory state is detrimental to collateral formation.[6,7] Inflammation can impair endothelial function, promote apoptosis of endothelial progenitor cells, and disrupt the signaling of key angiogenic factors like vascular endothelial growth factor (VEGF), thereby hindering the process of arteriogenesis.[21]

The biological rationale underpinning the HALP score can be deconstructed by examining its individual components. Hemoglobin is critical for oxygen transport, and anemia has been previously linked to poorer cardiovascular outcomes and impaired adaptive responses to ischemia.[22] A low hemoglobin level may limit oxygen delivery to the peri-ischemic tissue, blunting the hypoxic drive that stimulates VEGF release and subsequent collateral growth.[1] Albumin is not only a marker of nutritional status but also a potent antioxidant and anti-inflammatory agent.[23] Hypoalbuminemia, as seen in our poor CCC group, indicates a state of chronic inflammation and oxidative stress, which can directly damage the endothelium and inhibit its reparative and proliferative capacities. This aligns with studies showing that low albumin levels are associated with more severe CAD and worse prognosis.[24] Lymphopenia is a common consequence of chronic inflammation and is associated with poor prognosis in heart failure and CAD.[25] Lymphocytes, particularly T-cells, play a crucial role in vascular repair and angiogenesis.[26] A low lymphocyte count may signify an impaired immune response necessary for the tissue remodeling required for collateral vessel development. Finally, a high platelet count (thrombocytosis), which lowers the HALP score, can promote a pro-thrombotic microenvironment and release inflammatory mediators like CD40 ligand, further exacerbating endothelial dysfunction.[27]

The novel aspect of our study is the introduction and validation of the HALP score in this context. The strength of HALP lies in its ability to integrate multiple physiological pathways into a single metric. When we compare our results with other composite indices, HALP appears to offer a more comprehensive prognostic snapshot. For instance, while the NLR primarily reflects the systemic inflammatory burden, it does not account for nutritional status or oxygen-carrying capacity. Our study found that HALP (OR=0.822) had a comparable, if not marginally stronger, independent predictive value than NLR (OR=0.704) and NPAR (OR=0.766) in the multivariate model. This suggests that the additional dimensions of nutrition (albumin) and oxygen delivery (hemoglobin) captured by HALP provide incremental prognostic information beyond pure inflammation.

When we contextualize our findings within the broader literature on HALP, a coherent picture emerges. For example, it was demonstrated that a low HALP score was a strong predictor of mortality in cancer patients, a condition also characterized by chronic inflammation and malnutrition.[28–30] Similarly, in cardiovascular settings, HALP was founded to be a prognostic marker in acute coronary syndrome.[16] Our study extends the applicability of the HALP score to the microvascular and adaptive physiological process of collateralization, suggesting that HALP is a versatile marker of a patient's overall resilience and capacity to mount an effective compensatory response to chronic ischemic stress.

The ROC analysis yielded an optimal HALP cutoff value of ≤31.2 for predicting poor CCC with 78% sensitivity and 82% specificity. This cutoff provides a tangible and easily calculable metric for clinicians to risk-stratify patients with CTOs. Identifying patients with a low HALP score could help pinpoint those at high risk for having inadequate collateral support. This subgroup might benefit from more aggressive risk factor modification, intensified monitoring, and potentially earlier revascularization, even in the absence of severe symptoms, to protect the viable myocardium at risk. The high sensitivity and specificity are comparable to, and in some cases better than, other proposed biomarkers for collateral prediction, highlighting its clinical potential.

Limitations

The strengths of our study include its systematic, single-center design, the use of consecutive patients to minimize selection bias the use of consecutive patients to minimize selection bias, and the blinded, quantitative assessment of coronary angiograms by two experienced interventional cardiologists, which resulted in the low inter- and intra-observer variability. However, several limitations must be acknowledged. First, the retrospective design is inherently susceptible to selection bias and unmeasured confounding, despite our use of consecutive patients. Second, the single-center nature of the study may limit the generalizability of our findings, and the proposed HALP cutoff of 31.2 requires external validation in larger, multi-center, ethnically diverse populations. Second, the cross-sectional design establishes an association but cannot prove causation. While we adjusted for major clinical confounders, the possibility of residual confounding from unmeasured variables (e.g., medication adherence, duration of occlusion, genetic factors) persists. Third, we measured HALP at a single time point; investigating the dynamic changes in HALP over time and its correlation with the evolution of collateral circulation could provide deeper insights into the causal relationship. Finally, while we documented the association, further basic science research is needed to elucidate the precise mechanistic pathways through which the components of HALP directly influence arteriogenesis.

CONCLUSION

As a result, this study identifies the HALP score as a novel, powerful, and independent predictor of coronary collateral development in patients with stable CAD and CTO. It outperforms or complements existing inflammatory markers by providing a holistic view of a patient's inflammatory, nutritional, and hematological status. Its derivation from routine, inexpensive blood tests makes it an attractive tool for clinical risk stratification. Future prospective, longitudinal studies are warranted to validate our findings and to explore whether interventions aimed at improving the HALP score (e.g., nutritional support, managing anemia) can subsequently lead to improved collateral formation and better clinical outcomes.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Health Sciences Researches Ethics Committee of Yüksek İhtisas University of Health Sciences (Date: 30.10.2025, Decision No: 353).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

All authors contributed significantly to the study's conception, design, data acquisition, analysis, and interpretation. All authors reviewed and approved the final version of the manuscript.

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