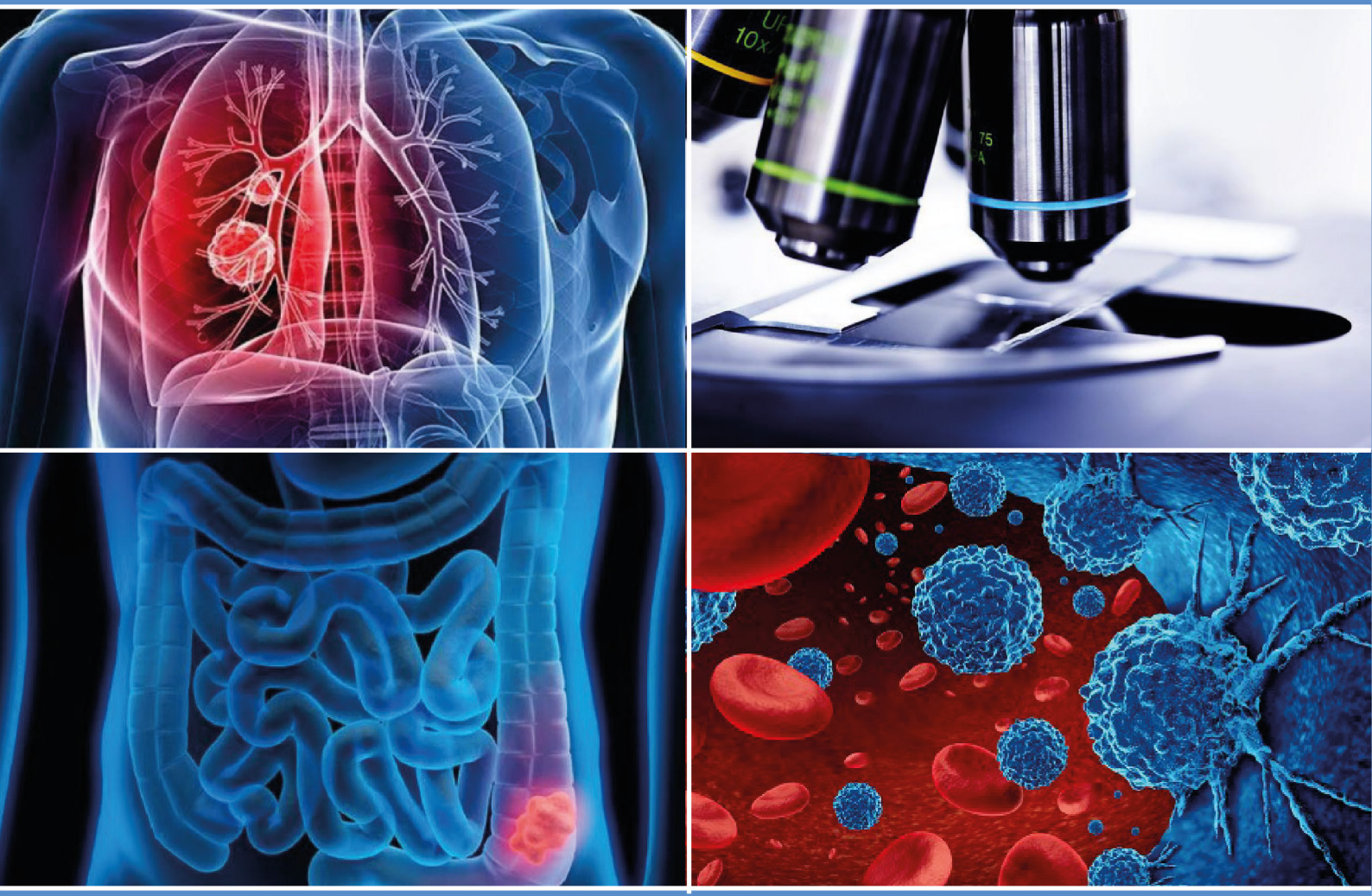
e-ISSN: 2980-0854

JCHOR

Journal of Current Hematology & Oncology Research



Volume: 4 Issue: 3 Year: 2026

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Original Article

DOI: 10.51271/JCHOR-0086

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

Can Özlü*[1], Cumali Yalçın[2], Aysun Gönderen[1], Aycan Acet[2], Doğa Kaçmaz Kipergil[2]

[1]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Kütahya Health Sciences University, Kütahya, Turkiye
[2]Department of Internal Medicine, Faculty of Medicine, Kütahya Health Sciences University, Kütahya, Turkiye

Cite this article: Özlü C, Yalçın C, Gönderen A, Acet A, Kaçmaz Kipergil D. Prognostic value of HALP score and Systemic Immune-inflammation Index in multiple myeloma. *J Curr Hematol Oncol Res.* 2026;4(3):74-79. doi:10.51271/JCHOR-0086

***Corresponding Author:** Can Özlü, can.ozlu@ksbu.edu.tr

Received: 17/03/2026 ◆ **Accepted**: 01/06/2026 ◆ **Published**: 08/08/2026

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.

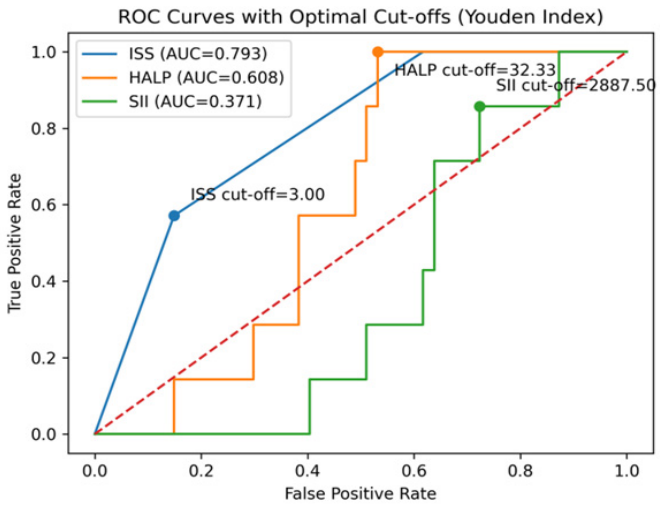

Figure 1. Receiver operating characteristic (ROC) curves demonstrating the predictive performance of ISS, HALP, and SII for mortality. Optimal cut-off points were determined using the Youden index and are indicated on the curves.

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.

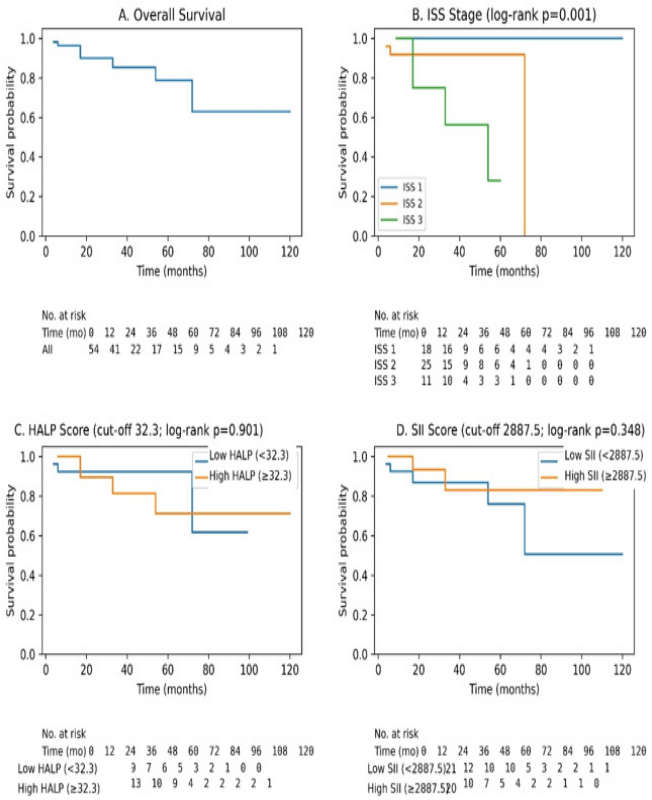

Figure 2. Kaplan–Meier survival curves in patients with newly diagnosed multiple myeloma. (**A**) Overall survival of the study cohort. (**B**) Survival according to ISS stage (log-rank p=0.001). (**C**) Survival stratified by HALP score (cut-off:32.3; p=0.901). (**D**) Survival stratified by SII (cut-off:2887.5;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

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

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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Journal of Current Hematology & Oncology Research

Original Article

DOI: 10.51271/JCHOR-0087

Predictive factors for invasive cervical cancer in patients referred for colposcopy after abnormal cervical smear screening

Yeşim Özkaya Uçar*[1], Okan Aytekin[1], Arife Ebru Kuzu[1], Nazlı Tunca Şanlıer[2], Mehmet Ünsal[1], Fatih Kılıç[1], Abdurrahman Alp Tokalıoğlu[3], Taner Turan[1]

[1]Department of Gynecologic Oncology, Ankara Bilkent City Hospital, Ankara, Turkiye
[2]Department of Obstetrics and Gynecology, Çiftlik State Hospital, Niğde, Turkiye
[3]Department of Gynecologic Oncology, Ankara Training and Research Hospital, University of Health Sciences, Ankara, Turkiye

Cite this article: Özkaya Uçar Y, Aytekin O, Kuzu AE, et al. Predictive factors for invasive cervical cancer in patients referred for colposcopy after abnormal cervical smear screening. *J Curr Hematol Oncol Res.* 2026;4(3):80-85. doi:10.51271/JCHOR-0087

***Corresponding Author:** Yeşim Özkaya Uçar, yesimozkaya@gmail.com

Received: 02/05/2026 ◆ **Accepted**: 03/06/2026 ◆ **Published**: 08/08/2026

ABSTRACT

Aims: To evaluate the clinical and pathological factors associated with invasive cervical cancer in patients referred for colposcopy after abnormal cervical smear screening.

Methods: This retrospective cohort study included 5,033 patients aged 18 years and older who underwent colposcopic evaluation between September 2019 and December 2025 at a tertiary gynecologic oncology center after an abnormal cervical smear result. Patients were classified according to the presence or absence of histopathologically documented invasive cervical cancer based on the highest-grade diagnosis available during follow-up. Age, smear category, human papillomavirus (HPV) status, colposcopic biopsy findings, endocervical curettage (ECC) findings, and final pathology results were analyzed. Logistic regression analysis was performed to identify variables independently associated with invasive cervical cancer.

