Diagnostic Value of HALP Score in Detecting Diabetic Nephropathy in Patients with Type 2 Diabetes Mellitus

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Abstract

Introduction  Hemoglobin, albumin, lymphocyte, and platelet (HALP) score has been used to predict the prognosis in several types of cancers for the last few years. We aimed to reveal whether HALP score has high sensitivity and specificity in the detection of diabetic nephropathy.

Methods  A cross-sectional study developed in Abant Izzet Baysal University Hospital in Bolu, Türkiye. Patients with type 2 diabetes mellitus (DM) were enrolled in the study. Study cohort included patients with diabetic nephropathy and patients without diabetic nephropathy. Pregnant women, subjects with malignancy, active infections conditions, and rheumatologic or hematologic diseases were excluded. We retrospectively analyzed and compared the HALP scores of the type 2 DM patients with and without diabetic nephropathy. Moreover, we sought correlation between HALP score and fasting glucose, glycated hemoglobin (HbA1c), and estimated glomerular filtration rate (eGFR).

Results  A total of 356 DM patients, 162 with nephropathy and 194 without nephropathy were included in the study. The HALP score was 44.86 (4.5–119.9) in the nephropathic group, while it was 55.14 (13.2–173.7) in the nonnephropathic group (p < 0.001). HALP score was negatively correlated with HbA1c (r = −0.66, p = 0.003) and fasting glucose (r = −0.65, p = 0.002), while positive correlation was found between HALP score and eGFR (r = 0.13, p = 0.02). HALP score lower than 45.9% have 73% sensitivity and 52% specificity in detecting diabetic nephropathy (area under the curve: 0.64, p < 0.001, 95% confidence interval: 0.59–0.70).

Conclusion  We suggest that HALP score can become a simple and easy to assess marker for diabetic nephropathy in addition to standard tests.
Introduction

The prevalence of type 2 diabetes mellitus (DM) and mortality due to diabetic complications are increasing in the modern world.1 Countries all over the world make significant economic expenditures for the prevention and treatment of DM. Early diagnosis and treatment of DM and its complications are of great importance in every sense.2 Defective glucose use due to insufficient insulin secretion and insulin resistance in peripheral tissue play a role in the pathogenesis of DM. As a result of the decreased effect of insulin on metabolism, oxidative stress and inflammation increases due to substrate accumulation in the cell. Due to the oxidative stress, peripheral neuropathy, retinopathy, and nephropathy, which are complications of diabetes, develop.3

Although DM can be diagnosed by clinicians fairly easily, monitoring the patient and the course of the disease and its complications are still challenging. Moreover, some patients may already have microvascular complications of DM by the time they get diagnosed. Even if they do not, clinicians should scan for complications like retinopathy, nephropathy, and neuropathy.4 But we still do not have the tools for diagnosing the complications at early stages. For instance, we can scan for nephropathy and still miss it at early stages. In the early stages of diabetic nephropathy (DN), estimated glomerular filtration rate (eGFR) can be higher and daily variation can cause urine albumin to creatinine ratio to appear as normal.4,5 Therefore, high-risk patients must be identified even before we can detect early stages of microvascular complications of DM. Hemoglobin (Hb), albumin, lymphocyte, and platelet (HALP) score can show nutritional and inflammatory status of patients. This could help clinicians to predict the prognosis of different diseases. HALP score has been used by many researchers to predict the prognosis in several types of cancers for the last few years.6-9 Hb and albumin can reflect the nutritional status of the patient and albumin alone has been considered as a positive prognostic factor for cancer patients. Lymphocyte and platelet values can give a hint of the patients’ immune status; already included in scores like platelet-to-lymphocyte ratio. By combining these four parameters Chen et al successfully created a simple clinical tool to predict prognosis of cancer patients.9 Recent studies have extended the research on HALP score in to new areas such as stroke, hyperemesis gravidarum, vasculitis, and acute heart failure patients.10

Glomerular hyperfiltration and proteinuria is usually seen in the early stages of diabetic kidney disease and is mainly related to decreased levels of erythropoietin secretion.11 Angiotensin II, which is a key component in renin-angiotensin-aldosterone system (RAAS), stimulates erythropoietin and also acts as a growth factor in the bone marrow. RAAS has been shown to be suppressed in diabetic patients, especially with hypertension. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers suppress RAAS, therefore causing anemia.11

