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Prognostic value of HALP score and Systemic Immune-inflammation Index in multiple myeloma

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ABSTRACT

Aims: Multiple myeloma (MM) is a heterogeneous hematologic malignancy requiring reliable prognostic stratification. Inflammation- and nutrition-based biomarkers such as the hemoglobin-albumin-lymphocyte-platelet (HALP) score and Systemic Immune-inflammation Index (SII) have been proposed as accessible prognostic indicators. This study evaluated their prognostic value and compared their performance with the International Staging System (ISS).

Methods: This retrospective study included 54 patients with newly diagnosed MM. Baseline clinical and laboratory parameters were recorded at diagnosis. Overall survival (OS) was defined as the time from diagnosis to death from any cause or last follow-up. Survival outcomes were analyzed using Kaplan-Meier and log-rank tests, and independent predictors were assessed using multivariate Cox regression analysis. Receiver operating characteristic (ROC) analysis with the Youden index determined optimal cut-off values.

Results: The median age was 68 years (range, 40-85), and 53.7% of patients were male. According to ISS, 33.3% of patients were stage I, 46.3% stage II, and 20.4% stage III. During follow-up, 7 patients (13.0%) died. Higher ISS stage was significantly associated with mortality (p=0.007) and remained an independent predictor of OS in multivariate analysis (HR=3.84, 95% CI: 1.33-11.05, p=0.0127). ROC analysis demonstrated the strongest discriminative performance for ISS (AUC=0.793), compared with HALP (AUC=0.608) and SII (AUC=0.371). Optimal cut-off values were 3.0 for ISS, 32.3 for HALP, and 2887.5 for SII. Kaplan-Meier analysis showed significantly inferior survival in patients with ISS ≥3 (log-rank p=0.001), whereas HALP and SII did not significantly stratify OS (p=0.901 and p=0.348, respectively).

Conclusion: Although HALP showed a non-significant trend toward poorer survival at lower values, inflammation-based indices provided limited additional prognostic value beyond established staging systems.

Keywords: Multiple myeloma, overall survival, HALP score, Systemic Immune-inflammation Index

INTRODUCTION

Multiple myeloma (MM) is the second most common hematologic malignancy, characterized by the clonal proliferation of monoclonal plasma cells in the bone marrow and the subsequent production of monoclonal proteins.[1] Survival times for MM patients exhibit substantial heterogeneity, ranging from a few months to more than a decade. This heterogeneous nature necessitates accurate risk stratification to design personalized treatment strategies.[2-4]

Currently, the most widely used prognostic tools, the International Staging System (ISS) and the revised ISS (R-ISS), focus primarily on tumor burden and cytogenetic risks.[5] However, these systems do not fully reflect the patient's overall inflammatory status or nutritional profile. Moreover, the high cost and limited accessibility of cytogenetic and molecular testing in many centers underscore the need for simpler, low-cost prognostic markers obtainable from routine blood tests.[6,7] Among these markers, the Systemic Immune-inflammation Index (SII)-calculated from neutrophil, platelet, and lymphocyte counts-is a comprehensive indicator reflecting the balance between the inflammatory and immune responses.[8,9] Another composite index, the hemoglobin-albumin-lymphocyte-platelet (HALP) score, evaluates both systemic inflammation and the patient's nutritional status.[10-12]

The primary objective of this study is to investigate the prognostic impact of baseline HALP score and SII index on overall survival (OS) in newly diagnosed MM patients and to assess their relationship with the existing ISS staging system.

METHODS

Ethics

The study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Non-interventional Clinical Researches Ethics Committee

of Kütahya Health Sciences University (Date: 29.05.2025, Decision No: 2025/07-38).

Study Population

This retrospective cohort study included consecutive adult patients newly diagnosed with MM at the Department of Hematology, Kütahya Health Science University, between January 2015 and December 2025. Diagnosis was established according to International Myeloma Working Group criteria. Patients lacking complete baseline laboratory data or presenting with active infection, inflammatory disorders, or concurrent malignancies were excluded.