Results: Invasive cervical cancer was identified in 32 of 5,033 patients (0.64%). Patients with invasive cancer were significantly older than those without invasive disease (49.8±11.0 vs 41.8±11.3 years, p=0.00026). High-risk smear findings were more common in the invasive cancer group than in the non-invasive group (46.9% vs 6.1%, p<0.001). Invasive cancer was detected in 4.34% of patients with high-grade squamous intraepithelial lesion or worse (HSIL+) on colposcopic biopsy versus 0.07% of those with non-HSIL biopsy findings (OR 65.99, 95% CI 20.04-217.25, p<0.001). Similarly, invasive cancer was identified in 11.6% of patients with HSIL+ on ECC compared with 0.31% of those with non-HSIL ECC results (OR 42.47, 95% CI 20.76-86.88, p<0.001). In multivariable analysis, older age, high-risk smear findings, HSIL+ on colposcopic biopsy, and HSIL+ on ECC remained significantly associated with invasive cervical cancer. Some invasive cancers were identified only in final pathology specimens, suggesting that preoperative assessment may underestimate invasive disease in a subset of patients.

Conclusion: Invasive cervical cancer was uncommon but clinically relevant in patients referred for colposcopy after abnormal cervical smear screening. Older age, high-risk smear findings, HSIL+ on colposcopic biopsy, and HSIL+ on ECC were the variables most strongly associated with invasive disease. An integrated interpretation of cytology, HPV status, biopsy, ECC, and clinical context may improve recognition of patients at increased risk for invasive cervical cancer.

Keywords: Cervical cancer, colposcopy, cytology, HPV, endocervical curettage, invasive disease

INTRODUCTION

Cervical cancer continues to impose a substantial global disease burden despite major advances in screening, human papillomavirus (HPV) vaccination, and early detection strategies.[1,2] It remains one of the most common gynecologic malignancies in women worldwide, particularly in settings where screening coverage, follow-up, and access to preventive care remain suboptimal.[3] Because the natural history of cervical carcinogenesis usually includes a prolonged precancerous phase, screening programs create an opportunity to detect clinically significant lesions before invasive disease develops.[4]

Cervical cytology has long served as one of the main tools in screening practice and still plays an important role in identifying patients who require further diagnostic evaluation.[5] Abnormal smear results often reflect an underlying spectrum of disease ranging from transient HPV-related changes to high-grade squamous intraepithelial lesions and, in some cases, invasive cervical cancer.[6] For this reason, clinicians routinely refer patients with abnormal cytology for colposcopic examination, which allows direct assessment of the cervix and targeted tissue sampling when necessary.[7] In daily practice, colposcopy-directed biopsy and endocervical curettage (ECC) provide tissue-based

information that helps distinguish preinvasive disease from more advanced pathology and guides subsequent management. Even so, the relationship between screening abnormalities and invasive cancer is not straightforward. High-risk cytologic findings clearly increase the probability of clinically significant cervical pathology, but invasive disease does not arise exclusively within those categories.[8] Some patients with markedly abnormal cytology have no invasive disease on further evaluation, whereas others with less alarming smear results may still harbor invasive cancer. This discrepancy suggests that cytology alone cannot fully capture the biological and anatomical complexity of cervical disease at the time of colposcopic assessment.

HPV-related information adds another important layer to risk stratification. Persistent infection with high-risk HPV genotypes, especially HPV16 and HPV18, drives the development of most cervical cancers and their precursor lesions.[9] Accordingly, HPV testing has become a central component of modern screening and triage algorithms.[10] Colposcopic biopsy and ECC may help answer that question more directly because they reflect tissue-level abnormalities rather than screening risk alone.[11] In particular, high-grade lesions identified on biopsy or ECC may indicate not only severe intraepithelial disease but also a greater likelihood of occult invasion, especially in patients with endocervical extension or limited lesion visibility.[12] However, in patients referred after abnormal smear screening, it remains unclear which combination of clinical and histopathological findings is most informative for identifying the subgroup already harboring invasive cervical cancer.

In the present study, we evaluated a large cohort of patients referred for colposcopy after abnormal cervical smear screening and examined the clinical and pathological factors associated with invasive cervical cancer. Specifically, we analyzed age, smear category, HPV status, colposcopic biopsy findings, and ECC findings to determine which variables were most strongly associated with invasive disease.

METHODS

This study was approved by the No. 1 Scientific and Ethical Review Board for Medical Researches of Ankara Bilkent City Hospital (Date: 22.04.2026, Decision No: TABED: 1-26-2515) and was conducted in accordance with institutional ethical standards and the principles of the Declaration of Helsinki.

This retrospective cohort study was conducted at the Department of Gynecologic Oncology Surgery, Ankara Bilkent City Hospital, Obstetrics and Gynecology Hospital. Patients aged 18 years and older who were referred for colposcopic evaluation because of an abnormal cervical smear result and who underwent colposcopy between September 2019 and December 2025 were considered eligible for inclusion. Patients were included if HPV test results and genotyping data were available and if sufficient follow-up and/or treatment data were present to allow histopathological confirmation of the final diagnosis. Patients with missing HPV data, absent histopathological outcome data, or insufficient follow-up to verify the final diagnosis were excluded. Clinical and pathological data were retrieved retrospectively from the institutional electronic medical record system and colposcopy database. Recorded variables included age at presentation, cervical smear result, HPV test result and genotype, adequacy of colposcopic examination, colposcopic biopsy result, ECC result, and final histopathological diagnosis.

Smear results were categorized according to cytologic risk status and, for the purpose of analysis, were grouped as high-risk smear and non-high-risk smear. For the purpose of analysis, high-risk smear was defined as HSIL, ASC-H, AGC, and AIS, whereas non-high-risk smear included ASC-US, LSIL, negative for intraepithelial lesion or malignancy, and insufficient smear. HPV status was classified as HPV16/18-related positivity, other HPV-positive or genotype-unspecified status, HPV negativity, or unknown HPV status. Unknown HPV status was retained as a separate category in all analyses, including the multivariable model. All patients underwent colposcopic examination according to routine institutional practice following an abnormal smear result. Directed cervical biopsy and ECC were performed when clinically indicated based on colposcopic findings and transformation zone characteristics. The primary study outcome was the presence of invasive cervical cancer. Invasive cancer was defined as the histopathological detection of squamous cell carcinoma, microinvasive squamous cell carcinoma, or adenocarcinoma in any of the diagnostic or therapeutic specimens, including colposcopic biopsy, ECC, or final pathology obtained after an excisional or surgical procedure. Adenocarcinoma in situ was not classified as invasive cancer. For analytical purposes, colposcopic biopsy and ECC findings were further classified as high-grade squamous intraepithelial lesion (HSIL) + and non-HSIL, with the HSIL+ category including high-grade squamous intraepithelial lesions and more advanced pathological findings. Final diagnosis was established on the basis of the highest-grade histopathological finding documented during follow-up. Final pathology referred to the definitive histopathological result obtained from excisional or surgical specimens during follow-up, including conization, LEEP, or hysterectomy when such procedures were performed.

Statistical Analysis

For data analyses, the cohort was divided into 2 groups according to the presence or absence of histopathologically documented invasive cervical cancer. Patients with invasive cervical cancer were compared with all remaining patients without histopathologically documented invasive disease based on the highest-grade diagnosis available during follow-up. Continuous variables were expressed as mean±standard deviation, whereas categorical variables were presented as number and percentage. Continuous variables were compared using the independent-samples t test. Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to evaluate the association of colposcopic biopsy and ECC findings with invasive cervical cancer. To identify independent predictors of invasive cervical cancer, a 2-step logistic regression analysis was performed. The first model included age, smear category, and HPV16/18-related positivity. In the second model, colposcopic biopsy findings and ECC findings were added to these variables. Results were reported as ORs, 95% CIs, and p values. A 2-sided p value of <0.05 was considered statistically significant.

RESULTS

A total of 5,033 patients were included in the study cohort, and invasive cervical cancer was identified in 32 patients (0.64%). A simplified flow diagram of the final analytic cohort is presented in **Figure 1**. Invasive cancer was defined as the presence of squamous cell carcinoma, microinvasive squamous cell carcinoma, or adenocarcinoma in any of the diagnostic steps, including colposcopic biopsy, ECC, or final pathology. Among the 32 invasive cancer cases, 22 were squamous cell carcinoma, 1 was microinvasive squamous cell carcinoma, and 9 were adenocarcinoma. Patients with invasive cancer were significantly older than those without invasive disease (49.8±11.0 years vs 41.8±11.3 years, p=0.00026). High-risk smear findings were also markedly more common in the invasive cancer group than in the non-invasive group (46.9% vs 6.1%, p<0.001). Although HPV16/18-related positivity was frequent among patients with invasive cancer, its distribution was less distinct than that of age and smear category. Baseline demographic and clinical characteristics of the study population are summarized in **Table 1**.

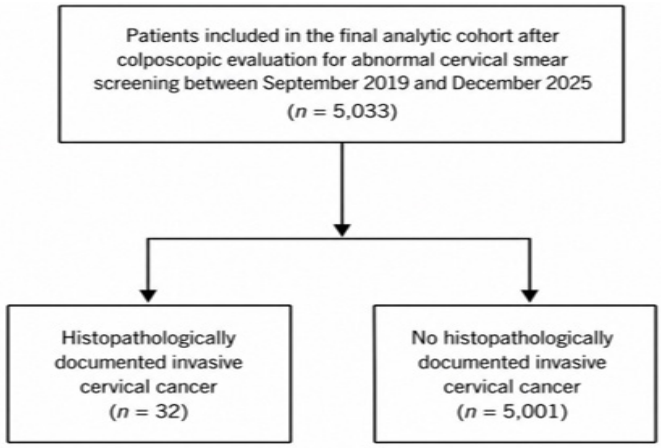

Figure 1. Simplified flow diagram of the final analytic cohort

Table 1. Baseline characteristics of patients with and without invasive cervical cancer

Variable	Invasive cancer (n=32)	Non-invasive disease (n=5001)	p value
Age (years), mean±SD	49.8±11.0	41.8±11.3	<0.001
High-risk smear, n (%)	15 (46.9)	307 (6.1)	<0.001
Non-high-risk smear, n (%)	17 (53.1)	4678 (93.9)	
HPV16/18-related positivity, n (%)	17 (53.1)	2523 (50.5)	
Other HPV-positive/ genotype unspecified, n (%)	4 (12.5)	1002 (20.0)	0.031*
HPV negative, n (%)	3 (9.4)	923 (18.5)	
HPV status unknown, n (%)	8 (25.0)	553 (11.1)	
Adequate colposcopy, n (%)	32 (100)	4860 (97.2)	0.63
Inadequate colposcopy, n (%)	0 (0)	136 (2.7)	

SD: Standard deviation, HPV: Human papillomavirus, *p value represents the overall comparison across HPV status categories

Notably, invasive disease was not limited to patients with the traditional high-risk smear categories. Among the 32 patients diagnosed with invasive cervical cancer, only 15 (46.9%) had high-risk smear findings, whereas 17 patients (53.1%) were in the non-high-risk smear category. When the rates were calculated within smear groups, invasive cancer was detected in 4.66% of patients with high-risk smear findings and in 0.36% of those without high-risk smear findings. These findings suggest that although high-risk cytology is strongly associated with invasive disease, invasive cervical cancer may also be encountered in patients outside the traditionally high-risk smear categories.