Albumin is synthesized in the liver and then it is released into the bloodstream. In healthy individuals it is kept at a steady plasma level and it is the main source of plasma osmotic pressure.12

Lymphocytes play an essential role in immune modulation and neutrophil/lymphocyte ratio (NLR) is used as a marker of inflammation in recent trials. In recent years, lymphocyte count has been used in a number of different scoring systems.13,14 Platelet/lymphocyte ratio (PLR), NLR, monocyte/lymphocyte ratio (MLR), and systemic immune-inflammation index (SII) have all included lymphocyte counts as a parameter of systemic inflammation marker in the scoring systems.13,14

Platelets functions in hemostasis are well described but recently its effects on angiogenesis, tumor metastasis, and cancer-related inflammation have been investigated. When HALP score was first created it was used to predict the outcome of cancer patients and since then it has been widely investigated in cancer patients. As discussed, platelet has a role in cancer progression so it is understandable that HALP score included platelet as one of the prediction factors in the first place.15 But platelet also has a role in inflammation and has been used as a prognostic factor in critically ill patients and patients with sepsis.16 Platelets influence inflammation not only by releasing proinflammatory substances but also by interacting with immune cells. Recent studies suggest that platelet has an active role in acute inflammation too.17

As discussed above, all the parameters that make up the HALP score could be used as a prognostic marker individually. But scoring systems like the HALP score strengthen the prognostic value of the individual marker. So, we aimed to investigate whether HALP score was associated with DN, a microvascular complication of DM, in subjects with type 2 DM.

Materials and Methods

Study Population

The present study was conducted with 356 DM patients who applied to the internal medicine outpatient clinic between August 2022 and January 2023. These subjects were retrospectively included in the study. Of the 356 patients, 162 had DN according to their records. Patients were categorized into two groups, whether they have nephropathy or not. Exclusion criteria were as follows: younger than 40 years of age, pregnancy, malignancy, active infections conditions, and rheumatological and hematological diseases.

Clinical and Laboratory Analyses

Age, gender, year of DM diagnosis, diabetes therapy, body mass index (BMI), waist circumference, systolic/diastolic blood pressure, and diabetic microvascular complications (retinopathy, neuropathy, nephropathy) were recorded from the patient files. Also, serum biochemistry (urea, creatinine, eGFR, aspartate [AST] and alanine transaminases, albumin, C-reactive protein [CRP], fasting blood glucose, glycated Hb [HbA1c] trigylceride, low-density lipoprotein [LDL], high-density lipoprotein [HDL], spot urine creatinine, and spot urine protein) and hemogram parameters (white blood cell [WBC] count, neutrophil count, lymphocyte count [lym], Hb, hematocrit, and platelet count [PLT]) were recorded trough the hospitals patient database.
HALP score is calculated with the formula of (Hb x serum albumin x lym)/PLT. Also, patients with DN were detected with the following formula: spot urine protein/spot urine creatinine. Data of the DN and control groups were compared.

Statistical Analyses
The Statistical Package of Social Sciences (SPSS) software (IBM Statistics 20.0 for Windows, Chicago, Illinois, United States) was used for analyses. Normal distribution of continuous variables was evaluated by Kolmogorov–Smirnov test. Data that fit the normal distribution were presented as mean ± standard deviation, and those that did not fit were presented as median and minimum-maximum. The categorical variables were shown as frequencies and proportions, and analyzed by using the chi-square test. The difference of the mean and median between the two groups was compared with the Mann–Whitney U test and the independent samples t-test. Pearson’s correlation test was used to evaluate the correlation. Finally, the sensitivity and specificity of HALP score in detecting DN was tested with receiver operating characteristic (ROC) analysis. Binary logistic regression analysis, taking into account diabetes duration, BMI, HbA1c, and eGFR along with HALP score, was conducted to reveal whether HALP score was an independent risk factor for DM. p-Values lower than 0.05 were accepted as statistically significant.