Data Collection and Variables

Baseline demographic, clinical, and laboratory parameters obtained at diagnosis were collected from electronic medical records. Disease stage was determined using the ISS. Inflammation-based indices were calculated using baseline laboratory values as follows:

HALP score=hemoglobin×albumin×lymphocyte count÷platelet count SII=platelet count×neutrophil count÷lymphocyte count

OS was defined as the time from diagnosis to death from any cause or last follow-up.

Statistical Analysis

Continuous variables were expressed as median (range) and categorical variables as number (percentage). Group comparisons were performed using the Mann-Whitney U test or Chi-square test, as appropriate. OS was estimated using the Kaplan-Meier method and compared with the log-rank test. Independent predictors of survival were evaluated using multivariate Cox proportional hazards regression analysis. Because β2-microglobulin constitutes a component of the ISS staging system, it was not included simultaneously in the multivariate model to avoid collinearity. Hazard ratios (HRs) were reported with 95% confidence intervals (CIs). Discriminative performance of ISS, HALP, and SII was assessed using receiver operating characteristic (ROC) curve analysis, and optimal cut-off values were determined by the Youden index. All statistical analyses were performed using IBM SPSS Statistics (version 29.0), and a two-sided p value <0.05 was considered statistically significant.

RESULTS

A total of 54 patients with newly diagnosed MM were analyzed. The median age at diagnosis was 68 years (range, 40-85), and 53.7% of patients were male. Baseline clinical and laboratory characteristics are summarized in **Table 1**. Median hemoglobin and albumin levels were 9.9 g/dl (7.0-14.65) and 37 g/L (20-49), respectively. The median HALP score was 34.09 (1.23-168.35), and the median SII was 3956 (1337-16738). According to the ISS, 33.3% of patients were classified as stage I, 46.3% as stage II, and 20.4% as stage III. Lytic bone disease was observed in 53.7% of patients, and 48.1% underwent autologous stem cell transplantation. The median follow-up duration was 18 months (range: 5-120). During follow-up, 7 patients (13.0%) died.

Table 1. Sociodemographic data of the patients

Variable	Median (min-max) or n (%)
Age (years)	68 (40-85)
WBC (/μL)	6210 (2120-15270)
Neutrophil (/μL)	3530 (1562-5145)
Lymphocyte (/μL)	1560 (560.00-5720)
Monocyte (/μL)	520 (130- 2810)
Hgb (g/dl)	9.90 (7.0–14.65)
Platelet (μ/L)	183.000 (31.000-362.000)
LDH (U/L)	175 (83-345)
Total protein	79 (68–129)
Albumin (g/L)	37 (20-49)
Calcium (g/L)	9.0 (7.50-16.60)
Serum creatinine (mg/dl)	0.96 (0.69–7.29)
Beta-2 microglobulin (mg/dl)	4.00 (1.50–18.20)
Kappa/lambda (mg/L)	4.97 (0.001–147)
HALP	34.09 (1.227–168.35)
SII	3956 (1337–16738)
Gender	
Female	25 (46.3%)
Male	29 (53.7%)
Chain type	
IgG	31 (57.4%)
IgA	13 (24.1%)
IgM	1 (1.9%)
Free light chain	7 (13.0%)
Non-secretory	2 (3.7%)
Lytic lesions	
No	25 (46.3%)
Yes	29 (53.7%)
ISS	
1	18 (33.3%)
2	25 (46.3%)
3	11 (20.4%)
ASCT	
No	28 (51.9%)
Yes	26 (48.1%)
Mortality	
No	47 (87.0%)
Yes	7 (13.0%)

Min: Minimum, Max: Maximum, WBC: White blood cell, Hgb: Hemoglobin, LDH: Lactate dehydrogenase, HALP: Hemoglobin-albumin-lymphocyte-platelet, SII: Systemic Immune-inflammation Index, IgG: Immunoglobulin G, IgA: Immunoglobulin A, IgM: Immunoglobulin M, ISS: International Staging System

Factors Associated with Mortality

Univariate analyses comparing patients who died and those who survived are presented in **Table 2**. Patients who died had significantly higher ISS stages compared with survivors (median ISS: 3 vs 2, p=0.007). Higher beta-2 microglobulin levels were significantly associated with increased mortality in univariate analysis (p=0.044). No statistically significant differences were observed between mortality groups with respect to age (p=0.171), HALP score (p=0.375), or SII index (p=0.286).

