ORIGINAL ARTICLE

Association of Hemoglobin–Albumin–Lymphocyte–Platelet Count (HALP) Score and Type 2 Diabetes Retinopathy

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Abstract

Introduction: Diabetic retinopathy (DR) represents a frequent microvascular consequence of type 2 diabetes mellitus (T2DM). Both inflammatory activity and nutritional status influence its development. The hemoglobin–albumin–lymphocyte–platelet (HALP) index is a composite marker that reflects these factors and has been explored in several diseases. This study assessed its association with the occurrence and severity of DR.

Materials and methods: We carried out a cross-sectional analysis of 150 individuals with T2DM (equal male–female distribution, mean age 58.9 ± 10.9 years). Retinal changes were graded through fundus examination. Laboratory values for calculating the HALP index were obtained. Statistical analysis included *t*-tests, Mann–Whitney *U* tests, and receiver operating characteristic (ROC) curves.

Results: DR was found in 43.4% of patients, predominantly in the moderate stage. The mean HALP index was 34.3 ± 36.6. Differences in HALP values between the DR and non-DR groups were not statistically significant ($p = 0.249$), although lower scores tended to appear in DR. ROC analysis showed modest discriminatory power (AUC 0.555 for DR; 0.599 for moderate–severe DR). Hemoglobin was significantly higher among those with moderate–severe DR ($p = 0.006$).

Conclusion: Although the HALP index did not independently predict DR, its downward trend in advanced stages suggests potential as part of a multifactorial risk assessment. Owing to its affordability and simplicity, the HALP index may complement existing tools for identifying patients at higher risk of vision-threatening DR.

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Introduction

Diabetic retinopathy (DR) remains one of the most common microvascular complications of diabetes and is a major cause of visual disability worldwide.[1] Its occurrence is strongly related to disease duration, with up to three-quarters of patients eventually showing retinal involvement.[1,2] DR is classified into nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR is initially asymptomatic, presenting with microaneurysms and hemorrhages, while PDR is marked by neovascularization and carries a high risk of severe vision loss.[3]

Multiple factors—poor glycemic control, hypertension, dyslipidemia, and chronic hyperglycemia—contribute to diabetic eye disease progression.[4] Persistent hyperglycemia promotes oxidative stress, endothelial dysfunction, and accumulation of advanced glycation end products, which together compromise the blood-retinal barrier.[5] This environment leads to ischemia and stimulates the release of vascular endothelial growth factor (VEGF), driving pathological neovascularization.[3]

Inflammation also plays a central role in DR. Elevated cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are commonly observed in affected patients,[6,7] while leukocyte adhesion and oxidative stress further aggravate vascular occlusion and ischemia.[5] Platelets contribute by releasing inflammatory mediators and forming aggregates with leukocytes, worsening microvascular damage.[8–10]

Nutritional status also influences DR. Low albumin levels indicate both malnutrition and systemic inflammation and are linked to retinal edema and poorer outcomes.[11–13] Anemia, common in diabetic patients with kidney disease, exacerbates retinal hypoxia and accelerates VEGF-driven damage.[14,15] These factors highlight the importance of integrating nutritional and inflammatory markers in DR-related research.

Hemoglobin–Albumin–Lymphocyte–Platelet Score: Concept, Calculation, Existing Evidences and Its Clinical Applications in Various Diseases

The hemoglobin–albumin–lymphocyte–platelet (HALP) index is a recently proposed composite biomarker designed to capture both nutritional reserve and inflammatory burden. It is calculated as:

HALP score = (hemoglobin × albumin × lymphocytes) / platelets

A low HALP value suggests poor nutritional status together with heightened inflammation, both of which are linked to unfavorable outcomes in various clinical conditions.[16] Initially developed in oncology research, it has since been applied to cardiovascular disease, acute heart failure, and ischemic stroke, where lower scores were associated with worse survival and functional recovery.[6,17–19]

The HALP score as a diagnostic and prognostic marker has been explored in several clinical scenarios. In hepatocellular carcinoma, a lower HALP score has been associated with poor prognosis, correlating with tumor aggressiveness and lower survival rates.[17] Similarly, in acute heart failure, studies have shown that the HALP score can predict short-term mortality, reflecting the combined impact of inflammation and malnutrition on cardiovascular outcomes.[19] In ischemic stroke, a low HALP score has been linked to worse neurological outcomes and higher mortality.[6]

These studies collectively suggest that the HALP score serves as an effective prognostic marker by encapsulating the interplay between systemic inflammation and nutritional status. Given the shared pathophysiological mechanisms, namely inflammation and nutritional imbalance, the HALP score may hold potential as a diagnostic and prognostic marker in DR.