Results
A total of 356 patients, 162 with nephropathy and 194 without nephropathy, who were followed up in our clinic with the diagnosis of type 2 DM, were included in the study. When the demographic data were evaluated, the mean age was similar between the groups (p = 0.24). Likewise, there were similar number of women in both groups (p = 0.2). The mean duration of diagnosis of type 2 DM was 4 (1–20) years in the nephropathic group, while it was 3 (1–24) years in the nonnephropathic group (p = 0.01). And also cigarette and alcohol use were found to be similar between the groups (p = 0.392, p = 0.362, respectively). The distribution of height, weight, and waist circumference was found to be similar between the two groups (p = 0.45, p = 0.065, p = 0.18, respectively) and the BMI was 29.9 (17–49) kg/m² in the group with nephropathy, while it was 31.7 (20–55) kg/m² in the nonnephropathic group. It was found to be significantly higher in the nonnephropathic group (p = 0.009). Systolic and diastolic blood pressures were similar between the two groups (p = 0.851, p = 0.144, respectively). Demographic and physical parameters of patients are summarized in Table 1.

Hb and hematocrit levels of the study groups were similar (p = 0.214, p = 0.794, respectively). WBC count and neutrophil count was found to be significantly higher in the nephropathic group (p = 0.001, p < 0.001, respectively). When the lymphocyte count was compared, it was found to be significantly lower in the nephropathic group (p < 0.001). And platelet counts were significantly higher in the nephropathic group (p = 0.046). Complete blood count (CBC) parameters of the patients are given in Table 2.

Fasting glucose, creatinine, urea, albumin, CRP, AST, ALT, cholesterol, and total cholesterol were found to be similar between both groups (p = 0.472, p = 0.08, p = 0.139, p = 0.268, p = 0.173, p = 0.339, p = 0.051, p = 0.139, respectively). As expected, the GFR was 91.7 (15–160) mL/min/1.73 m² in the DN group, while it was 102.8 (14–211) mL/min/1.73 m² in the nonnephropathic group (p < 0.001). On the other hand, triglyceride levels were found to be lower in the nephropathic group (p = 0.033).

The HALP score was 44.86 (4.5–119.9) in the nephropathic group, while it was 55.14 (13.2–173.7) in the nonnephropathic group, and it was found to be significantly lower in the group with nephropathy (p < 0.001). Table 3 shows the biochemical parameters and HALP score of the study population.

While diabetic retinopathy, one of the microvascular complications of diabetes, was found to be similar in both groups (p = 0.488), diabetic neuropathy was found to be significantly higher in the nephropathic group (p < 0.001). Table 4 shows the rates of diabetic chronic complications in the study cohort.

According to Pearson’s correlation analysis, HALP score correlated negatively with HbA1c (r = −0.66, p = 0.003) and fasting glucose (r = −0.65, p = 0.002), while positive correlation was found with GFR (r = 0.13, p = 0.02). There was no significant correlation between HALP score and age (r = −0.04, p = 0.66).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic and physical parameters of the patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With diabetic nephropathy</td>
</tr>
<tr>
<td></td>
<td>Median (min–max)</td>
</tr>
<tr>
<td>Age</td>
<td>57 (36–87)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.62 (1.4–1.9)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80 (45–150)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>103 (75–160)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.9 (17–49)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>125 (90–200)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>80 (50–110)</td>
</tr>
<tr>
<td>Diabetes duration (y)</td>
<td>4 (1–20)</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index.
Note: Significant p-values are expressed as bold characters.
Table 2 Complete blood count parameters of the patients

<table>
<thead>
<tr>
<th></th>
<th>With diabetic nephropathy</th>
<th>Without diabetic nephropathy</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (µL)</td>
<td>7.6 (3.8–14.4)</td>
<td>7 (3.4–24)</td>
<td>0.001</td>
</tr>
<tr>
<td>Neu (µL)</td>
<td>4.7 (1.7–12.9)</td>
<td>4.17 (1.7–19.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lym (µL)</td>
<td>1.98 (0.4–3.4)</td>
<td>2.24 (1.1–5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>13.2 (7.8–17.6)</td>
<td>13.6 (6.7–17.9)</td>
<td>0.214</td>
</tr>
<tr>
<td>Htc (%)</td>
<td>39.8 (25–52)</td>
<td>39.8 (14.5–51.8)</td>
<td>0.794</td>
</tr>
<tr>
<td>PLT (µL)</td>
<td>262.5 (60–641)</td>
<td>235 (66–915)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Abbreviations: Hb, hemoglobin; Htc, hematocrit; Lym, lymphocyte count; Neu, neutrophil count; PLT, platelet count; WBC, white blood cell.
Note: Bold p-values are statistically significant.