Similarly, hematologic and biochemical parameters including hemoglobin (p=0.211), lymphocyte count (p=0.197), LDH (p=0.257), albumin (p=0.605), creatinine (p=0.486), calcium (p=0.670), platelet count (p=0.670), and total protein (p=0.699) were not significantly associated with mortality. Clinical characteristics such as gender, lytic bone lesions, chain type, and treatment variables also showed no significant association with mortality (all p>0.05).

Table 2. Univariate analysis of clinical and laboratory parameters according to mortality status

Variable	Death (n=7)	Alive (n=47)	p value
Beta-2 microglobulin (mg/L)	5.20 (3.65–18.20)	3.73 (1.50–7.50)	0.044
Calcium (mg/dl)	8.92 (8.50–13.80)	9.00 (7.50–16.60)	0.670
Hgb (g/dl)	11.20 (8.50–13.80)	9.80 (0.70–14.60)	0.211
Serum creatinine (mg/dl)	0.79 (0.66–5.30)	0.96 (0.08–7.29)	0.486
Kappa/lambda	8.76 (0.04–44.70)	4.35 (0.00–147.00)	0.958
Lymphocyte (/µL)	1770 (1240–4850)	1500 (560–5720)	0.197
Monocyte (/µL)	530 (410–2810)	520.00 (130.00–2040.00)	0.588
Neutrophil (/µL)	3230 (1550–6120)	3600 (520–8580)	0.511
Platelet (µ/L)	198.000 (126.000–289.000)	202.000 (31.000–362.000)	0.670
WBC (/µL)	5690 (3250–12650)	6260.00 (2120–15270)	0.708
Albumin (g/L)	39.00 (33–46)	37.00 (20–49)	0.605
CRP (mg/L)	9.80 (1.00–36.10)	6.00 (0.39–134.0)	0.767
LDH (U/L)	199 (120–281)	171 (83–345)	0.257
Total protein (g/L)	80 (65–129)	79 (46 –114)	0.699
Age	65.00 (45–74)	69.00 (40–85)	0.171
Gender			
Female	2 (28.6%)	23 (48.9%)	0.547
Male	5 (71.4%)	24 (51.1%)	
ASCT			
No	5 (71.4%)	24 (51.1%)	0.524
Yes	2 (28.6%)	23 (48.9%)	
Lytic lesions			
Yes	5 (71.4%)	24 (51.1%)	0.547
No	2 (28.6%)	23 (48.9%)	
Comorbid conditions			
Hypertension	3 (42.8%)	11 (23.4%)	0.374
Diabetes mellitus	2 (28.5%)	9 (19.1%)	0.612
Cardiovascular disease	1 (14.2%)	6 (12.7%)	0.884
Renal failure	1 (14.2%)	5 (10.6%)	0.813
HALP score	38.18 (32.33–76.43)	33.67 (2.78–168.35)	0.375
SII	3646.76 (1575.00–5163.75)	4182.24 (133.71–16738.88)	0.286
ISS stage			
1	0	18 (38.3%)	0.007
2	3 (42.9%)	22 (46.8%)	
3	4 (57.1%)	7 (14.9%)	

Hgb: Hemoglobin, WBC: White blood cell, CRP: C-reactive protein, LDH: Lactate dehydrogenase, HALP: Hemoglobin-albumin-lymphocyte-platelet, SII: Systemic Immune-inflammation Index, ISS: International Staging System

Multivariate Cox Regression Analysis

A multivariate Cox proportional hazards regression model including age and ISS stage was constructed to evaluate independent predictors of OS (Table 3). ISS stage remained independently associated with mortality risk (HR=3.84, 95% CI: 1.33-11.05, p=0.0127). Age was not independently associated with OS (HR=0.62, 95% CI: 0.31-1.26, p=0.1887).