Given that DR shares pathophysiological pathways with these disorders, particularly chronic inflammation and malnutrition, the HALP index may have utility in ophthalmic settings. Preliminary data suggest that patients with reduced HALP are more likely

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to show advanced DR.[16] One proposed mechanism is that a low HALP score reflects an elevated inflammatory state and suboptimal nutritional status, both of which can accelerate microvascular damage in the retina. However, the evidence is not yet conclusive, and further research is needed to establish the HALP score's reliability as a biomarker for the diagnosis and severity assessment of DR.

A variety of inflammatory biomarkers have been evaluated for their association with DR. Markers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and the neutrophil-to-lymphocyte ratio (NLR) have shown promise in reflecting the inflammatory milieu of diabetic patients.[6,7] In contrast, nutritional markers such as albumin and hemoglobin, while traditionally used to assess nutritional status, have also been linked to DR severity.[12–15]

The HALP score is unique because it consolidates these parameters into a single index, providing a more holistic measure of the patient's systemic state. While individual markers offer insight into specific aspects of inflammation or nutrition, the HALP score may capture the synergistic effect of these factors on retinal health. The integration of these markers into a single score simplifies clinical decision-making and could potentially facilitate early intervention in patients at high risk for DR progression.

The prevalence and progression of DR vary among different populations because of genetic, environmental, and socioeconomic factors. In Western populations, the focus has often been on the roles of glycemic control and hypertension in DR development.[2] However, in Asian populations, including India, additional factors such as malnutrition and differential inflammatory responses have been highlighted.[4]

Several studies have suggested that nutritional deficiencies and inflammatory conditions may be more pronounced in regions with limited health care resources, potentially exacerbating the risk and progression of DR.[13] In this context, the HALP score, reflecting both nutritional and inflammatory status, may offer a more sensitive indicator of DR risk in these populations. Moreover, the relative simplicity and cost-effectiveness of the HALP score make it an attractive option for large-scale screening in resource-constrained settings.

Role of Lifestyle and Comorbidities in Diabetic Retinopathy

Lifestyle factors, including diet, physical activity, and smoking, significantly impact both inflammatory and nutritional status. A diet deficient in antioxidants and essential nutrients can contribute to malnutrition and exacerbate inflammation, thereby increasing the risk of DR.[6,13] Smoking, in particular, has been associated with elevated inflammatory markers and a higher risk of vascular complications in diabetic patients.[20]

Comorbid conditions, especially cardiovascular disease and chronic kidney disease, further complicate the relationship between diabetes and DR. These conditions are themselves associated with chronic inflammation and nutritional deficits, and they may amplify the deleterious effects of diabetes on retinal vessels. The HALP score, by reflecting these systemic changes, may also serve as an indicator of overall vascular health, linking DR to broader cardiovascular risks.[18,19]

Potential Mechanisms Linking Hemoglobin–Albumin–Lymphocyte–Platelet Score Components to Diabetic Retinopathy

The individual components of the HALP score have distinct roles in the pathophysiology of DR:

Hemoglobin: Anemia, frequently observed in diabetic patients, may exacerbate retinal hypoxia. Hypoxia is a potent inducer of VEGF and neovascularization, thereby contributing to the progression of DR.[14,15]

Albumin: Low albumin levels, reflecting malnutrition and elevated inflammation, may compromise antioxidant defense mechanisms. Hypoalbuminemia has been linked to increased vascular permeability and edema in the retina.[11,12]

Lymphocytes: As key components of the immune system, lymphocytes help modulate inflammation. Reduced lymphocyte counts may indicate immunosuppression and chronic inflammation, both of which can contribute to retinal microvascular damage.[20,21]

Platelets: Platelets are not only essential for clotting but also play an active role in inflammation. Elevated platelet counts, or dysregulated platelet function, can lead to microthrombus formation and vascular occlusion, thereby worsening retinal ischemia.[8–10]

Collectively, the interaction among these components may create a milieu conducive to the development and progression of DR. A low HALP score, indicating poor nutritional status and heightened inflammation, could thus serve as a surrogate marker for increased DR risk and severity.