When histopathological findings were evaluated, the strongest associations with invasive cervical cancer were observed for HSIL+ findings on colposcopic biopsy and ECC. Among patients with HSIL+ on colposcopic biopsy, the rate of invasive cancer was 4.34%, whereas this rate was only 0.07% in those with non-HSIL biopsy findings (OR 65.99, 95% CI 20.04–217.25, p<0.001). Similarly, invasive cancer was identified in 11.6% of patients with HSIL+ findings on ECC, compared with 0.31% of patients with non-HSIL ECC results (OR 42.47, 95% CI 20.76–86.88, p<0.001). Detailed associations between biopsy, ECC findings, and invasive cancer are presented in **Table 2**. A visual summary of the independent predictors identified in the multivariable model is presented in **Figure 2**.

In the logistic regression analysis, older age and a high-risk smear result remained significantly associated with invasive cervical cancer in the clinical/pretest model, whereas HPV16/18-related positivity was not independently associated with invasive disease. In model 1, age increased the odds of invasive cancer by 6% per year (OR 1.06, 95% CI 1.02-1.09, p<0.001), and high-risk smear findings were associated with a markedly increased risk (OR 12.39, 95% CI 6.07-25.28, p<0.001). After the addition of colposcopic biopsy and ECC findings in the expanded model, age remained independently associated with invasive cancer (OR 1.10, 95% CI 1.06-1.14, p<0.001), as did high-risk smear findings (OR 3.23, 95% CI 1.45-7.21, p=0.004), HSIL+ on colposcopic biopsy (OR 54.43, 95% CI 14.65-202.27, p<0.001), and HSIL+ on ECC (OR 6.43, 95% CI 2.82-14.62, p<0.001). HPV16/18-related positivity did not retain statistical significance in the expanded model (OR 0.67, 95% CI 0.30-1.49, p=0.328). The results of both regression models are shown in **Table 3**.

The diagnostic pathway of invasive disease was also examined in detail. Invasive cancer was detected in 22 patients at colposcopic biopsy, in 13 patients at ECC, and in 18 patients in the final pathology specimen. When the detection patterns were analyzed, invasive disease was found only in the final pathology specimen in 9 patients, only in colposcopic biopsy in 6 patients, and only in ECC in 1 patient. In some cases, invasive disease was identified at more than one diagnostic step, including biopsy plus ECC, biopsy plus final pathology, or biopsy plus ECC plus final pathology. These findings indicate that invasive cervical cancer may become evident at different stages of the diagnostic process and that preoperative assessment may not fully capture the presence of invasive disease in all patients. The distribution of these diagnostic patterns is presented in **Table 4**.

DISCUSSION

In this large colposcopy cohort, invasive cervical cancer was uncommon; however, several variables were strongly associated with invasive disease. The main findings of this

Table 2. Association of colposcopic biopsy and ECC findings with invasive cervical cancer

Variable	Invasive cancer (n=32)	Non-invasive disease (n=5001)	Odds ratio (95% CI)	p value
HSIL+ on colposcopic biopsy	29	639	65.99 (20.04–217.25)	<0.001
Non-HSIL on colposcopic biopsy	3	4362	1.00 (reference)	
HSIL+ on ECC	17	130	42.47 (20.76–86.88)	<0.001
Non-HSIL on ECC	15	4871	1.00 (reference)	

ECC: Endocervical curettage, CI: Confidence interval, HSIL: High-grade squamous intraepithelial lesion

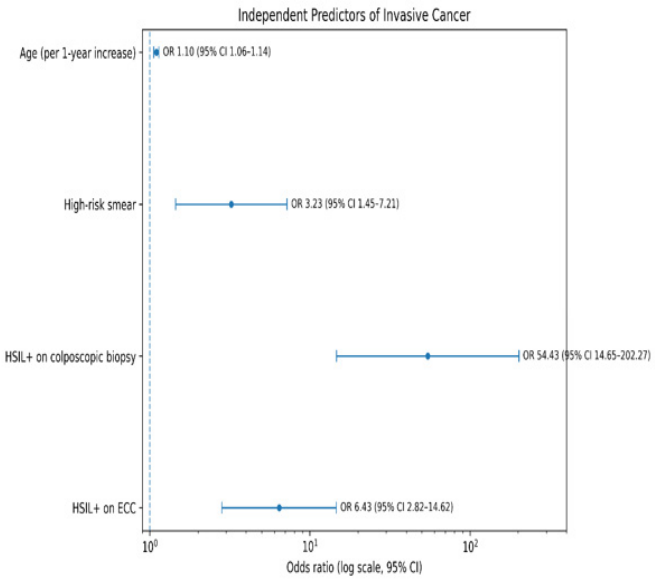

Figure 2. Forest plot of independent predictors of invasive cervical cancer identified in the multivariable logistic regression model

ECC: Endocervical curettage, CI: Confidence interval, HSIL: High-grade squamous intraepithelial lesion, OR: Odds ratio

Table 3. Logistic regression analysis for invasive cervical cancer

Model 1. Clinical/pretest model			
Variable	**OR**	**95% CI**	**p value**
Age (per 1-year increase)	1.06	1.02–1.09	<0.001
High-risk smear	12.39	6.07–25.28	<0.001
HPV16/18-related positivity	1.51	0.74–3.11	0.258
Model 2. Expanded model			
Age (per 1-year increase)	1.10	1.06–1.14	<0.001
High-risk smear	3.23	1.45–7.21	0.004
HPV16/18-related positivity	0.67	0.30–1.49	0.328
HSIL+ on colposcopic biopsy	54.43	14.65–202.27	<0.001
HSIL+ on ECC	6.43	2.82–14.62	<0.001

OR: Odds ratio, CI: Confidence interval, HPV: Human papillomavirus, HSIL: High-grade squamous intraepithelial lesion, ECC: Endocervical curettage

Table 4. Diagnostic steps at which invasive cancer was identified

Pattern of detection	Number of patients
Final pathology only	9
Colposcopic biopsy only	6
ECC only	1
Biopsy + ECC	7
Biopsy + final pathology	4
Biopsy + ECC + final pathology	5
Total	32

ECC: Endocervical curettage

study were that older age, high-risk smear findings, HSIL+ on colposcopic biopsy, and HSIL+ on ECC were the variables most strongly associated with invasive cervical cancer, with these factors remaining significant in multivariable analysis. These results suggest that although invasive cancer is rare among patients referred after abnormal cervical smear screening, a subgroup of patients carries a distinctly higher risk and may require more careful diagnostic assessment and treatment planning.

One of the most relevant findings was the independent effect of age. Patients with invasive cervical cancer were significantly older than those without invasive disease, and age remained significant in both regression models. This finding is clinically plausible, as increasing age is associated with reduced visibility of the transformation zone and a greater likelihood of endocervical localization, which may decrease the diagnostic yield of surface-directed sampling.[13] Our results therefore suggest that age should be considered a clinically meaningful factor when estimating the likelihood of invasive disease in patients referred for colposcopy.

High-risk smear findings were also strongly associated with invasive cervical cancer. This is consistent with the established relationship between increasing cytologic severity and the probability of clinically significant cervical pathology.[14] However, an important observation in our cohort was that invasive cancer was not limited to the traditional high-risk smear categories. More than half of the invasive cases occurred in patients outside the high-risk smear group. This finding suggests that cytology alone may underestimate invasive disease in a subset of patients.

Another notable result was the limited independent contribution of HPV16/18-related positivity in the expanded multivariable model. Although HPV16 and HPV18 are central to cervical carcinogenesis and remain highly relevant in screening and triage algorithms,[15,16] their predictive contribution appeared to decrease after tissue-based findings from biopsy and ECC were incorporated into the analysis. This likely reflects the fact that HPV status is most informative at the screening stage, whereas histopathological findings provide more direct information about already established invasive disease.

The strongest associations in this study were observed for HSIL+ findings on colposcopic biopsy and ECC. Biopsy and ECC findings should therefore be interpreted as tissue-based findings obtained during diagnostic evaluation, rather than as baseline screening predictors. In particular, the very high OR for HSIL+ on colposcopic biopsy suggests that advanced histopathological abnormalities detected during colposcopic assessment may serve as a major warning sign

for underlying invasion. A similar, although less pronounced, association was also observed for ECC. This is clinically important because ECC may detect lesions extending into the endocervical canal, particularly in cases where lesion visibility is limited.[17] Our findings therefore support the continued value of ECC in selected patients.

An additional clinically relevant finding was that invasive disease was not identified at the same diagnostic step in all patients. In some cases, invasion was detected on colposcopic biopsy or ECC, whereas in others it became evident only in the final pathology specimen. This pattern suggests that preoperative assessment may underestimate invasive disease in a subset of patients, even when biopsy and ECC are performed. The invasive cancers detected only in excisional or surgical specimens highlight that initial colposcopic biopsy and ECC may not completely exclude invasive disease in selected patients. Therefore, clinical, cytologic, and pathologic findings should be interpreted together. Similar observations have been reported in studies addressing pathologic upgrade to invasive carcinoma after preoperative diagnosis of high-grade cervical disease.[18] From a practical perspective, this finding supports a cautious approach in patients with older age and concerning cytologic or histopathological findings, even if definite invasion is not demonstrated at the initial sampling stage.

Limitations

This study has several strengths, including a large real-world cohort and the simultaneous evaluation of age, cytology, HPV status, biopsy findings, ECC findings, and final pathology within the same analytical framework. However, some limitations should also be acknowledged. The retrospective design may have introduced selection and information bias. Because unknown HPV status was more frequent among invasive cases than among non-invasive cases, the possibility of informative missingness should also be considered. However, no imputation procedure was applied, and unknown HPV status was analyzed as a distinct category. HPV vaccination status was not available in the dataset and could not be evaluated, which should be considered when interpreting the findings, particularly given the study period. In addition, although the overall cohort was large, the number of invasive cervical cancer cases was relatively small, which may have limited the precision and stability of the multivariable estimates. Therefore, these findings should be interpreted with caution and should not be considered a definitive risk prediction model. Operator- and observer-related variability in colposcopic and histopathological assessment should also be considered.

CONCLUSION

Overall, our findings indicate that invasive cervical cancer is uncommon but clinically relevant among patients referred for colposcopy after abnormal cervical smear screening. Older age, high-risk smear findings, HSIL+ on colposcopic biopsy, and HSIL+ on ECC were the variables most strongly associated with invasive disease. A more integrated interpretation of cytology, HPV status, biopsy, ECC, and clinical context may improve recognition of patients at increased risk for invasive cervical cancer.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the No. 1 Scientific and Ethical Review Board for Medical Researches of Ankara Bilkent City Hospital (Date: 22.04.2026, Decision No: TABED: 1-26-2515).

