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Clinical application of HALP score in the determination of nodal non-Hodgkin lymphoma prognosis

Victor TOMACINSCHII[1,2], Sanda BURUIANA[1], Maria ROBU[1]

Keywords: Non-Hodgkin lymphoma, HALP score, prognosis

Abstract

Introduction*: Non-Hodgkin's lymphomas (NHL) are hematopoietic tumors that develop from the malignant proliferation of the lymphatic tissue. The onset of NHL can occur in any organ and tissue, at the same time the most frequent localization is represented by the primary involvement of the lymph nodes (52-70%). The hemoglobin, albumin, lymphocytes, and platelets compose a score (HALP score), have recently been evaluated to predict the prognosis of cancer patients. However, there are limited reports of the use of HALP score in the determination of survival prognosis with NHL.*

Objective*: This study aims to appreciate the usefulness of the HALP score in the determination of overall survival (OS) indicators in patients with nodal non-Hodgkin's lymphomas.*

Material and methods: *57 patients diagnosed with nodal NHL in the Oncology Institute of the Republic of Moldova have been evaluated. The HALP score was calculated using formula: hemoglobin (g/L) × albumin (g/L) × lymphocytes (%) / platelets (/L).*

Results*: Out of the patients enrolled in study 35 (61.4 %) were female. Aggressive lymphomas were diagnosed in 45 cases (78.9%), and indolent lymphomas in 12 patients (21.1%). On receiver operating characteristic curve (ROC) analysis, the predictive ability of the HALP score to envisage the risk of unfavorable events was significant (p= 0.038; AUC:0.685). The cut-off value based on ROC was 583,5. As a result, it was observed that in case of aggressive NHLs HALP patients with a low HALP score have a shorter period of OS: median OS-13(±4,4) months compared with the group of patients with high HALP score where the median OS was not reached, p=0,049. In contrast, in indolent lymphomas, HALP score failed to show significant differences in survival between groups of patients with high or low HALP score(p=0,081).*

Conclusions*: The HALP score, appears to be a valuable tool in determining the prognosis of patients with nodal NHL. A low HALP score was associated with lower OS rates - 13(±4,4) months in case of aggressive NHLs. (p=0,049). However, in case of indolent NHLs HALP score failed to perform as a useful prognostic score in the estimation of OS.*

[1]"Nicolae Testemitanu" State University of Medicine and Pharmacy, Chisinau, Republic of Moldova

[2]Institute of Oncology, Chisinau, Republic of Moldova

Corresponding author:
Victor Tomacinschii, Department of Hematology, Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Republic of Moldova,
phone +37369754013;
email: victor.tomacinschii@usmf.md

Introduction

Non-Hodgkin's lymphomas (NHL) are hematopoietic tumors that develop from the malignant proliferation of the lymphatic tissue. NHL is one of the most common hematological neoplasms and accounts for around 3% of cancer cases worldwide. NHL was ranked as the fifth to ninth most frequent malignancy in most countries worldwide in 2020, with an estimated number of 544,000 new cancer cases. [1,2] The acquisition of new theoretical knowledge related to the clinical-biological, immunohistochemical peculiarities as well as related to the molecular pathways of tumor transformation was extrapolated on the latest WHO classifications of hematopoietic and lymphoid tissue tumors by expanding the number of included nosological entities.[3,4]

Non-Hodgkin lymphomas (NHL) can be classified as indolent or aggressive based on their clinical behavior. Indolent B-cell lymphomas, such as follicular lymphomas, marginal zone lymphoma, and small lymphocytic lymphoma, for example, develop as chronic incurable diseases in which the clinical course is slow-progressing and oligosymptomatic for a long time but treatment requires regular exposure to toxic cytostatic drugs and/or radiation therapy. [5]

On the other hand, aggressive B-cell lymphomas represent a diverse category of lymphomas that may involve precursor lymphoid neoplasms (B-lymphoblastic leukemia/lymphoma NOS and B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities) as well as a variety of mature B-cell lymphomas, like Burkitt lymphoma, mantle cell lymphoma, primary effusion lymphoma, and diffuse large B-cell lymphoma. They exhibit aggressive behavior, with frequent extranodal involvement and urgent treatment needed, otherwise, they result in the patient's death.[6]