Materials and Methods

Study Design

A cross-sectional analysis was conducted on 150 patients with type 2 diabetes mellitus (T2DM).

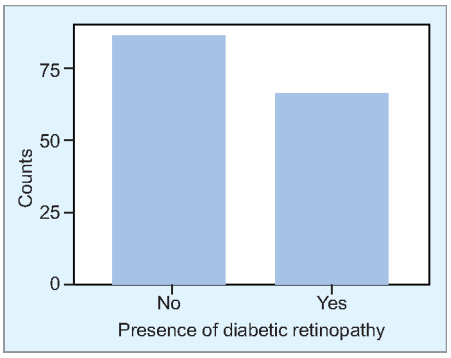

Fig. 1: Presence of diabetic retinopathy among study population

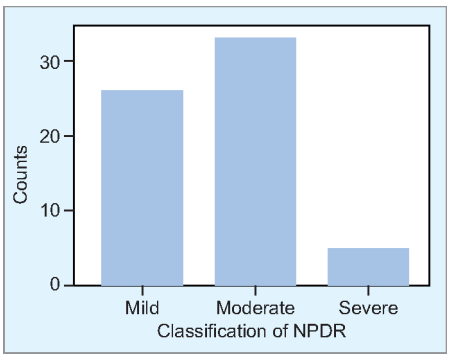

Fig. 2: Classification of non proliferative diabetic retinopathy

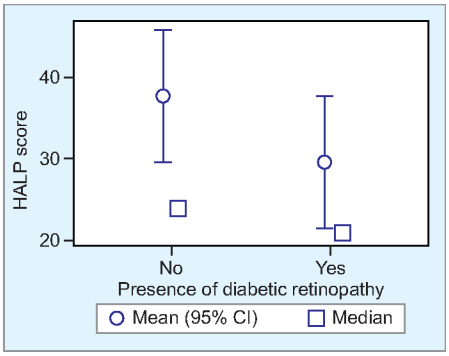

Fig. 3: Comparison of HALP score in patients with and without diabetic retinopathy

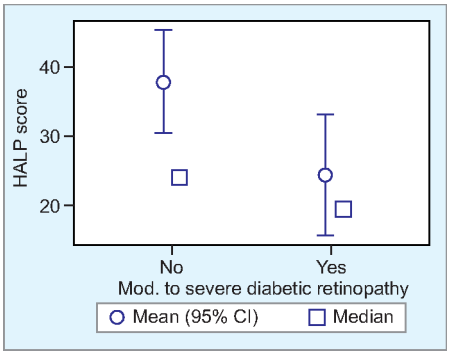

Fig. 4: Comparison of HALP score in patients with and without moderate to severe Diabetic retinopathy

Participant Profile

The sample included 75 males and 75 females, with a mean age of 58.9 years, representing a typical at-risk population for DR.

Data Collection

Clinical and demographic data were collected alongside laboratory measurements required to calculate the HALP score.

Data Analysis

Statistical tests, including Student's *t*-tests, Mann–Whitney *U* tests, and receiver operating characteristic (ROC) curve analysis, were applied to evaluate differences between the DR and non-DR groups and to assess the HALP score's discriminative power.

Diabetic Retinopathy Assessment

All participants underwent fundus examination, with grading into mild, moderate, or severe nonproliferative diabetic retinopathy (NPDR).

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median [interquartile range (IQR)] and compared using an independent *t*-test or Mann–Whitney *U* test. Categorical variables were compared using the Chi-squared test. ROC analysis assessed diagnostic performance. $p < 0.05$ was considered statistically significant.

Ethical Approval

Approved by the Institutional Ethics Committee; informed consent was obtained from all participants.

Results

Out of the total study population, there were 75 males (50.0%) and 75 females (50.0%), indicating an equal gender distribution. The cumulative percentage shows that males accounted for the first 50.0% of the sample, and the inclusion of females completed the total 100% representation, as shown in Table 1. This balanced proportion minimizes gender-related selection bias and allows for gender-based subgroup analysis, if required.