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

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

Author Contributions

Concept: YÖU, OA; Design: YÖU, TT; Control/Supervision: MÜ, FK; Data Collection and/or Processing: YÖU, AEK, NTŞ; Analysis and/or Interpretation: YÖU, TT, OA; Literature Review: YÖU, MÜ, AAT; Manuscript Writing: YÖU, FK, AAT, TT; Critical Review: All Authors.

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Journal of Current Hematology & Oncology Research

Original Article

DOI: 10.51271/JCHOR-0088

The predictive and prognostic value of the Advanced Lung Cancer Inflammation Index in metastatic NSCLC receiving second-line nivolumab: a multicenter retrospective cohort study

Ali Aytaç*[1], Bilgin Demir[2], Kübra Canaslan[1], Halil İbrahim Ellez[1], Yasemin Aydınalp Camadan[1]

[1]Department of Medical Oncology, Mehmet Akif İnan Training and Research Hospital, Şanlıurfa, Turkiye
[2]Division of Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Aydın Adnan Menderes University, Aydın, Turkiye

Cite this article: Aytaç A, Demir B, Canaslan K, Ellez Hİ, Aydınalp Camadan Y. The predictive and prognostic value of the Advanced Lung Cancer Inflammation Index in metastatic NSCLC receiving second-line nivolumab: a multicenter retrospective cohort study. *J Curr Hematol Oncol Res.* 2026;4(3):86-92. doi:10.51271/JCHOR-0088

***Corresponding Author:** Ali Aytaç, dr_aliaytac@hotmail.com

Received: 09/05/2026 ◆ **Accepted**: 15/06/2026 ◆ **Published**: 08/08/2026

ABSTRACT

Aims: The Advanced Lung Cancer Inflammation Index (ALI)—calculated from body-mass index (BMI), serum albumin, and neutrophil-to-lymphocyte ratio (NLR)—is an accessible composite biomarker of systemic inflammation and nutritional status. Its prognostic value in second-line immune checkpoint inhibitor (ICI) therapy in an ICI-naive population remains undefined.

Methods: This multicenter retrospective cohort study included 249 metastatic non-small cell lung cancer (NSCLC) patients treated with second-line single-agent nivolumab without prior immunotherapy exposure. ALI was categorized using a receiver operating characteristic (ROC)-derived cut-off of 27.27. Treatment response was assessed by RECIST 1.1. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan-Meier and Cox regression models.

Results: High baseline ALI (≥27.27) was associated with significantly longer median PFS (10.05 vs. 6.01 months; p=0.012) and OS (13.89 vs. 6.27 months; p<0.001). In multivariable analyses, high ALI remained independently associated with improved PFS (HR 0.688; p=0.011) and OS (HR 0.585; p=0.002). The overall objective response rate (ORR) was 35.3% and disease control rate (DCR) was 43.0%; both were numerically higher in the high-ALI group but did not reach statistical significance, and no significant differences were observed in ORRs.

Conclusion: Baseline ALI is an independent prognostic biomarker for PFS and OS in ICI-naive metastatic NSCLC patients receiving second-line nivolumab, representing a cost-effective tool for pre-treatment risk stratification. Prospective validation is warranted.

Keywords: Non-small cell lung cancer, Advanced Lung Cancer Inflammation Index, nivolumab, immunotherapy, prognosis, biomarker

INTRODUCTION

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide, with the majority of patients presenting with advanced or metastatic disease at diagnosis,[1] where long-term survival outcomes remain poor despite recent therapeutic advances.[2] The introduction of immune checkpoint inhibitors (ICIs) targeting the programmed cell death protein 1 (PD-1)/PD-L1 axis has substantially transformed the treatment landscape of metastatic NSCLC.[3,4] Pivotal trials including CheckMate 017 and CheckMate 057 established nivolumab as a standard second-line option in this setting.[4,5] Nevertheless, despite improvements in first-line outcomes with immunotherapy-based regimens, a substantial proportion of patients develop primary or acquired resistance and require subsequent systemic treatment. In this context, the identification of reliable, readily available biomarkers to predict benefit from second-line immunotherapy represents a critical and currently unmet clinical need.

Systemic inflammation and nutritional status have been increasingly recognized as key determinants of cancer progression, treatment response, and survival. Tumor-related inflammation contributes to immunosuppression, tumor proliferation, angiogenesis, and resistance to therapy.[6,7] Among several inflammation-based prognostic scores, the Advanced Lung Cancer Inflammation Index (ALI)—calculated as body-mass index (BMI)×serum albumin/neutrophil-to-lymphocyte ratio (NLR)—has emerged as a simple and reproducible composite biomarker integrating both host nutritional and inflammatory status.[8]

Several studies have demonstrated the prognostic relevance of ALI in lung cancer. In metastatic NSCLC, low ALI has been consistently associated with poor overall survival (OS) and adverse clinical features, including higher tumor burden and impaired performance status. Moreover, ALI has been identified as an independent prognostic factor for OS, outperforming several conventional inflammatory markers in retrospective analyses.[9] Similarly, ALI has also shown prognostic significance in early-stage NSCLC, surgical cohorts, and patients receiving radiotherapy, further supporting its robustness across different disease stages and treatment modalities.[10,11]

More recently, emerging evidence has suggested that ALI may also be associated with outcomes in patients receiving ICIs. In a multicenter cohort of advanced NSCLC patients treated with PD-1/PD-L1 inhibitors, higher ALI values were correlated with improved survival, particularly in the immunotherapy monotherapy setting, suggesting a potential role of ALI in reflecting tumor-immune interaction and host immunocompetence.[12] However, most available data are derived from first-line immunotherapy settings, and there is a paucity of evidence regarding the predictive value of ALI in patients undergoing second-line immunotherapy after progression on prior systemic treatment.

Given the increasing use of immunotherapy beyond first-line treatment in metastatic NSCLC, identifying reliable and easily accessible biomarkers that can predict response in the second-line setting is clinically important. Inflammation-based indices such as ALI are particularly attractive due to their cost-effectiveness, routine availability, and reflection of both tumor biology and host systemic condition.

To address this gap, we conducted a multicenter retrospective cohort study evaluating the prognostic and predictive value of baseline ALI in patients with metastatic NSCLC receiving second-line nivolumab. A key methodological strength of this study is the restriction of the cohort to ICI-naive patients—those who had not received immunotherapy in the first-line setting—thereby eliminating prior ICI exposure as a confounding variable and allowing a cleaner assessment of ALI's independent role. We hypothesized that higher baseline ALI would be independently associated with improved progression-free survival (PFS) and OS in this population.

METHODS

Ethics

Ethical approval for this multicenter non-interventional clinical study was obtained from the Non-interventional Clinical Researches Ethics Committee of Aydın Adnan Menderes University (Date: 13.03.2026, Decision No: E-53043-469-050.04-831562). The study was conducted in accordance with the Declaration of Helsinki. As this was a retrospective study based on existing medical records, individual patient informed consent was waived by the ethics committee.

Study Design and Patient Population

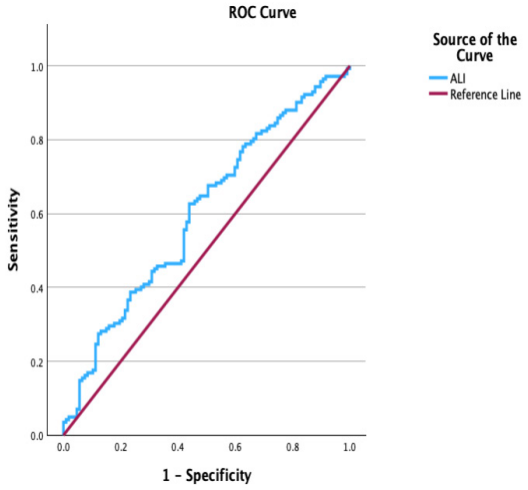
This multicenter retrospective cohort study included patients with metastatic NSCLC treated with second-line single-agent nivolumab at two centers in Turkiye. Eligible patients were adults with histologically confirmed metastatic NSCLC who had received at least one cycle of nivolumab in the second-line setting. Medical records from both centers were retrospectively reviewed for eligibility and data extraction. Patients were excluded if they had received prior ICI therapy, had incomplete medical records precluding data extraction, had active autoimmune disease requiring systemic treatment, had severe hepatic or renal impairment, or had an ECOG performance status of 3-4.

Data Collection

Demographic, clinical, pathological, and laboratory data were collected from electronic medical records at both centers. Variables included age, gender, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, histological subtype, metastatic sites, comorbidities, and prior treatment regimens. Laboratory parameters required for calculation of ALI—including BMI, serum albumin, and NLR—were recorded prior to nivolumab initiation. Tumor response and survival outcomes were retrieved from medical records at both institutions. Radiologic evaluations performed in routine clinical practice were used to assess treatment response according to RECIST 1.1 criteria.

Definition of ALI

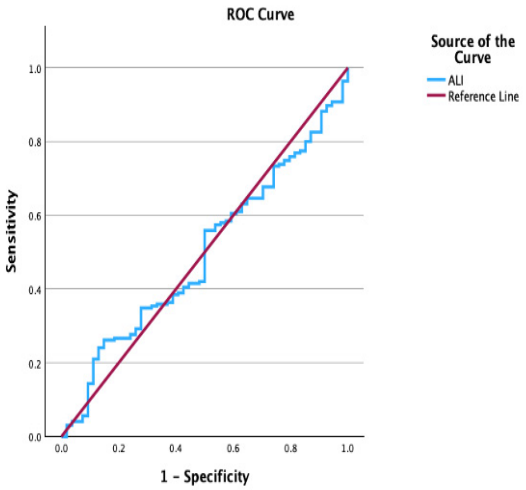
ALI was calculated using the following formula: ALI=BMI×serum albumin/NLR. ALI was evaluated both as a continuous variable and as a categorical variable. Receiver operating characteristic (ROC) analysis was performed to identify the optimal cut-off value for mortality, and the cut-off with the highest Youden index was selected (**Supplementary Figures S1.1** and **S1.2**). Based on this analysis, patients were classified into low-ALI (<27.27) and high-ALI (≥27.27) groups. Although the discriminatory ability of ALI for progression was limited, the same threshold was retained across all efficacy analyses to ensure consistency and clinical interpretability.



Supplementary Figures S1.1. Receiver operating characteristic (ROC) curve for overall survival (OS) showing the optimal ALI cut-off value (27.27)
ALI: Advanced Lung Cancer Inflammation Index

Treatment Response and Survival Outcomes

All patients received nivolumab at a dose of 3 mg/kg administered intravenously every two weeks. Tumor response to nivolumab was assessed according to RECIST 1.1 criteria. Best overall response was categorized as complete response



Supplementary Figures S1.2. Receiver operating characteristic (ROC) curve for progression-free survival (PFS) showing the optimal ALI cut-off value (27.27)
ALI: Advanced Lung Cancer Inflammation Index

(CR), partial response (PR), stable disease (SD), or progressive disease (PD). Objective response rate (ORR) was defined as the proportion of patients achieving CR or PR; disease control rate (DCR) was defined as the proportion achieving CR, PR, or SD. PFS was defined as the time from nivolumab initiation to documented disease progression or death from any cause. OS was defined as the time from nivolumab initiation to death from any cause. Patients without events at last follow-up were censored on the date of last contact.