Accurate prediction of the prognosis of NHL patients is critical for guiding treatment decisions and improving patient outcomes. To assess the prognosis and treatment response rate, several classic prognostic scores have been developed and have become quite popular among practitioners (IPI[7] and R-IPI[8], FLIPI[9], MIPI[10], etc.). In the last decade, taking into account the increase in the penetrability of molecular biology techniques, the integration of molecular biology markers into classic prognostic scores (m7-FLIPI[11,12], R/R IPI[13]) or the development of new prognostic scores entirely based on cytogenetic and molecular biology markers (LymForest-25 Model[14], IAC-FL[15]), is becoming increasingly popular. The latter are, without a doubt, more refined and with a higher degree of sensitivity compared to the classic scores, but they have the great disadvantage of incurring high costs on the part of healthcare systems, and this limits their widespread use.

For these reasons, the need to develop/adapt prognostic scores based on usual clinical and paraclinical parameters, with wide use in clinical practice, remains a hot topic.

The hemoglobin, albumin, lymphocyte, and platelet (HALP) score is a simple way to assess systemic inflammation and nutritional status of the patients[16,17] and has been shown to be a significant predictive factor in several benign pathologies[16–19], but also in different types of cancers such as: prostatic cancer[20], small cell lung cancer[17], metastatic renal cell cancer[21], endometrial cancer[22], etc. The purpose of this study is to assess the usefulness of the HALP score in determining overall survival (OS) features in patients with nodal non-Hodgkin lymphoma.

Material and methods

This study was performed in the Oncologic Institute, Chisinau, Republic of Moldova. Adult patients (aged over 18 years old) diagnosed with Non-Hodgkin lymphoma were included in the current study. In order to be included in the study, the diagnosis of the patients had to be confirmed in accordance with the criteria of the World Health Organization Classification of the tumors of the Hematopoietic and lymhoid tissue[4]. Patients with non-compliant diagnoses or with confirmation only on histological principles were excluded from the study. To confirm the hypothesis, a study was conducted on 57 patients diagnosed with nodal forms of NHL.

Basic clinical and laboratory parameters were obtained from medical records including age, gender, disease stage, IPI score, presence of B symptoms, Eastern Cooperative Oncology Group performance status (ECOG), red blood cell count, white blood cell count, platelet count, absolute neutrophil count, absolute lymphocyte count, serum LDH levels, serum albumin concentration, and hemoglobin concentration. The HALP score was calculated using formula: hemoglobin (g/L) × albumin (g/L) × lymphocytes (%) / platelets (/L). Starting values for the HALP score and laboratory parameters were defined as measurements made a maximum of 3 weeks before the start of treatment.

To perform statistical analysis, SPSS v. 26.0 software package (SPSS Inc., Chicago, IL, USA) was used. Descriptive statistics are presented as the mean and standard deviation values and percentage distribution.

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ROC curve analysis was used to determine the cutoff values of the HALP score in predicting mortality. The significance level was accepted as $p < 0.05$.

Results

Ou of the 57 patients enrolled in the study, 35 (61.4%) were female and 22 (38.6%) were male. The mean age of the patients was 59.09 years (range 22-83 years). According to age groups distribution, patients aged between 61 and 70 years were the most often affected, recording 19 (33.3%), cases followed by those aged between 51 and 60 years with 17 (29.82%) patients and the patients from the age category 71 and 80 years old - 7(12.28%) cases.(Figure 1)