Among the study participants, 86 individuals (56.6%) did not have DR, while 66 individuals (43.4%) were diagnosed with DR. The cumulative percentage indicates that the absence of retinopathy accounted for over half of the sample (56.6%), with the inclusion of those affected bringing the total to 100%. This distribution highlights that nearly two-fifths of the study population had DR, underscoring the clinical relevance of screening and early detection in diabetic patients, as shown in Table 2.

Among participants diagnosed with nonproliferative diabetic retinopathy (NPDR), 26 individuals (40.6%) had mild NPDR, 33 individuals (51.6%) had moderate NPDR, and five individuals (7.8%) had severe NPDR. The cumulative percentage shows that mild and moderate NPDR together accounted for 92.2% of cases, while severe NPDR constituted the smallest proportion (7.8%), as shown in Table 3. This distribution indicates that moderate NPDR was the most prevalent stage in the study population.

The study population had a mean age of 58.9 years (SD = 10.9), a median age of 58 years, and an IQR of 16.5 years, with age distribution approximating normality (Shapiro–Wilk $p = 0.417$). The mean hemoglobin level was 101 gm/L (SD = 70.5; IQR = 37.0), with a median of 92.5 gm/L, showing a nonnormal distribution ($p < 0.001$). Serum albumin was normally distributed (mean 32.0 gm/L, SD = 5.89; IQR = 8.18; median 32.2 gm/L; $p = 0.379$). Lymphocyte count (mean 1.80×10^9/L, SD = 1.36; IQR = 1.21; median 1.39×10^9/L; $p < 0.001$), platelet count (mean 209×10^9/L, SD = 114; IQR = 111; median 179×10^9/L; $p < 0.001$), and HALP score (mean 34.3, SD = 36.6; IQR = 24.6; median 22.8; $p < 0.001$) all demonstrated significant skewness, as shown in Table 4. Thus, while age and serum albumin followed a normal distribution, hemoglobin, lymphocyte count, platelet count, and HALP score were nonnormally distributed, informing the use of parametric or nonparametric statistical tests in further analyses.

Comparison of laboratory parameters between groups revealed that hemoglobin levels showed no significant difference by the independent-samples *t*-test ($p = 0.944$; mean difference = −0.81 gm/L), whereas the Mann–Whitney *U* test detected a significant difference ($p = 0.006$), with a median difference of approximately 10 gm/L, highlighting the impact of nonnormal distribution. Serum albumin levels showed no significant difference between groups on either the *t*-test ($p = 0.956$) or the Mann–Whitney *U* test ($p = 0.950$). Similarly, lymphocyte counts (*t*-test $p = 0.321$;

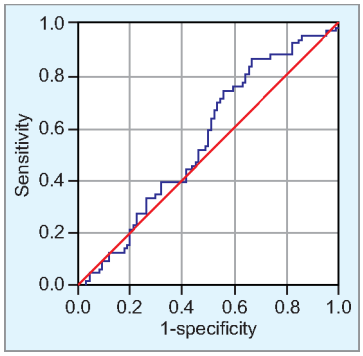

Fig. 5: ROC curve for HALP score in predicting occurence of diabetic retinopathy (AUC -0.555)

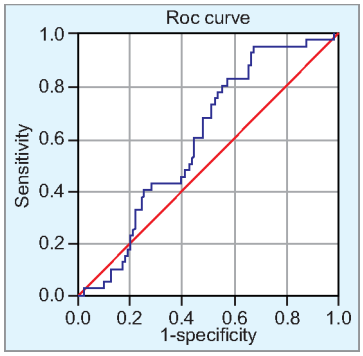

Fig. 6: ROC curve for HALP score in predicting moderate to severe diabetic retinopathy (AUC-0.599)

Table 1: Distribution of gender among study participants

Frequencies of gender			
Gender	*Counts*	*% of total*	*Cumulative %*
Male	75	50.0%	50.0%
Female	75	50.0%	100.0%

Table 2: Presence of DR among study participants

Presence of DR	*Counts*	*% of total*	*Cumulative %*
No	86	56.6%	56.6%
Yes	66	43.4%	100.0%

Table 3: Classification of nonproliferative diabetic retinopathy (NPDR)