Table 3. Multivariate Cox regression analysis including age and ISS stage as predictors of overall survival

Variable	HR	95% CI lower	95% CI upper	p-value
Age	0.6231	0.3078	1.2615	0.1887
ISS (ref<3)	3.8366	1.3322	11.0495	0.0127

ISS: International Staging System, HR: Hazard ratio, CI: Confidence interval

Survival and Discriminative Analyses

ROC analysis was performed to evaluate the discriminative ability of ISS stage, HALP score, and SII index for predicting mortality (Figure 1). ISS demonstrated the highest predictive performance with an area under the curve (AUC) of 0.79. HALP showed modest discriminative capacity (AUC=0.61), whereas SII exhibited limited predictive ability (AUC=0.37). Optimal cut-off values determined using the Youden index were 3.0 for ISS, 32.3 for HALP, and 2887.5 for SII.

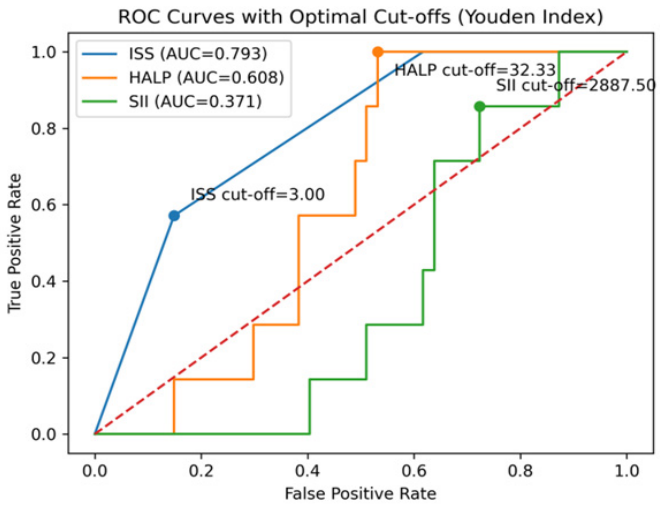

Figure 1. Receiver operating characteristic (ROC) curves demonstrating the predictive performance of ISS, HALP, and SII for mortality. Optimal cut-off points were determined using the Youden index and are indicated on the curves.

ISS: International Staging System, HALP: Hemoglobin-albumin-lymphocyte-platelet, SII: Systemic Immune-inflammation Index, AUC: Area under the curve

Kaplan-Meier survival analysis demonstrated heterogeneous OS outcomes within the study cohort (**Figure 2A**). Median OS was not reached during the follow-up period. Stratification according to the ISS revealed a significant separation of survival curves (**Figure 2B**). Patients with ISS ≥3 exhibited markedly inferior OS compared with those with ISS <3 (log-rank p=0.001), indicating a strong prognostic impact of advanced disease stage.