Statistical Analysis

The data analyses were performed using IBM SPSS Statistics v29 (IBM Corp., Armonk, NY, USA) and R v4.5 (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were summarized as number (percentage) and continuous variables as median (range). Baseline characteristics were compared between ALI groups using the Chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. ROC analysis was used to evaluate the discriminatory performance of ALI and to determine the optimal cut-off value using Youden's index. Survival curves were estimated using the Kaplan-Meier method and compared with the log-rank test. Median follow-up was estimated separately for each endpoint using the reverse Kaplan–Meier method. As this estimate is driven by the timing of censored observations rather than their absolute number, median follow-up values may differ between PFS and OS analyses depending on the distribution of censoring times for each endpoint. Cox proportional hazards regression analyses were performed to identify prognostic factors for PFS and OS; variables significant in univariate analyses were entered into multivariable models. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. A two-sided $p<0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

A total of 249 patients with metastatic NSCLC who received second-line single-agent nivolumab were included. The median age was 66 years (range, 37-87), and 226 patients (90.8%) were male. Histologically, 126 patients (50.6%) had non-squamous NSCLC and 123 (49.4%) had squamous NSCLC. Most patients were active/former smokers (236/247, 95.5%) and had an ECOG performance status of 0-1 (220, 88.4%). Baseline patient characteristics are summarized in **Table 1**.

Determination of ALI Cut-off

ROC analysis identified 27.27 as the optimal ALI cut-off. For mortality, the area under the curve (AUC) was 0.601, with a Youden index of 0.188, sensitivity of 62.7%, and specificity of 56.1%. For progression, the AUC was 0.495, with a Youden index of 0.059, suggesting limited discriminatory performance. Using this cut-off, 136 patients (54.6%) were classified as low ALI and 113 (45.4%) as high ALI. Patients in the high-ALI group had significantly higher BMI and albumin levels (both $p\leq0.001$); other baseline characteristics were generally balanced between the groups (**Table 1**).

Treatment Response

The ORR was 35.3% and the DCR was 43.0% in the overall cohort. ORR and DCR were numerically higher in the high-ALI group than in the low-ALI group (41.6% vs. 30.1%, p=0.064; 49.6% vs. 37.5%, p=0.072, respectively) (**Figure 1**). Best overall response distribution did not significantly differ between the two groups (p=0.275) (**Figure 2**).

All patients who discontinued nivolumab did so due to disease progression. No treatment discontinuations attributable to immune-related adverse events or other toxicities were recorded.

Progression-free Survival

At a median follow-up of 25.5 months, the median PFS in the overall cohort was 7.58 months (95% CI, 6.10-9.06). Patients with low ALI had a median PFS of 6.01 months (95% CI, 4.92-7.10), whereas those with high ALI had a median PFS of 10.05 months (95% CI, 8.02-12.07; log-rank p=0.012; **Figure 3**). In multivariable analysis, high ALI remained independently associated with improved PFS (HR 0.688, 95% CI 0.516-0.918; p=0.011), while older age, ECOG performance status 2-4, liver metastasis, and adrenal metastasis remained independently associated with worse PFS (**Table 2**).

Overall Survival

At a median follow-up of 15.01 months, the median OS in the overall cohort was 9.29 months (95% CI, 7.09-11.49). Median OS was 6.27 months (95% CI, 4.56-7.98) in the low-ALI group and 13.89 months (95% CI, 10.39-17.40) in the high-ALI group (log-rank p<0.001; **Figure 4**). High ALI remained independently associated with improved OS in multivariable analysis (HR 0.585, 95% CI 0.414-0.827; p=0.002). Older age (HR 1.026; p=0.028), ECOG performance status 2-4 (HR 1.729; p=0.041), and chronic obstructive pulmonary disease (COPD) (HR 1.489; p=0.036) were independently associated with worse OS (**Table 3**).

Sensitivity Analyses

Using a literature-based ALI cut-off of 18, high ALI was associated with improved OS in univariate analysis (HR 0.696, 95% CI 0.498-0.973; p=0.034), but this association did not remain statistically significant in the multivariable model (HR 0.734, 95% CI 0.521-1.036; p=0.078). Similarly, the association between ALI and PFS was not statistically significant with this cut-off (HR 0.829, 95% CI 0.618-1.112; p=0.210).

Table 1. Baseline characteristics of the patients according to ALI group

Variable	Total (n=249)	Low ALI (n=136)	High ALI (n=113)	p value
Age, years, median (range)	66 (37-87)	66 (37-87)	66 (47-84)	0.536
Gender, male, n (%)	226 (90.8)	124 (91.2)	102 (90.3)	0.805
Histology, n (%)				0.764
Non-squamous	126 (50.6)	70 (51.5)	56 (49.6)	
Squamous	123 (49.4)	66 (48.5)	57 (50.4)	
Smoking status, n (%)*				0.549
Never smoker	11 (4.5)	5 (3.7)	6 (5.3)	
Active/former smoker	236 (95.5)	129 (96.3)	107 (94.7)	
Smoking exposure, pack-years†	40 (0-150)	38 (0-150)	40 (0-135)	0.449
ECOG performance status, n (%)				0.210
0-1	220 (88.4)	117 (86.0)	103 (91.2)	
2-4	29 (11.6)	19 (14.0)	10 (8.8)	
First-line treatment, n (%)				0.459
Platinum-pemetrexed	47 (18.9)	22 (16.2)	25 (22.1)	
Platinum-gemcitabine	76 (30.5)	42 (30.9)	34 (30.1)	
Platinum-taxane	118 (47.4)	66 (48.5)	52 (46.0)	
Other	8 (3.2)	6 (4.4)	2 (1.8)	
PD-L1 status, n (%)				0.059
Unknown	118 (47.4)	74 (54.4)	44 (38.9)	
<1%	56 (22.5)	25 (18.4)	31 (27.4)	
1-49%	48 (19.3)	26 (19.1)	22 (19.5)	
≥50%	27 (10.8)	11 (8.1)	16 (14.2)	
Metastatic sites, n (%)				
Lung	120 (48.2)	64 (47.1)	56 (49.6)	0.694
Liver	40 (16.1)	25 (18.4)	15 (13.3)	0.274
Bone	88 (35.3)	53 (39.0)	35 (31.0)	0.189
Adrenal	38 (15.3)	21 (15.4)	17 (15.0)	0.931
Brain	28 (11.2)	14 (10.3)	14 (12.4)	0.602
Distant lymph node	98 (39.4)	50 (36.8)	48 (42.5)	0.358
Comorbidities, n (%)				
COPD	66 (26.5)	37 (27.2)	29 (25.7)	0.784
Hypertension	83 (33.3)	46 (33.8)	37 (32.7)	0.857
Diabetes mellitus	45 (18.1)	24 (17.6)	21 (18.6)	0.848
Coronary artery disease	51 (20.5)	29 (21.3)	22 (19.5)	0.718
Hyperlipidemia	10 (4.0)	4 (2.9)	6 (5.3)	0.519
Nivolumab cycles, median (range)	6 (1-120)	6 (1-80)	8 (1-120)	<0.001
BMI, kg/m², median (range)	24.2 (15.2-39.1)	23.9 (15.2-37.1)	24.9 (15.6-39.1)	0.001
Albumin, g/dl, median (range)	3.8 (2.1-4.9)	3.6 (2.1-4.6)	4.0 (2.4-4.9)	<0.001
ALI, median (range)	24.1 (1.6-176.4)	14.4 (1.6-27.2)	43.9 (27.3-176.4)	<0.001

ALI: Advanced Lung Cancer Inflammation Index, BMI: Body-mass index, COPD: Chronic obstructive pulmonary disease, ECOG: Eastern Cooperative Oncology Group performance status, PD-L1: Programmed death-ligand 1, NSCLC: Non-small cell lung cancer. *n=247; †n=245. Values are median (range) unless otherwise stated.

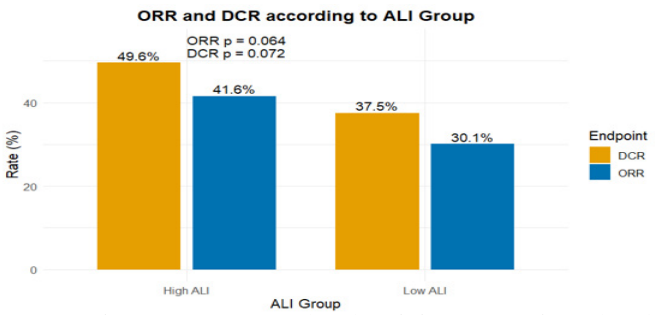


Figure 1. Objective response rate (ORR) and disease control rate (DCR) according to baseline ALI groups in patients treated with nivolumab

p-values were calculated using the Chi-square test. ALI: Advanced Lung Cancer Inflammation Index, DCR: Disease control rate, ORR: Objective response rate

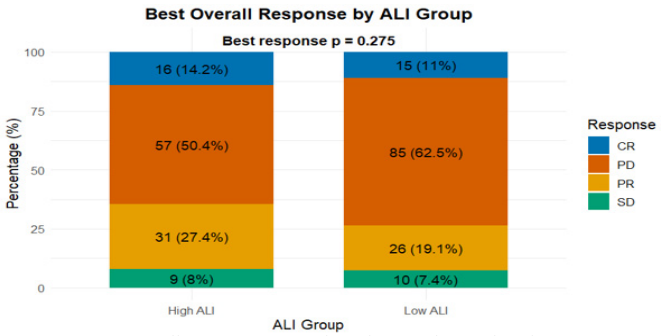


Figure 2. Best overall response to nivolumab according to baseline ALI groups

ALI: Advanced Lung Cancer Inflammation Index, CR: Complete response, PD: Progressive disease, PR: Partial response, SD: Stable disease

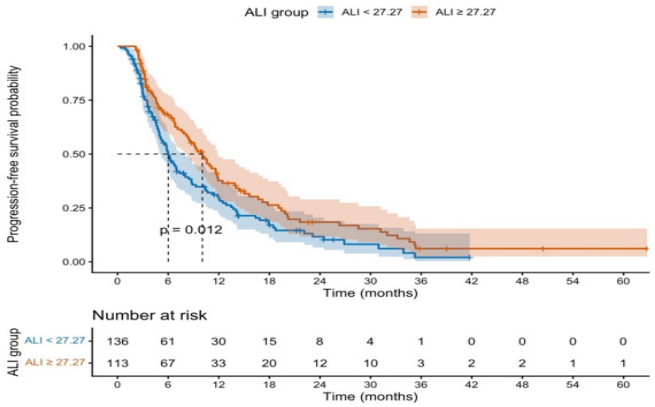


Figure 3. Kaplan-Meier curves for progression-free survival according to baseline ALI group