Classification of NPDR	*Counts*	*% of total*	*Cumulative %*
Mild	26	40.6%	40.6%
Moderate	33	51.6%	92.2%
Severe	5	7.8%	100.0%

Table 4: Descriptive statistics of study variables

	Age (years)	*Hb (gm/L)*	*Albumin (gm/L)*	*Lymphocyte count (cells × 10^9/L)*	*Platelet count (cells × 10^9/L)*	*HALP score*
Mean	58.9	101	32.0	1.80	209	34.3
Median	58	92.5	32.2	1.39	179	22.8
Standard deviation	10.9	70.5	5.89	1.36	114	36.6
IQR	16.5	37.0	8.18	1.21	111	24.6
Shapiro–Wilk *p*	0.417	<0.001	0.379	<0.001	<0.001	<0.001

Table 5: Comparison of study variables between groups

		Statistic	*p*	*Mean difference*
Hb	Student's *t*	–0.0700	0.944	–0.8101
	Mann–Whitney *U*	2,095	0.006	10.0000
Albumin	Student's *t*	0.0556	0.956	0.0540
	Mann–Whitney *U*	2,755	0.950	0.0999
Lymphocyte count	Student's *t*	0.9964	0.321	0.2227
	Mann–Whitney *U*	2,626	0.503	0.0929
Platelet count	Student's *t*	0.2463	0.806	4.5994
	Mann–Whitney *U*	2,680	0.558	–8.0001
HALP score	Student's *t*	1.3571	0.177	8.1442
	Mann–Whitney *U*	2,467	0.249	3.1580

Table 6: Comparison of study variables by presence of DR

	Presence of DR	*Mean*	*Median*	*SD*
Hb	No	100.52	99.50	23.75
	Yes	101.33	87.00	103.90
Albumin	No	32.05	31.20	6.47
	Yes	31.99	32.55	5.10
Lymphocyte count	No	1.90	1.44	1.54
	Yes	1.67	1.33	1.09
Platelet count	No	211.37	173.50	127.14
	Yes	206.77	186.00	94.34
HALP score	No	37.85	23.64	38.40
	Yes	29.70	20.41	33.88

Table 7: Comparison of study variables by presence of moderate to severe DR

	Moderate to severe DR	*Mean*	*Median*	*SD*
Hb	No	98.70	95.50	22.92
	Yes	106.97	82.50	132.945
Albumin	No	32.17	32.05	6.23
	Yes	31.62	32.20	4.853
Lymphocyte count	No	1.93	1.49	1.48
	Yes	1.43	1.18	0.894
Platelet count	No	213.46	178.50	123.17
	Yes	197.95	179.00	81.987
HALP score	No	37.83	24.37	38.77
	Yes	24.47	19.50	27.914

Mann–Whitney *U* test $p = 0.503$), platelet counts (*t*-test $p = 0.806$; Mann–Whitney *U* test $p = 0.558$), and HALP score (*t*-test $p = 0.177$; Mann–Whitney *U* test $p = 0.249$) did not differ significantly between groups, as shown in Table 5. Overall, only hemoglobin demonstrated a significant intergroup difference when evaluated with a nonparametric test, suggesting that skewed data distribution may have obscured differences in parametric testing.

Participants without DR had a mean hemoglobin level of 100.52 gm/L (median 99.50; SD = 23.75), whereas those with DR had a mean of 101.33 gm/L (median 87.00; SD = 103.90), reflecting substantial variability in the DR group. Serum albumin levels were nearly identical between groups (32.05 gm/L without DR vs 31.99 gm/L with DR), with minimal median difference. Lymphocyte counts were slightly higher in the no-DR group (1.90×10^9/L) compared to the DR group (1.67×10^9/L). Similarly, platelet counts were marginally higher in participants without DR (211.37×10^9/L) versus those with DR (206.77×10^9/L), with comparable medians. Notably, the HALP score was higher among participants without DR (mean 37.85) than among those with DR (mean 29.70), suggesting a potential link between lower HALP scores and the presence of DR, as shown in Table 6. Overall, these descriptive findings indicate that reduced lymphocyte counts, platelet counts, and HALP scores may be associated with DR, warranting further confirmation through formal statistical testing.