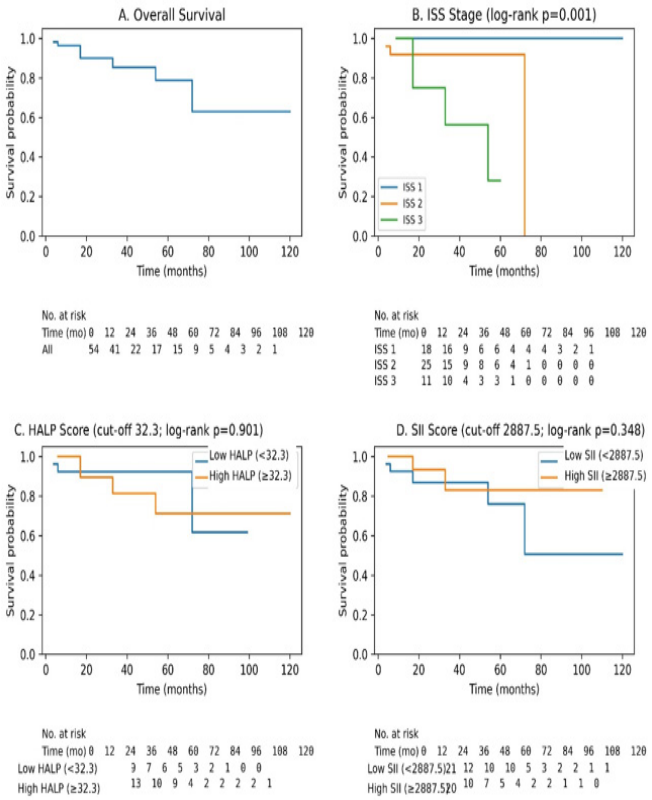

Figure 2. Kaplan–Meier survival curves in patients with newly diagnosed multiple myeloma. (**A**) Overall survival of the study cohort. (**B**) Survival according to ISS stage (log-rank p=0.001). (**C**) Survival stratified by HALP score (cut-off:32.3; p=0.901). (**D**) Survival stratified by SII (cut-off:2887.5; p=0.348). Numbers at risk are shown below each panel.

ISS: International Staging System, HALP: Hemoglobin-albumin-lymphocyte-platelet, SII: Systemic Immune-inflammation Index

In contrast, survival stratification based on the HALP score using the ROC-derived cut-off value of 32.3 did not demonstrate a significant difference in OS between groups (**Figure 2C**; log-rank p=0.901). Similarly, the SII, dichotomized at the optimal ROC-derived cut-off value of 2887.5, failed to significantly discriminate survival outcomes (**Figure 2D**; log-rank p = 0.348).

DISCUSSION

In this study, we evaluated the prognostic significance of inflammation- and nutrition-based biomarkers, namely the HALP score and SII, in patients with newly diagnosed MM, and compared their predictive performance with the established ISS staging system. Our findings indicate that ISS stage remained the strongest independent predictor of OS, whereas the HALP score and SII showed limited discriminative capacity for mortality prediction and failed to significantly stratify OS when ROC-derived cut-off values were applied.

MM is characterized by considerable biological and clinical heterogeneity, highlighting the need for prognostic approaches that extend beyond traditional tumor burden-based staging systems. Although ISS and R-ISS continue to represent the cornerstone of risk stratification, these models primarily reflect disease biology and cytogenetic risk rather than patient-related factors such as systemic inflammation and nutritional status.[13,14] Growing evidence suggests that cancer-related inflammation plays an important role in tumor progression, immune dysregulation, and treatment resistance in hematologic malignancies.[13] Consequently, composite inflammatory biomarkers derived from routine laboratory parameters have attracted increasing attention as practical and accessible prognostic tools.

The HALP score combines hemoglobin, albumin, lymphocyte count, and platelet count, thereby capturing multiple aspects of patient condition, including anemia severity, nutritional reserve, immune competence, and systemic inflammatory response. Previous studies across various solid tumors have consistently reported an association between lower HALP scores and inferior survival outcomes.[15-18] Similarly, Vlatka et al.[18] demonstrated that reduced HALP scores were linked to unfavorable clinicopathological characteristics and poorer survival in hematologic malignancies. Our findings partially support these observations, as patients with lower HALP values showed a trend toward poorer OS in Kaplan-Meier analysis, although this difference did not reach statistical significance. These findings suggest that host-related biological factors may influence disease trajectory in MM beyond tumor burden alone.

A possible explanation for the limited additional prognostic value of the HALP score in our study may be its overlap with established staging systems such as ISS. In particular, albumin is a shared component of both HALP and ISS and reflects not only nutritional status but also disease burden and inflammatory status in MM. This may partly explain why HALP showed only modest predictive performance and did not significantly differentiate survival outcomes in our cohort.