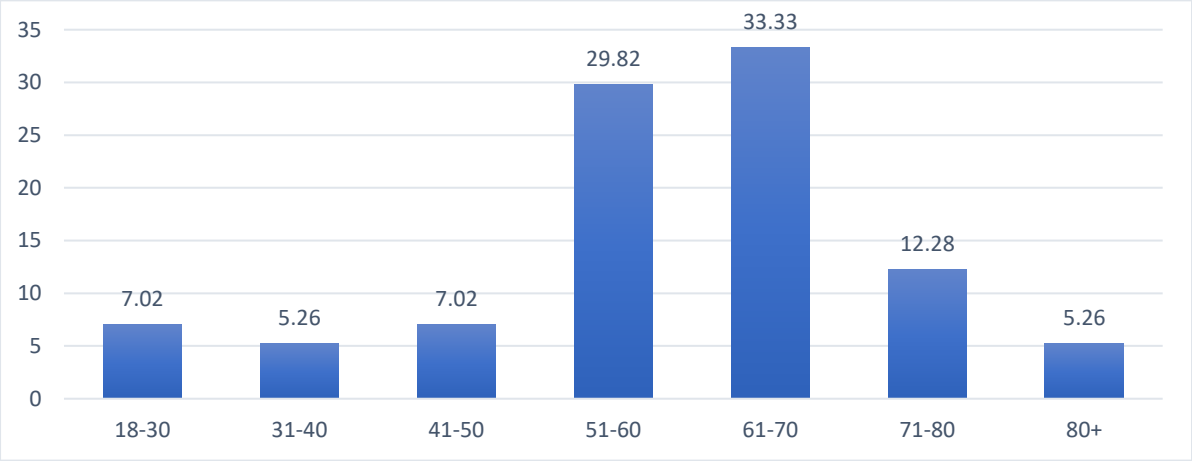

Figure 1. Distribution of patients within the study group depending on age category

Most of the patients were diagnosed in generalized stages: stage III – 16 (28,1%), cases, stage IV – 30 (52,6%) patients. Localized stages being diagnosed in 19,3%: stage I - 3(5,3%) patients, and stage II – 8(14,0%) patients. (Figure 2 a)

According to the primary area of involvement the patients from the study group were distributed as follows. Peripheral lymph nodes were the most common area of the primary involvement - 37 (64.91%), seconded by onset in the mediastinum - 14 (24.56 %), abdominal lymph nodes being involved in 6 (10.52%). (Figure 2 b).

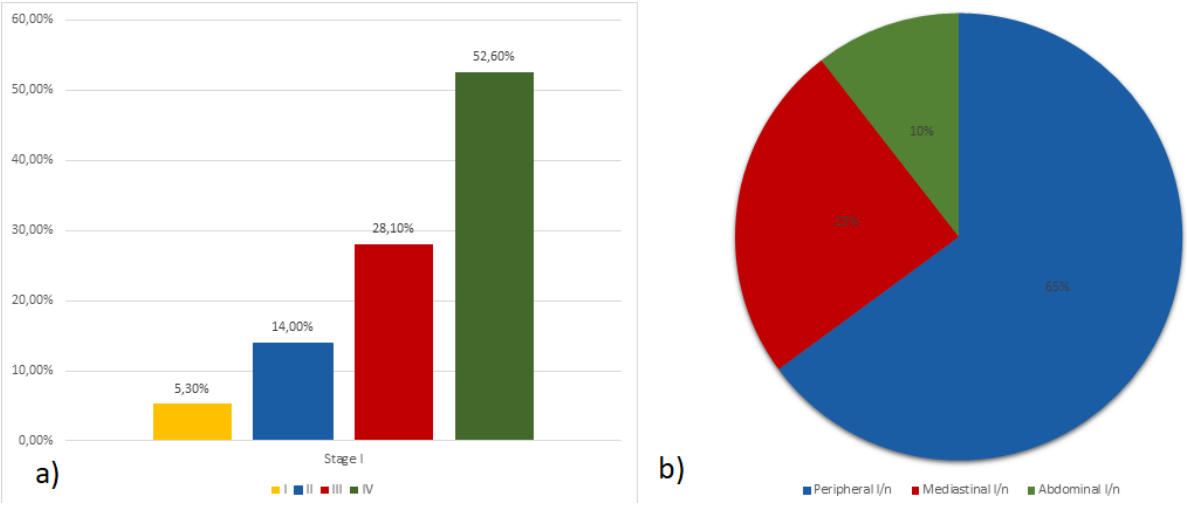

Figure 2. Distribution of patients within the study group depending on the clinical stage (a) and primary site of involvement (b).

Aggressive Non-Hodgkin lymphomas were diagnosed in 45 cases (78.9%), and indolent lymphomas in 12 patients (21.1%).