High ALI (≥27.27) vs. low ALI (<27.27); log-rank p=0.012. ALI: Advanced Lung Cancer Inflammation Index, CI: Confidence interval, PFS: Progression-free survival

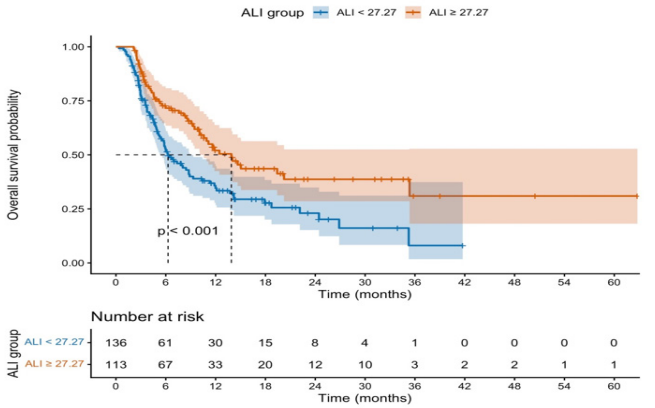


Figure 4. Kaplan-Meier curves for overall survival according to baseline ALI group

High ALI (≥27.27) vs. low ALI (<27.27); log-rank p<0.001. ALI: Advanced Lung Cancer Inflammation Index, CI: Confidence interval, OS: Overall survival

DISCUSSION

In this multicenter retrospective cohort study, we evaluated the prognostic and potential predictive role of ALI in patients with metastatic NSCLC treated with second-line nivolumab. Higher baseline ALI was independently associated with improved PFS and OS, while no significant association was observed between ALI and radiological response outcomes. These findings suggest that ALI may function primarily as a prognostic rather than a direct predictive biomarker of tumor response in this setting.

Systemic inflammation plays a central role in cancer progression and treatment outcomes. In the landmark study by Jafri et al.,[8] involving 173 patients with metastatic NSCLC, a lower ALI (<18) was associated with significantly worse survival outcomes (median OS 3.4 vs. 8.3 months). That study included a heterogeneous population treated predominantly

Table 2. Univariate and multivariable Cox regression analyses for progression-free survival

Variable	Univariate HR (95% CI)	p value	Multivariable HR (95% CI)	p value
Gender (female vs. male)	1.299 (0.825-2.045)	0.259	-	-
Age, years	1.035 (1.016-1.053)	<0.001	1.033 (1.014-1.052)	<0.001
Histology (SCC vs. non-SCC)	1.252 (0.943-1.663)	0.121	-	-
Smoking (active/former vs. never)	0.982 (0.483-1.994)	0.959	-	-
ECOG PS (2-4 vs. 0-1)	2.054 (1.309-3.223)	0.002	1.721 (1.069-2.771)	0.025
Lung metastasis	1.005 (0.758-1.333)	0.972	-	-
Liver metastasis	1.514 (1.032-2.220)	0.034	1.504 (1.015-2.228)	0.042
Bone metastasis	1.288 (0.957-1.733)	0.094	-	-
Adrenal metastasis	1.469 (1.003-2.150)	0.048	1.677 (1.141-2.466)	0.009
Brain metastasis	1.228 (0.792-1.904)	0.358	-	-
COPD	1.321 (0.961-1.817)	0.087	-	-
ALI ≥27.27 vs. <27.27	0.694 (0.522-0.923)	0.012	0.688 (0.516-0.918)	0.011

ALI: Advanced Lung Cancer Inflammation Index, CI: Confidence interval, COPD: Chronic obstructive pulmonary disease, ECOG PS: Eastern Cooperative Oncology Group performance status, HR: Hazard ratio, SCC: Squamous cell carcinoma. First-line treatment group was not significant in univariate analysis and was excluded.

Table 3. Univariate and multivariable Cox regression analyses for overall survival

Variable	Univariate HR (95% CI)	p value	Multivariable HR (95% CI)	p value
Gender (female vs. male)	1.091 (0.616-1.931)	0.765	-	-
Age, years	1.034 (1.013-1.056)	0.002	1.026 (1.003-1.049)	0.028
Histology (SCC vs. non-SCC)	1.447 (1.037-2.018)	0.029	1.228 (0.866-1.742)	0.249
Smoking (active/former vs. never)	1.437 (0.532-3.885)	0.475	-	-
ECOG PS (2-4 vs. 0-1)	2.291 (1.402-3.743)	<0.001	1.729 (1.023-2.920)	0.041
Liver metastasis	1.791 (1.186-2.702)	0.006	1.493 (0.971-2.297)	0.068
Bone metastasis	1.419 (1.009-1.997)	0.045	1.349 (0.948-1.918)	0.096
COPD	1.501 (1.048-2.150)	0.027	1.489 (1.026-2.160)	0.036
ALI (continuous)	0.991 (0.982-0.999)	0.031	-	-
ALI ≥27.27 vs. <27.27	0.560 (0.398-0.788)	<0.001	0.585 (0.414-0.827)	0.002

ALI: Advanced Lung Cancer Inflammation Index, CI: Confidence interval, COPD: Chronic obstructive pulmonary disease, ECOG PS: Eastern Cooperative Oncology Group performance status, HR: Hazard ratio, SCC: Squamous cell carcinoma

with chemotherapy, reflecting the pre-immunotherapy era. Ozyurek et al.[13] similarly reported that ALI <18 was associated with shorter OS in 112 stage IV NSCLC patients, with a negative correlation between ALI and systemic inflammatory markers such as C-reactive protein, reinforcing the biological link between ALI and systemic inflammation.

In contrast, our study focused exclusively on a homogeneous cohort receiving second-line ICI therapy with nivolumab. We observed a stronger association between ALI and long-term survival outcomes, particularly for OS (HR 0.585). Unlike chemotherapy-based cohorts where ALI may primarily reflect tumor burden and cachexia-related systemic decline, in immunotherapy-treated populations ALI may more specifically reflect host immune competence and systemic inflammatory balance, both of which are closely linked to ICI efficacy.

A notable finding was the higher optimal ALI cut-off value (27.27) compared with those reported in previous studies (approximately 18-23). This likely reflects differences in patient populations and treatment eras. Earlier studies by Jafri et al.[8] and Bacha et al.[14] included more heterogeneous patients with higher systemic inflammatory burden and poorer nutritional status. Patients selected for immunotherapy often have better baseline performance status and more favorable metabolic profiles, shifting the distribution of ALI values toward higher levels. Variation in optimal cut-off values across cohorts is expected and likely reflects biological heterogeneity rather than methodological inconsistency. Despite these differences, the direction of the association remains highly consistent across studies, with lower ALI uniformly indicating poorer survival outcomes.

Our findings also align with earlier inflammation-based prognostic models such as the C-reactive protein-albumin score described by Forrest et al.,[15] which demonstrated that systemic inflammatory status strongly influences survival in advanced NSCLC. While such earlier models were developed in the pre-immunotherapy era, ALI may provide a broader biological assessment by incorporating both nutritional status and immune cell dynamics—particularly relevant in patients receiving ICIs, where therapeutic efficacy depends on host immune competence.

Limitations

Several limitations should be acknowledged. The retrospective design may introduce selection bias and limits causal inference. Although multicenter, the study population was relatively limited in size and derived from a single country, which may affect generalizability. ALI was assessed only at baseline, and dynamic changes during treatment were not evaluated. Information on PD-L1 expression and molecular alterations was not uniformly available and could not be incorporated into the analysis.

Nevertheless, our study has important strengths. To our knowledge, this is one of the largest homogeneous real-world cohorts specifically evaluating ALI in patients receiving second-line nivolumab, with a critical methodological distinction: all patients were ICI-naive at enrollment, ensuring that the observed associations reflect ALI's prognostic role in the context of de novo ICI exposure. This design significantly reduces confounding and strengthens internal validity. The consistency of results across both PFS and OS endpoints further supports the robustness of ALI as a prognostic marker. Additionally, the use of a data-driven ROC-derived cut-off supported by sensitivity analyses with a literature-based threshold enhances reproducibility and clinical applicability.

CONCLUSION

This multicenter study demonstrates that baseline ALI is an independent prognostic biomarker for both PFS and OS in ICI-naive patients with metastatic NSCLC receiving second-line nivolumab. As an accessible, low-cost composite of nutritional and inflammatory host status, ALI holds promise as a practical stratification tool in routine oncological practice. These findings provide a rationale for prospective evaluation of ALI-guided patient selection strategies in the second-line immunotherapy setting.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval for this multicenter non-interventional clinical study was obtained from the Non-interventional Clinical Researches Ethics Committee of Aydın Adnan Menderes University (Date: 13.03.2026, Decision No: E-53043-469-050.04-831562).

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

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

Author Contributions

Concept: AA; Design: AA; Control: AA, BD, KC; Resources: AA, BD, KC; Materials: AA, KC, BD, HİE, YAC; Data Collection and/or Processing: AA, KC, BD, HİE, YAC; Analysis and/or Interpretation: AA, KC; Literature Review: All Authors; Writing the Article: AA, KC; Critical Review: All Authors.

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Journal of Current Hematology & Oncology Research

Original Article

DOI: 10.51271/JCHOR-0089

IgG-defined hypogammaglobulinemia at diagnosis and survival outcomes in diffuse large B-cell lymphoma[a]

Sinem Öztekin[1], Ünal Ataş[2], Utku Iltar[2], Orhan Kemal Yücel[2], Ozan Salim*[2], Levent Ündar[2]

[1]Department of Internal Medicine, Finike State Hospital, Antalya, Turkiye
[2]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Akdeniz University, Antalya, Turkiye

Cite this article: Öztekin S, Ataş Ü, Iltar U, Yücel OK, Salim O, Ündar L. IgG-defined hypogammaglobulinemia at diagnosis and survival outcomes in diffuse large B-cell lymphoma. *J Curr Hematol Oncol Res.* 2026;4(3):93-98. doi:10.51271/JCHOR-0089

***Corresponding Author:** Ozan Salim, ozansalim@gmail.com

Received: 30/03/2026 ◆ **Accepted**: 22/06/2026 ◆ **Published**: 08/08/2026

ABSTRACT

Aims: To evaluate the prognostic value of hypogammaglobulinemia at diagnosis in patients with diffuse large B-cell lymphoma (DLBCL) and its association with clinical characteristics and survival outcomes.

Methods: A total of 177 adult patients with newly diagnosed DLBCL and available serum immunoglobulin G (IgG) levels were retrospectively analyzed. IgG-defined hypogammaglobulinemia was defined as IgG <700 mg/dl at diagnosis.