Table 3 Biochemical parameters and HALP score of the patients

<table>
<thead>
<tr>
<th></th>
<th>With diabetic nephropathy</th>
<th>Without diabetic nephropathy</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>8.35 (4.9–17.8)</td>
<td>7.4 (5–14)</td>
<td>0.001</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>161 (65–565)</td>
<td>145 (66–473)</td>
<td>0.472</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.83 (0.5–3.9)</td>
<td>0.82 (0.4–3.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>189 (52–318)</td>
<td>200 (50–378)</td>
<td>0.139</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>91.7 (15–160)</td>
<td>102.8 (14–211)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>5.4 (1.8–13.6)</td>
<td>5.7 (2.5–10.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>3.9 (0.1–150)</td>
<td>5 (0.1–250)</td>
<td>0.173</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.4 (1.4–5.4)</td>
<td>4.4 (3.7–5.6)</td>
<td>0.268</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>18 (9–297)</td>
<td>19 (6–58)</td>
<td>0.399</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>20 (6–216)</td>
<td>17 (6–76)</td>
<td>0.027</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>112 (29–202)</td>
<td>120 (21–244)</td>
<td>0.051</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>45.9 (13–92)</td>
<td>43.4 (14–80)</td>
<td>0.035</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>138 (47–411)</td>
<td>154 (54–1050)</td>
<td>0.033</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>191 (52–318)</td>
<td>200 (50–378)</td>
<td>0.139</td>
</tr>
<tr>
<td>HALP score (%)</td>
<td>44.86 (4.5–119.9)</td>
<td>55.14 (13.2–173.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, aspartate transaminase; AST, alanine transaminase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HALP, hemoglobin, albumin, lymphocyte, and platelet; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Note: Bold p-values are statistically significant.

Table 4 Comparison of diabetic complications in the study cohort

<table>
<thead>
<tr>
<th></th>
<th>With diabetic nephropathy</th>
<th>Without diabetic nephropathy</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With diabetic retinopathy</td>
<td>23 (6.4)</td>
<td>29 (8.0)</td>
<td>0.488</td>
</tr>
<tr>
<td>With diabetic neuropathy</td>
<td>78 (21.7)</td>
<td>55 (15.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note: Bold p-value is statistically significant.

p = 0.5), gender (r = 0.1, p = 0.09), diabetes duration (r = –0.1, p = 0.06), and diabetes treatment (r = 0.16, p = 0.18).

When the reliability of the HALP score in detecting diabetic kidney injury was evaluated according to the ROC analysis, it was found that the HALP score lower than 45.9% has 73% sensitivity and 52% specificity in detecting DN (area under the curve: 0.64, p < 0.001, 95% confidence interval [CI]: 0.59–0.70). Fig. 1 shows the ROC curve of HALP score in detecting DN.

Binary logistic regression analysis, taking into account diabetes duration, BMI, HbA1c, and eGFR along with HALP score, revealed that HALP score was an independent risk
factor for DN ($p < 0.001$, odds ratio: 1.02, 95% CI: 1.01–1.04). A unit decrease in HALP score increased the risk of DN by 1.02 times.

**Discussion**

The present study showed that HALP score could be a reliable marker of DN since it was significantly reduced in diabetic subjects with DN compared to those without DN. Moreover, HALP score was significantly correlated with biochemical markers of type 2 DM (fasting glucose and HbA1c) and with eGFR levels. Finally, HALP score has considerable sensitivity and specificity in detecting nephropathy in diabetic subjects.

In recent years easy accessible prediction tools and scoring systems have been proposed in a wide variety of diseases. These scores have the potential of early detection and prediction of outcome without the need of extra testing. PLR, NLR, MLR, SII, and HALP score are all derived from CBC analysis. CBC is a routine test in the clinical setting especially for diabetic patient care.