On receiver operating characteristic curve (ROC) analysis, the predictive ability of the HALP score to envisage the risk of unfavorable events was significant (p= 0.038; AUC:0.685). (Figure 3)

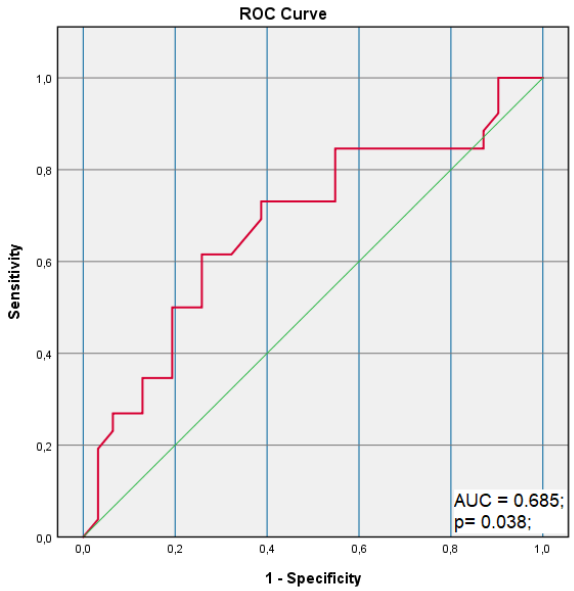

Figure 3. The results of the receiver operating characteristic (ROC) curve analysis using survival status as a classification variable to determine the ability of HALP score to determine the risk of an unfavorable outcome within the patients of the study group.

The cut-off value based on ROC analysis was equal to 583,5. As a consequence, the patients were divided into two subgroups: patients with a low HALP score (<583.5) and patients with a high HALP score (>583.5). As a result, we observed that in case of aggressive NHLs patients with a low HALP score have a shorter period of OS: median OS-13 (±4,4) months compared with the group of patients with high HALP score where the median OS was not reached (p=0,049). In contrast, in case of patients with indolent NHLs, HALP score failed to show significant differences in survival between the two subgroups of patients with high or low HALP score (p=0,081). (Figure 4).

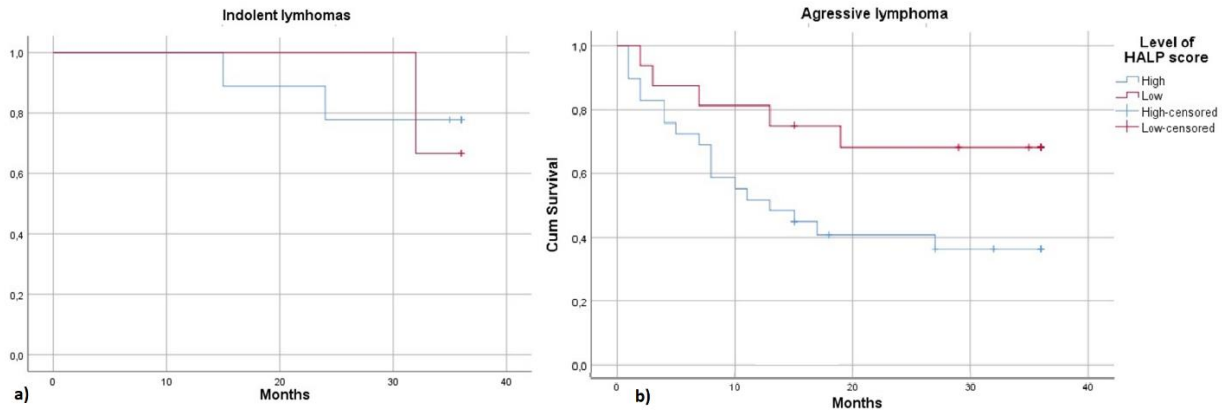

Figure 4. Kaplan Meier estimates of overall survival(OS), depending on the level of the HALP score in the case of aggressive (b) and indolent(a) NHLs.