Results: IgG-defined hypogammaglobulinemia was identified in 27 patients (15.3%). There were no significant differences between patients with and without IgG-defined hypogammaglobulinemia in terms of age and gender distribution. However, IgG-defined hypogammaglobulinemia was associated with more frequent B symptoms, extranodal involvement, elevated lactate dehydrogenase levels, poor Revised International Prognostic Index (R-IPI) scores, lower serum albumin levels, and a higher rate of infections during follow-up. The median follow-up time was 33 months (range, 0,1-166 months). Patients with IgG-defined hypogammaglobulinemia had significantly shorter progression-free survival (PFS) (p=0.044) and overall survival (OS) (p=0.001). In univariable analysis, IgG-defined hypogammaglobulinemia, ECOG performance status >1, poor R-IPI score, low albumin levels, presence of B symptoms, bone marrow involvement, and infection during follow-up were associated with inferior survival outcomes. In multivariable analysis, IgG-defined hypogammaglobulinemia was not an independent prognostic factor for PFS but remained independently associated with OS in the model including R-IPI.

Conclusion: IgG-defined hypogammaglobulinemia at diagnosis may be associated with inferior survival outcomes in patients with DLBCL. Further prospective multicenter studies are needed to clarify its independent prognostic significance and potential role in risk stratification.

Keywords: Diffuse large B-cell lymphoma, IgG-defined hypogammaglobulinemia, immunoglobulin G, prognosis, survival

Presented as an oral presentation at the 46th Ulusal Hematoloji Kongresi, Turkiye, October 28-31, 2020.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common histological subtype of non-Hodgkin lymphoma (NHL) and represents a clinically, morphologically, and biologically heterogeneous disease.[1] Prognostic assessment in DLBCL is commonly based on clinical variables such as age, serum lactate dehydrogenase levels, performance status, disease stage, and extranodal involvement, which are incorporated into the International Prognostic Index (IPI), as well as the rituximab-era adaptations including the revised IPI (R-IPI) and NCCN-IPI.[2-4] However, these models still have limitations, particularly in individual risk stratification in the rituximab era.

In this context, molecular features have gained increasing importance. Gene expression profiling has identified germinal center B-cell-like and activated B-cell-like subtypes, while cell-of-origin classification using the Hans algorithm and genetic alterations such as MYC, BCL2, and/or BCL6 rearrangements have been shown to significantly influence prognosis and therapeutic approaches in DLBCL.[5-10] In addition, several other biomarkers, including MYC, TP53, CD5, Ki-67 proliferation index, and beta-2 microglobulin, have also been investigated for their prognostic relevance.[11,12] These findings highlight the ongoing need for novel prognostic markers that are non-invasive, easily accessible, and cost-effective, in addition to existing clinical scoring systems.

In the current literature, hypogammaglobulinemia has been well characterized in chronic lymphocytic leukemia and certain indolent lymphoma subtypes, where it is primarily associated with an increased risk of infections

and adverse clinical outcomes.[13-15] More recently, there has been growing interest in the role of immune dysfunction and immunoglobulin levels in B-cell lymphomas. In patients with NHL, low pre-treatment immunoglobulin levels have been associated with increased mortality and hospitalization rates.[16]

In DLBCL, however, data remain limited. Earlier studies have mainly focused on secondary hypogammaglobulinemia following rituximab-based therapy and its association with infections.[17,18] In contrast, a limited number of recent studies defining hypogammaglobulinemia as a decrease in any immunoglobulin class at diagnosis have reported a prevalence of approximately 20% and suggested an association with inferior progression-free and overall survival (OS).[19-21]

In this study, we aimed to evaluate the prognostic value of IgG-defined hypogammaglobulinemia, whose role in DLBCL remains incompletely defined, in conjunction with other clinical and laboratory parameters.

METHODS

The study was approved by the Clinical Researches Ethics Committee of Akdeniz University Faculty of Medicine (Date: 04.03.2020, Decision No: 245). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Adult patients (≥18 years) diagnosed with DLBCL and treated with rituximab-based first-line immunochemotherapy (R-CHOP or R-mini-CHOP) at the Hematology Department of Akdeniz University Faculty of Medicine Hospital between October 2007 and December 2019 were retrospectively evaluated. To maintain a relatively homogeneous treatment cohort, patients with primary mediastinal B-cell lymphoma, primary bone lymphoma, central nervous system involvement, or other high-risk subtypes requiring alternative frontline treatment approaches (e.g., DA-R-EPOCH) were excluded from the study. Eligible patients with complete clinical and laboratory data were included in the study.

Data were collected from patient records, the electronic hospital database, hematology clinic records, the central laboratory database, the pathology archive system, and the National Death Notification System. Demographic and clinical characteristics of patients with DLBCL were recorded, including gender, age, Eastern Cooperative Oncology Group (ECOG) performance status, date of diagnosis, presence of bulky disease, bone marrow involvement, Ann Arbor stage, B symptoms, presence and number of extranodal sites, and serum levels of lactate dehydrogenase (LDH), albumin, and beta-2 microglobulin. Serum immunoglobulin G (IgG) levels at diagnosis were also recorded.

The R-IPI score was calculated using baseline clinical data. Treatment regimens, response to first-line therapy according to the International Working Group response criteria, presence and timing of relapse, date of last follow-up, and final status (remission, relapse, or death) were documented.

IgG-defined hypogammaglobulinemia was defined as a serum IgG level below the lower limit of normal (<700 mg/dl). Progression-free survival (PFS) was defined as the time from diagnosis to disease progression or death from any cause. OS was defined as the time from diagnosis to death from any cause or last follow-up. During follow-up, a total of 63 progression events and 37 deaths were observed and constituted the events for the PFS and OS analyses, respectively.

Statistical Analysis

All data analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as frequencies and percentages for categorical variables, and as mean±standard deviation or median (minimum–maximum) for continuous variables, as appropriate. Associations between categorical variables were evaluated using the Chi-square test or Fisher's exact test, as appropriate. Comparisons of continuous variables between groups were performed using parametric or non-parametric tests according to data distribution.

Survival analyses were conducted using the Kaplan–Meier method, and differences between groups were assessed with the log-rank test. Univariable and multivariable Cox proportional hazards regression models were used to identify prognostic factors associated with PFS and OS. The proportional hazards assumption was assessed for all Cox regression models and was found to be satisfied. Model adequacy was assessed during construction of the Cox regression models and was considered acceptable. Two separate multivariable models were constructed. Model 1 included age, ECOG performance status, serum albumin level, and IgG-defined hypogammaglobulinemia. Potential collinearity was evaluated during model construction. Because the R-IPI score incorporates age, serum LDH level, performance status, disease stage, and extranodal involvement, these variables were not entered simultaneously into the same model to minimize collinearity. Therefore, model 2 included the R-IPI risk group, serum albumin level, and IgG-defined hypogammaglobulinemia. Variables were selected based on clinical relevance and the results of univariable analyses. A p-value of <0.05 was considered statistically significant.

RESULTS

Of the 210 patients screened, 33 were excluded because of missing baseline IgG measurements, incomplete clinical data, or treatment other than rituximab-based first-line immunochemotherapy (R-CHOP or R-mini-CHOP), resulting in a final cohort of 177 patients. Among the included patients, IgG-defined hypogammaglobulinemia (IgG <700 mg/dl) was identified in 27 (15.3%), whereas 150 (84.7%) had normal IgG levels. Detailed demographic, clinical, and laboratory characteristics of the patients are summarized in **Table 1**.

There were no significant differences between patients with and without IgG-defined hypogammaglobulinemia in terms of age and sex distribution. However, the proportion of patients with ECOG performance status >1 and poor R-IPI scores, as well as the presence of B symptoms, extranodal involvement, and elevated LDH levels, were higher in the IgG-defined hypogammaglobulinemia group. In addition,

Table 1. Baseline characteristics according to IgG-defined hypogammaglobulinemia (IgG <700 mg/dl)

Variable	Non-HG (n=150)	HG (n=27)	p
Age, years, median (IQR)	58 (21)	64 (26.8)	0.290
Female gender, n (%)	70 (46.7%)	12 (44.4%)	0.831
ECOG >1, n (%)	26 (17.3%)	11 (40.7%)	0.006
Stage III–IV, n (%)	88 (59.1%)	22 (81.5%)	0.082
B symptoms, n (%)	66 (44.0%)	19 (70.4%)	0.012
Extranodal involvement, n (%)	81 (54.0%)	21 (77.8%)	0.021
Elevated LDH, n (%)	101 (67.3%)	24 (88.9%)	0.024
Poor R-IPI, n (%)	63 (42.0%)	17 (63.0%)	0.044
Albumin, g/dl, median (IQR)	4.0 (0.8)	3.2 (1.0)	<0.001
Beta-2 microglobulin, mg/L, median (IQR)	3.0 (2.4)	3.25 (2.7)	0.095
Total protein, g/dl, median (IQR)	6.8 (1.0)	5.0 (1.3)	<0.001
Globulin, g/dl, median (IQR)	2.8 (0.8)	1.9 (0.6)	<0.001
Ki-67 ≥80%, n (%)	50 (33.3%)	11 (40.7%)	0.814
Non-GCB subtype, n (%)	32 (21.3%)	7 (25.9%)	0.881
Febrile neutropenia, n (%)	39 (26.0%)	9 (33.3%)	0.442
≥1 Infection episode, n (%)	29 (19.3%)	14 (51.9%)	<0.001
R-min-CHOP, n (%)	6 (4.0%)	3 (11.1%)	0.110
Treatment response, n (%)			0.028*
CR	101 (67.3)	10 (37.0)	
PR	25 (16.6)	6 (22.2)	
PD	11 (7.3)	5 (18.5)	

IgG: Immunoglobulin G, HG: Immunoglobulin G-defined hypogammaglobulinemia, IQR: Interquartile range, ECOG: Eastern Cooperative Oncology Group, LDH: Lactate dehydrogenase, R-IPI: Revised International Prognostic Index, Non-GCB: Non-germinal center B-cell, CR: Complete response, PD: Progressive disease, PR: Partial response
*Fisher exact test used for treatment response comparison.

albumin, total protein, and globulin levels were significantly lower in patients with IgG-defined hypogammaglobulinemia. Although the frequency of stage III–IV disease was higher in this group, the difference did not reach statistical significance. Patients with IgG-defined hypogammaglobulinemia had higher frequency of ≥1 infection episode during follow-up. There were no significant differences between the groups regarding beta-2 microglobulin levels, Ki-67 index, non-germinal center B-cell (non-GCB) subtype, incidence of febrile neutropenia, or use of R-mini-CHOP.

During follow-up, the rate of experiencing at least one infection episode was significantly higher in the IgG-defined hypogammaglobulinemia group. Although the complete response (CR) rate after first-line therapy was lower and the rate of progressive disease (PD) was higher in patients with IgG-defined hypogammaglobulinemia, these differences did not reach statistical significance.