Despite this association, HALP did not reach statistical significance in univariate mortality analyses, and its discriminative ability remained modest in ROC evaluation. Several explanations may account for this finding. The relatively small number of mortality events may have limited statistical power. In addition, certain HALP components-particularly albumin-overlap with parameters already incorporated into ISS staging, potentially weakening its independent prognostic contribution. Furthermore, inflammatory and nutritional status are dynamic processes that may evolve during treatment, whereas our analysis relied solely on baseline measurements. Similar variability in the prognostic performance of inflammation-based indices has been reported in MM, suggesting that these markers may function more effectively as complementary rather than standalone prognostic tools.[6]

In contrast, SII did not demonstrate significant prognostic value in our cohort. Although SII has shown prognostic relevance across several malignancies and acute leukemias,[19-21] its role in MM remains uncertain. The lack of

predictive significance observed in our study may reflect the unique immune microenvironment of MM, where disease progression is strongly influenced by bone marrow niche interactions and plasma cell--mediated immune suppression rather than systemic inflammatory responses alone.[9] Moreover, neutrophil and platelet counts may be affected by marrow infiltration or treatment-related factors, which could further limit the specificity of SII as a prognostic indicator in MM.

Importantly, ISS stage remained the only independent predictor of OS in multivariate analysis, consistent with large international studies validating ISS as a robust prognostic system.[21,22] The superior discriminative performance of ISS observed in ROC analysis further reinforces its central role in risk stratification. Nevertheless, the survival differences observed with HALP suggest that inflammation- and nutrition-based biomarkers may provide additional prognostic information reflecting the patient's overall biological condition, which is not fully captured by traditional staging models.

Recent research increasingly highlights the interplay between tumor biology and host systemic status in determining MM prognosis. Emerging prognostic strategies incorporating inflammatory indices and circulating immune markers aim to refine individualized risk prediction models.[3,7] Incorporating easily obtainable biomarkers such as HALP into existing staging frameworks may therefore enhance clinical risk assessment, particularly in settings where access to advanced molecular testing remains limited.

Limitations

The study has several limitations. The retrospective and single-center design introduces potential selection bias, and the relatively small sample size with limited mortality events may have reduced statistical power. Cox proportional hazards assumption was not clearly violated; however, due to the limited number of mortality events, the Cox regression results should be interpreted cautiously. Data on progression-free survival (PFS) and time to next therapy were not consistently available in our retrospective dataset and therefore could not be included in the analysis. Additionally, longitudinal changes in inflammatory indices during treatment were not evaluated. Cytogenetic risk classification, which plays a central role in contemporary prognostic assessment in MM, was not consistently available in our dataset. Furthermore, treatment heterogeneity represents an important limitation, as outcomes in MM are influenced by factors such as transplant eligibility, induction regimens, maintenance therapy, and subsequent lines of treatment, which could not be uniformly evaluated in this retrospective analysis HALP and SII are dynamic variables, and evaluation based solely on baseline values may not adequately represent their clinical significance. Nevertheless, our study reflects real-world clinical practice and focuses on cost-effective biomarkers that can be readily obtained from routine laboratory testing.

CONCLUSION

As a result, while ISS staging remains the most reliable predictor of survival in newly diagnosed MM, the HALP score showed a potential association with OS and may reflect the prognostic contribution of host inflammatory and nutritional status. In contrast, SII demonstrated limited prognostic utility in this cohort. Larger prospective studies are needed to clarify the clinical relevance of inflammation-based composite indices and to determine whether integrating host-related biomarkers can further improve prognostic stratification in multiple MM.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Non-interventional Clinical Researches Ethics Committee of Kütahya Health Sciences University (Date: 29.05.2025, Decision No: 2025/07-38).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

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

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Author Contributions

Concept: CÖ, CY; Design: CÖ, CY; Control: CÖ, CY, AG, DKK; Resources: CÖ, CY, AG, AA, DKK; Materials: CÖ, CY, AG, DKK; Data Collection and/or Processing: CÖ, CY, AA, AG; Analysis and/or Interpretation: CÖ, CY, AA; Literature Review: CÖ, CY, AA, AG; Writing the Article: CÖ, CY; Critical Review: CÖ, CY.

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