Participants without moderate-to-severe DR had a mean hemoglobin level of 98.70 gm/L (median 95.50; SD = 22.92), whereas those with moderate-to-severe DR had a higher mean of 106.97 gm/L (median 82.50; SD = 132.95), reflecting marked variability in the latter group. Serum albumin levels were comparable between groups (32.17 vs 31.62 gm/L). Lymphocyte counts were higher in the no-DR group (1.93×10^9/L) compared to the moderate-to-severe DR group (1.43×10^9/L), suggesting a trend toward lymphopenia with increasing DR severity. Platelet counts were also slightly higher in the no-DR group (213.46×10^9/L) compared to the moderate-to-severe DR group (197.95×10^9/L). The HALP score was notably greater among participants without moderate-to-severe DR (mean 37.83) than among those with moderate-to-severe DR (mean 24.47), indicating a potential association between lower HALP scores and greater DR severity, as shown in Table 7. Overall, these descriptive trends suggest that reduced lymphocyte counts, platelet counts, and HALP scores may be linked to the progression of DR, although statistical validation is needed to establish significance.

Table 8: ROC curve analysis of HALP score for presence of DR

Area under the curve				
Test result variable(s): HALP score and presence of DR				
Area	*Standard error*[a]	*Asymptotic significance*[b]	*Asymptotic 95% confidence interval*	
			Lower bound	*Upper bound*
0.555	0.047	0.248	0.463	0.647

[a]Under the nonparametric assumption; [b]Null hypothesis: true area = 0.5

Table 9: ROC curve analysis of HALP score for predicting moderate to severe DR

Area under the curve				
Test result variable(s): HALP score and moderate to severe DR				
Area	*Standard error*[a]	*Asymptotic significance*[b]	*Asymptotic 95% confidence interval*	
			Lower bound	*Upper bound*
0.599	0.048	0.065	0.505	0.692

[a]Under the nonparametric assumption; [b]Null hypothesis: true area = 0.5

The area under the ROC curve (AUC) for the HALP score in predicting the presence of DR was 0.555 (SE = 0.047; 95% CI: 0.463–0.647), which was not statistically significant ($p = 0.248$), as shown in Table 8. This indicates that the HALP score had only a slightly better-than-chance ability to discriminate between participants with and without DR, and the result was not statistically significant.

The area under the ROC curve (AUC) for the HALP score in predicting moderate-to-severe DR was 0.599 (SE = 0.048; 95% CI: 0.505–0.692), with a p-value of 0.065, as shown in Table 9. Although the AUC indicates a modest discriminatory ability, the result did not reach statistical significance at the 0.05 threshold, suggesting that while the HALP score may have some predictive value for more advanced stages of DR, its performance in this study was limited.

Discussion

The study comprised 150 patients with equal gender distribution (75 males and 75 females) and a mean age of 58.9 ± 10.9 years. This demographic profile aligns with existing epidemiological data indicating that middle-aged and older adults are predominantly affected by DR.[1,22,23] Given the established link between prolonged diabetes duration and microvascular complications, our sample represents a typical at-risk population.

DR was present in 43.4% of participants, with 40.6% having mild nonproliferative diabetic retinopathy (NPDR), 51.6% moderate NPDR, and 7.8% severe NPDR. The proportion of moderate-to-severe DR cases (26.3%) is consistent with prior studies, which suggest that approximately 75% of long-term diabetes patients develop some form of DR.[1,2,22] These findings reinforce the necessity for early detection strategies, as progression from mild to severe NPDR is well documented in DR pathogenesis.[3] The distribution of DR severity also provides an opportunity to evaluate how biochemical markers, such as the HALP score, correlate with disease progression.

The HALP score, calculated as HGB × ALB × LYM / PLT, exhibited significant variability, with a mean of 34.3 ± 36.6, and exhibited a nonnormal distribution (Shapiro–Wilk test, $p < 0.001$). This heterogeneity reflects the diverse metabolic and inflammatory states among patients with T2DM.[16] Although hemoglobin levels showed no significant difference between the DR and non-DR groups ($p = 0.944$), they were significantly elevated in patients with moderate-to-severe DR compared to those with milder forms ($p = 0.007$, Mann–Whitney U test). Previous studies have linked altered hemoglobin levels with DR severity, suggesting that elevated hemoglobin may reflect a compensatory response to chronic retinal hypoxia.[14]

Albumin, lymphocyte count, and platelet count did not differ significantly between the DR and non-DR groups. However, the HALP score demonstrated a trend toward lower values in more severe DR, although this did not achieve statistical significance ($p = 0.065$). ROC analysis showed an area under the curve (AUC) of 0.555 ($p = 0.248$) for overall DR detection but increased to 0.599 ($p = 0.065$) for moderate-to-severe DR. While these AUC values indicate limited discriminative power, they suggest that the HALP score might be more relevant for identifying advanced DR stages.