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Discussion

A defining characteristic of cancer is systemic inflammation, and our body's inflammatory reaction to the tumor plays a critical role in promoting oncogenesis.[23] The HALP score is a composite score that includes four routine blood tests: hemoglobin, albumin, lymphocyte, and platelet counts, which are very straightforward to evaluate because they are routinely checked on a daily basis.[24] Each factor of the HALP score reflects various facets of the patient's health. Hemoglobin reflects the patient's oxygen-carrying capacity, albumin reflects the patient's nutritional status, immune function is indicated by lymphocyte count, and hemostatic capacity is indicated by platelet count. This scoring method has typically been used to predict the prognosis of certain types of tumors by demonstrating the two key functions (inflammation and nutrition status) in cancer prognosis. Chen et al. were the first to describe this scoring system for predicting gastric cancer prognosis.[25] Then, it was applied in the diferents fields of oncology to predict the prognosis of the cancer types, including hepatocelular carcinoma[26], esophageal squamous cell carcinoma[27], renal cell carcinoma[28], breast cancer[29,30], prostate cancer[20,31], lung cancer[17], colorectal cancer[32,33], and pancreatic cancer[16].

Only a few studies analyzing the prognostic significance of the HALP score in hematological malignancies are available, and even fewer are invesigatig the integration of this prognostic score to evaluate the therapeutic response of lymphomas.

The predictive significance of the HALP score was examined in a recent study published by Solmaz et al.[34] on 200 patients with multiple myeloma. The result reveals that the OS was statistically longer in patients with high HALP scores than in patients with low HALP scores (84 months versus 53 months; p = 0.0001). In addition, when the effects of NLR, PLR, HALP score and ISS stage on OS were examined by multivariate analysis, all these markers were found to be statistically significant predictors.

The most important evidence on the aggressive NHL comes from a 2021 report published by Vlatka et al[35], on 153 newly diagnosed diffuse large B-cell lymphoma. This study found that lower HALP was shown to be associated with unfavorable clinicopathological characteristics and a predictor of long term survival. Patients with Low HALP were found to have significantly more advanced stages of tumor (Ann Arbor Stage III and IV) (p = 0.001), worse ECOG performance status (p = 0.001), and increased LDH (p < 0.001). Patients with low HALP levels were also more likely to have B symptoms (p = 0.017), bone marrow infiltration (p 0.001), and a poorer prognosis (p 0.001). On a multivariable analysis, patients with low HALP were 3.7 times more likely to discontinue treatment than those with high HALP. Moreover, 5-year survival was considerably lower for patients with Low HALP (47.3% vs. 79.5%, p 0.001). In fact, on multivariable Cox regression, revealed that patients had a greater than 2.5 increased risk of death during the 5-year period if their HALP was low (p = 0.003). Previously, our working group also published some intermediate results of the present research focunsing the attention on DLBCL, highlighting similar results[36] Our final data confirm that the HALP score shows statistically significant survival differences in terms of OS (13±4.4 months), comparable to the literature data cited above.

In a different study Akkurd et al.[37], evaluated the prognostic impact on the overall survival of patients with peripheral T-cell lymphomas of different scores, including the HALP score. In the result, it was established that none of the evaluated scores has significance to predict overall survival in patients with peripheral T-cell lymphoma, and the IPI (International Prognostic Index) score remains superior in terms of prognostic sensitivity in this type of lymphoma.

To the best of our knowledge, no previous studies have been published to investigate the role of the HALP score in prognosticating the evolution of indolent non-Hodgkin's lymphomas. Our research is the first publication that also includes a group of patients with indolent NHL with nodal onset in which the prognostic impact of the HALP score was studied. In the case of these patients, however, the HALP score did not prove its applicability in determining OS. The most likely hypothesis that would come to explain the lack of prognostic impact of the HALP score in these patients is the fact that indolent NHL has a slowly progressive evolution and changes in the nutritional and inflammatory status that are the basis for evaluating the HALP score are rarely determined in indolent NHL at debut. Another limitation could be the relatively small group (12) of patients with indolent NHL included in the study.

The HALP score has several drawbacks despite showing substantial practical significance. First off, the HALP score is a composite measure that ignores other crucial prognostic variables like age, performance status, and disease stage. Second, the HALP score has not been

validated in all subtypes of NHL, and its prognostic value may vary depending on the subtype of NHL. Finally, the HALP score is static and does not account for variations in blood counts over time, which could affect the predictive value of the score.

Conclusions

The present study concluded the association between HALP score and prognosis of nodal agressive NHLs. A low HALP score was associated with lower OS rates - 13(±4,4) months in case of aggressive NHLs. (p=0,049). In the case of indolent NHLs, however, the HALP score failed to perform as a meaningful prognostic score in estimating OS.

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Conflicts of interest
There are no conflicts of interest.

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