Recently, HALP score has been proposed to assess the prognosis of various cancer types. Chen et al first described HALP score to predict prognosis of gastric carcinoma patients in 2015. Since then researchers all around the world have used HALP score mainly in cancer prognosis. But some researchers took another approach and used HALP score to differentiate malign causes from benign causes. Eskin et al used HALP score to determine if the extrahepatic biliary obstruction was a malign or benign origin and found that malign causes have a lower HALP score than benign causes. Likewise, Akbas et al used HALP score in mechanic intestinal obstruction and similar to Eskin et al, they found that malign causes of intestinal obstruction has lower HALP score than of benign causes and sensitivity was 85% and specificity was 78%. On the other hand, HALP score has been used in other illnesses like stroke or acute appendicitis and others. Cay and Duran used HALP score to predict weight loss after sleeve gastrectomy for obesity and found that higher HALP score was associated with greater weight loss. Li et al, however, explored the prognostic value of HALP score in cerebral venous sinus thrombosis retrospectively and found that HALP score greater than 31.54 was associated with good outcome. Benli and Tazeoglu analyzed data from 684 patient who were operated for acute appendicitis and found that a HALP score of lower than 31.2 was associated with postoperative complications. And Tian et al investigated the relationship of HALP score and acute ischemic stroke outcome. They found that higher HALP score was associated with decreased risk of recurrent stroke and mortality. All of these conditions are characterized with increased inflammatory burden. High inflammation is also a feature of DM. Accordingly, we reported decreased HALP score levels in DN patients compared to those without nephropathy.

All these research on different diseases has been made on the premise that HALP score is a good indicator of systemic inflammation and nutritional status. Kocaoglu and Alati modified the HALP score to predict poor outcome in patients with acute heart failure, but did not find significant difference. In our study, we found that HALP score is significantly low in patients with DN. It is consistent with the previous literature in the prediction of poor outcome but contradicts what Kocaoglu and Alati hypothesized.

Why HALP score was associated with DN? DN is closely associated with inflammation. Despite type 2 DM itself is already considered as an inflammatory condition, diabetic patient with DN have greater burden of inflammation compared to those without DN. Recently, the Care Time study showed increased inflammation in patients with DN. Kidney injury molecule-1, omentin, neuregulin, and uric acid/HDL cholesterol ratio are among other inflammatory predictors of diabetic kidney injury. Similarly, HALP score is associated with inflammatory conditions, thus we found decreased HALP score levels in subjects with DN, which is consistent with literature.

Although the creatinine and urea levels of the two groups were similar, GFR was naturally lower in the nephropathy group significantly. Also, understandably HbA1c level of the nephropathy group was 8.35% and significantly higher than the non-nephropathy group, which was 7.4%. This may reflect poor control of diabetes in the patients with complications. It is also natural that longer disease duration increases the complication risk. We found that patients with nephropathy have longer duration of diabetes than patients without nephropathy.

Recent studies in literature found that HALP score was associated with inflammatory conditions such as malignancy, autoimmune hepatitis, and immunoglobulin A nephropathy. All of these conditions are characterized with some degree of inflammatory burden as DN is. Hence, our results are in accordance with the literature findings.

As far as we know, this is the first study that investigated the relationship between HALP score and microvascular complication of type 2 DM. Since DM is a condition where systemic inflammation and oxidative stress are elevated and as a result microvascular complication occurs, it can be hypothesized that HALP score correlates with complications and outcome. Indeed, HALP score has just moderate sensitivity and average specificity in detecting DN. However, it is
the first study about HALP score’s role in this population. Further studies with larger cohort may outline its role in DN. On the other hand, easy to assess and inexpensive nature of HALP score will make it a useful tool in the evaluation of DN. Of course, patients with low HALP score may need confirmation with gold-standard laboratory tools. Therefore, as an indicator of nutrition and systemic inflammation HALP score is a good candidate for becoming a prognostic tool in type 2 diabetic patients without other inflammatory conditions.

Retrospective and single-center nature of the present study are two main limitations that we should mention. Third limitation could be lack of Hb variant analysis which could interfere with HALP scores. However, this is the first study that found association between HALP score and DN, and significant correlations between HALP score and metabolic parameters including HbA1c, fasting glucose, and GFR.

Conclusion

In conclusion, we suggest that HALP score can make a simple and easy to assess marker for DN in addition to standard tests. Therefore, we think that physicians could find it useful, along with standard diagnostic tests, in the evaluation of DN.

Note

This work has been presented as an abstract in 22nd European Congress of Internal Medicine which was held on March 2024, in Istanbul, Türkiye.

Authors’ Contributions


Compliance with Ethical Principles

This work was approved by the Bolu Abant Izzet Baysal University Ethics Committee (approval number: 2023/86).

Funding and Sponsorship

None.

Conflict of Interest

None declared.

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