The HALP score integrates parameters linked to inflammation and nutritional status. Albumin, known for its anti-inflammatory properties, has been associated with retinal vascular permeability, making it a relevant biomarker for DR severity.[11,12] Studies have also demonstrated that low serum albumin correlates with higher DR risk, further supporting its inclusion in composite indices.[13]

Lymphocyte count, reflective of immune function, plays a role in chronic inflammation, which is a key driver of DR pathogenesis.[20,21] Platelets, beyond their role in hemostasis, contribute to inflammatory cascades and microvascular dysfunction, exacerbating ischemic damage in the retina.[8–10] Given that the HALP score captures these parameters collectively, its association with DR severity aligns with research on inflammatory and nutritional markers in diabetic complications.

Although the HALP score alone did not emerge as a strong predictor of DR presence, its association with moderate-to-severe DR suggests a potential role in risk stratification. The relatively low AUC for overall DR detection (0.555) indicates limited predictive power in isolation; however, the trend seen in moderate-to-severe DR (AUC = 0.599) suggests possible clinical relevance when combined with other risk factors such as glycemic control and blood pressure.[6,17–19]

The observed increase in hemoglobin levels in moderate-to-severe DR cases can be interpreted in light of retinal hypoxia and compensatory mechanisms.[5] Elevated hemoglobin may lead to increased blood viscosity and vascular compromise, contributing to DR progression. This interplay underscores the multifactorial nature of DR, highlighting the need for composite indices such as the HALP score rather than reliance on single biomarkers.

Our findings align with existing research that has explored individual HALP score components in DR and other inflammatory conditions. Previous studies have reported that reduced albumin levels and altered

hemoglobin concentrations correlate with DR progression.[12–15] Moreover, research on HALP in cardiovascular and metabolic diseases suggests that it may serve as a prognostic indicator in conditions involving chronic inflammation and nutritional deficits.[6,17–20]

Although previous studies have highlighted the HALP score's prognostic value across various conditions such as acute ischemic stroke and cancer, its role in DR remains underexplored. The current study contributes to this growing body of evidence by demonstrating that, although the HALP score is not a strong independent predictor of DR presence, its association with disease severity warrants further investigation.

The results align with prior studies linking decreased albumin levels and altered hemoglobin concentrations with DR progression. The integrated approach of using the HALP score is supported by research emphasizing the prognostic value of composite biomarkers in diseases involving both inflammatory and nutritional imbalances. Although the HALP score was not a statistically robust independent predictor in this study, its potential to identify more severe DR cases merits further investigation.

Several biological mechanisms may underpin the relationship between a low HALP score and the severity of DR. First, a low hemoglobin level can result in retinal hypoxia, which is a well-known stimulus for the overproduction of VEGF, thereby promoting neovascularization and worsening DR.[14] Second, hypoalbuminemia, often indicative of both malnutrition and a heightened inflammatory state, can impair blood-retina barrier integrity, resulting in edema and exudation. Third, a decreased lymphocyte count may reflect an impaired immune response, resulting in persistent low-grade inflammation that further damages the retinal microvasculature. Finally, platelets are known to be involved in inflammatory processes and may contribute to microvascular occlusion when their function is altered.[8–10] Taken together, these findings indicate that the HALP score effectively reflects key nutritional and inflammatory parameters that contribute to the development and progression of DR.

Summary

This study examined the relationship between the HALP score and DR in individuals with T2DM. Findings revealed that, although the HALP score did not significantly distinguish between DR and non-DR patients overall, trends were observed that suggest its potential utility in identifying patients with moderate-to-severe DR. Specifically, although the HALP score's area under the ROC curve (AUC) for predicting the presence of DR was only 0.555 ($p = 0.248$), its AUC for moderate-to-severe DR was 0.599 ($p = 0.065$), indicating that the score may have better discriminative power for more advanced disease stages. Additionally, hemoglobin levels were significantly elevated in the moderate-to-severe DR subgroup, further highlighting the complex interplay between nutritional status and DR severity.

The findings of our study are in line with previous research that has emphasized the role of inflammatory and nutritional markers in the progression of DR. Several studies have identified lower levels of albumin and hemoglobin as being associated with more severe forms of DR.[12] Our observation that a lower HALP score trends toward an association with moderate-to-severe DR supports the hypothesis that systemic inflammation and malnutrition are key contributors to retinal microvascular damage.

While the overall HALP score did not significantly distinguish between the DR and non-DR groups, this could be attributed to the multifactorial nature of DR, where other variables such as glycemic control, duration of diabetes, and blood pressure may play critical roles. The relatively modest AUC values suggest that the HALP score, when used in isolation, may not be sufficient as a stand-alone diagnostic tool. However, it could be highly valuable as part of a composite panel of biomarkers for DR risk stratification, particularly in resource-limited settings where more expensive tests are not feasible.

Conclusion

The potential clinical implications of our findings are significant. Given the simplicity and cost-effectiveness of calculating the HALP score using routinely available laboratory parameters, it may serve as a practical tool for early DR screening and risk stratification, especially in primary care and resource-limited environments. Integrating the HALP score into routine diabetic assessments could allow clinicians to identify patients at higher risk of progressing to moderate or severe DR, thereby facilitating timely referrals for ophthalmologic evaluation and intervention.

Moreover, the HALP score could be particularly useful when combined with other clinical parameters such as glycemic control [glycated hemoglobin (HbA1c)], blood pressure, and lipid profiles. Such an integrative approach would provide a more comprehensive risk assessment model, ultimately aiding in the prevention of DR-related complications.

Recommendations

Enhance Risk Stratification

Integrate the HALP score with established DR risk factors (e.g., HbA1c, diabetes duration, and blood pressure) to develop a comprehensive risk prediction model for early identification of high-risk patients.

Conduct Longitudinal Analyses

Implement prospective studies to assess whether variations in the HALP score over time predict the progression of DR, thereby validating its prognostic utility.

Broaden the Scope of Biomarker Evaluation

Investigate the role of the HALP score in other diabetes-related microvascular complications, such as nephropathy and neuropathy, to determine its overall applicability as a systemic biomarker.

Assess the Impact of Targeted Interventions

Explore whether interventions aimed at improving nutritional and inflammatory status (e.g., optimizing albumin and hemoglobin levels) can favorably modify the HALP score and potentially slow the progression of DR.

Future Directions

While the HALP score alone may not be sufficient for DR screening, the observed trends suggest its potential role in a multifactorial risk assessment framework. Future studies should explore longitudinal associations between changes in the HALP score and DR progression. Additionally, integrating HALP with other biomarkers may improve predictive accuracy and support early intervention strategies in clinical practice. Expanding research in this area could provide cost-effective methods for enhancing DR risk stratification and guiding patient management.

Future research should focus on validating the HALP score as part of a composite risk model for DR. Longitudinal studies could assess whether changes in the HALP score over time correlate with DR progression or regression, providing insight into its utility for monitoring disease course. Additionally, exploring the integration of the HALP score with other emerging biomarkers, such as C-reactive protein (CRP), interleukin-6 (IL-6), or the neutrophil-to-lymphocyte ratio (NLR), may enhance its predictive power. A multicenter approach, particularly involving diverse populations, would also

help determine the generalizability of the findings.

This thesis explores the association between the HALP score and the severity of DR in individuals with T2DM. Recognizing the burden of DR as a major microvascular complication of diabetes, the study was motivated by the need to identify accessible composite biomarkers that reflect both inflammatory and nutritional status, thereby aiding in early detection and risk stratification.

Limitations

Cross-sectional design: Limits the ability to establish causal relationships between the HALP score and DR progression.

Sample size and diversity: The relatively small and geographically restricted sample may reduce the generalizability of the findings.

Biomarker variability: The nonnormal distribution and inherent variability of the HALP score components could affect the robustness of the statistical analysis.

Confounding factors: Potential confounders such as comorbidities, medication use, and lifestyle factors were not fully controlled, which might influence the observed associations.

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