The median follow-up time was 33 months (range, 0.1-166 months). Kaplan–Meier survival analysis demonstrated that the presence of IgG-defined hypogammaglobulinemia at diagnosis was associated with inferior PFS and OS. Patients with IgG-defined hypogammaglobulinemia had significantly shorter PFS compared to those without IgG-defined hypogammaglobulinemia (log-rank p=0.044) (**Figure 1a**). Similarly, OS was significantly shorter in the IgG-defined hypogammaglobulinemia group (log-rank p=0.001) (**Figure 1b**).

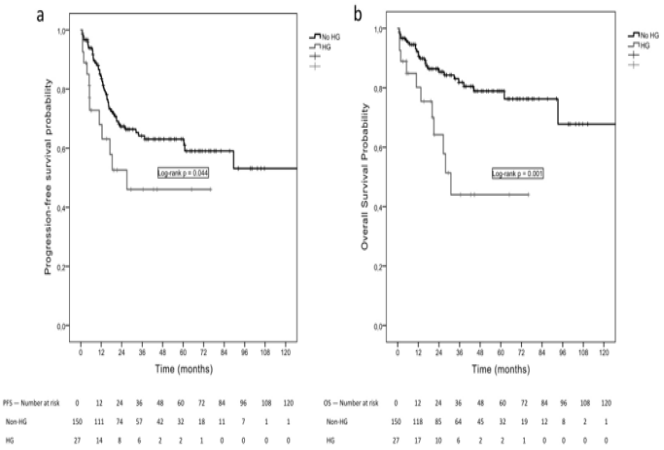

Figure 1. Kaplan–Meier curves of progression-free survival (PFS) **(a)** and overall survival (OS) **(b)** according to baseline IgG-defined hypogammaglobulinemia status (IgG <700 mg/dl).
IgG: Immunoglobulin G, HG: Hypogammaglobulinemia, PFS: Progression-free survival, OS: Overall survival

In univariable Cox regression analysis, IgG-defined hypogammaglobulinemia was associated with inferior PFS and OS. ECOG performance status >1, poor R-IPI score, low serum albumin levels, presence of B symptoms, and bone marrow involvement were also associated with adverse survival outcomes. Elevated LDH levels were significantly associated with OS but not with PFS. Increasing age was associated with PFS, whereas its association with OS did not reach statistical significance. The results of the univariable analyses are summarized in **Table 2**.

In multivariable analysis, IgG-defined hypogammaglobulinemia was not an independent prognostic factor for either PFS or OS in model 1, which included age, ECOG performance status, serum albumin, and IgG-defined hypogammaglobulinemia. In this model, only ECOG performance status >1 remained an independent adverse predictor for both PFS and OS. In model 2, which included the R-IPI risk group (a composite score incorporating age, serum LDH, performance status, disease stage, and extranodal involvement), serum albumin, and IgG-defined hypogammaglobulinemia, IgG-defined hypogammaglobulinemia was not independently associated with PFS but remained an independent adverse prognostic factor for OS. In the same model, poor R-IPI was significantly associated with both PFS and OS, while higher serum albumin levels were associated with improved OS. The results of the multivariable analysis are presented in **Table 3**.

DISCUSSION

In our study, patients with IgG-defined hypogammaglobulinemia at diagnosis had significantly shorter PFS and OS. In addition, these patients more frequently exhibited B symptoms, extranodal involvement, elevated LDH levels, poor R-IPI scores, and lower serum albumin levels, as well as a higher rate of infections during follow-up. These findings suggest that IgG-defined hypogammaglobulinemia may be associated with more aggressive disease characteristics.

DLBCL is a clinically and biologically heterogeneous disease, and prognostic assessment is commonly based on established scoring systems such as the IPI, R-IPI, and

Table 2. Univariable Cox regression analysis for PFS and OS

Variable	PFS HR (95% CI)	p value	OS HR (95% CI)	p value
IgG-defined HG	1.90 (1.01–3.57)	0.048	3.18 (1.56–6.49)	0.001
ECOG >1	4.67 (2.80–7.75)	<0.001	7.14 (3.70–13.67)	<0.001
R-IPI poor risk	2.35 (1.40–3.92)	0.001	3.53 (1.74–7.14)	<0.001
Elevated LDH	1.49 (0.82–2.71)	0.188	2.62 (1.02–6.71)	0.046
Albumin (per 1 g/dl increase)	0.61 (0.42–0.89)	0.009	0.39 (0.24–0.62)	<0.001
Age (per year increase)	1.02 (1.00–1.04)	0.025	1.02 (1.00–1.05)	0.062
B symptoms	2.59 (1.52–4.42)	<0.001	4.22 (1.93–9.26)	<0.001
Bone marrow involvement	1.86 (1.06–3.26)	0.031	2.54 (1.27–5.12)	0.009
Infection during follow-up	3.38 (2.03–5.62)	<0.001	6.67 (3.44–12.99)	<0.001

PFS: Progression-free survival, OS: Overall survival, HR: Hazard ratio, CI: Confidence interval, HG: Hypogammaglobulinemia, ECOG: Eastern Cooperative Oncology Group, R-IPI: Revised International Prognostic Index, LDH: Lactate dehydrogenase

Table 3. Multivariable Cox regression analysis for PFS and OS

Variable	PFS HR (95% CI)	p value	OS HR (95% CI)	p value
Model 1				
IgG-defined HG	1.27 (0.65–2.49)	0.476	1.69 (0.79–3.63)	0.170
ECOG >1	3.85 (2.17–6.67)	<0.001	4.63 (2.17–10.00)	<0.001
Albumin (per 1 g/dl increase)	0.85 (0.57–1.27)	0.434	0.66 (0.39–1.12)	0.121
Age (per year increase)	1.01 (0.99–1.03)	0.160	1.01 (0.99–1.04)	0.310
Model 2				
IgG-defined HG	1.58 (0.81–3.06)	0.176	2.29 (1.09–4.85)	0.030
R-IPI poor risk	2.14 (1.24–3.68)	0.006	2.73 (1.29–5.75)	0.008
Serum albumin (per 1 g/dl increase)	0.80 (0.53–1.20)	0.283	0.57 (0.34–0.96)	0.034

PFS: Progression-free survival, OS: Overall survival, HR: Hazard ratio, CI: Confidence interval, HG: Hypogammaglobulinemia, ECOG: Eastern Cooperative Oncology Group, R-IPI: Revised International Prognostic Index
Model 1 included age, ECOG performance status, serum albumin, and hypogammaglobulinemia.
Model 2 included the R-IPI risk group (which incorporates age, serum LDH, performance status, disease stage, and extranodal involvement), serum albumin, and hypogammaglobulinemia.
Variables were selected based on clinical relevance and results of univariable analysis.

NCCN-IPI.[2-4] However, the association between IgG-defined hypogammaglobulinemia and clinical outcomes observed in our study, beyond these conventional prognostic factors, suggests that existing models may be insufficient in certain patient subgroups and highlights the need for additional prognostic biomarkers.[11,12]

In chronic lymphocytic leukemia (CLL), hypogammaglobulinemia at diagnosis has been reported with variable frequencies (15-70%) and is well established to be associated with an increased risk of infections. However, its relationship with prognosis remains controversial, with some studies reporting no significant association and others identifying hypogammaglobulinemia as an independent adverse prognostic factor.[13-15,22-25] In patients with NHL, data on hypogammaglobulinemia are more limited, and most studies have focused on secondary hypogammaglobulinemia following rituximab-based therapy and its association with infection risk. These studies have demonstrated an increased risk of infections and infection-related mortality; however, the impact on survival remains largely unclear.[17,18] Notably, a recent study suggested that low pre-treatment immunoglobulin levels in NHL patients may be associated with increased mortality and hospitalization.[16] In addition, hypogammaglobulinemia in DLBCL has been shown to occur not only during treatment but also at diagnosis, where it may have clinical relevance, particularly in relation to infection risk.[26] Similarly, in our study, IgG-defined hypogammaglobulinemia at diagnosis was also associated with a higher rate of infections during follow-up.

Recent studies have suggested that hypogammaglobulinemia in treatment-naive, newly diagnosed DLBCL patients may be associated with inferior PFS and OS.[19-21] The relationship between hypogammaglobulinemia, defined as a decrease in any immunoglobulin class (IgG, IgA, or IgM), and prognosis was first evaluated by Singh et al.[19] in a cohort of approximately 200 newly diagnosed DLBCL patients. In that study, IgG-defined hypogammaglobulinemia was observed in 22% of patients, while IgG deficiency (<700 mg/dl) was reported in approximately 13.5%, and was associated with inferior survival outcomes. These findings were subsequently supported by Pan et al.[20] in a larger cohort of 553 patients, in which hypogammaglobulinemia was reported in 19% of cases and IgG-defined hypogammaglobulinemia (<700 mg/dl) in 5.0%. In that study, hypogammaglobulinemia was associated with both inferior PFS and OS. More recently, Lindberg et al.,[21] in a study including 585 patients, reported hypogammaglobulinemia in 24% and IgG-defined hypogammaglobulinemia (<700 mg/dl) in 18% of patients, demonstrating an association not only with survival outcomes but also with an increased risk of infections.

In our study, IgG-defined hypogammaglobulinemia was defined solely based on serum IgG levels, using a similar cutoff value (<700 mg/dl) as in previous studies. According to this definition, the prevalence of IgG-defined hypogammaglobulinemia was 15.3%, which is consistent with reported rates of IgG deficiency in the literature. Furthermore, we similarly demonstrated that IgG-defined hypogammaglobulinemia was associated

with inferior survival outcomes. However, patients with IgG-defined hypogammaglobulinemia also had a higher frequency of adverse baseline clinical characteristics, including poor ECOG performance status, B symptoms, extranodal involvement, elevated LDH levels, poor R-IPI scores, and lower albumin levels. Therefore, IgG-defined hypogammaglobulinemia may partly reflect higher tumor burden, systemic inflammation, or poorer general condition rather than representing a purely independent prognostic factor. Consistent with this interpretation, IgG-defined hypogammaglobulinemia was not retained as an independent predictor across all multivariable models and remained independently associated only with OS in one model. Accordingly, our findings support an association between baseline IgG-defined hypogammaglobulinemia and adverse outcomes, although causality and independent prognostic significance require further validation.

Limitations

This study has several limitations. First, the retrospective single-center design and relatively limited sample size may have affected the statistical power of some analyses and restricted the availability of certain prognostic variables. In particular, molecular markers such as MYC, BCL2, and double-hit/triple-hit status were not consistently available because of the long study period and retrospective nature of the study and therefore could not be incorporated into the multivariable analyses. Furthermore, despite efforts to minimize heterogeneity through strict inclusion criteria, temporal differences in patient management over the study period cannot be excluded. Second, hypogammaglobulinemia was defined solely based on serum IgG levels, while other immunoglobulin isotypes and subclasses were not evaluated. Therefore, our findings should be interpreted as reflecting baseline IgG deficiency rather than global hypogammaglobulinemia. Furthermore, primary immunodeficiencies were not systematically excluded in patients with hypogammaglobulinemia and changes in immunoglobulin levels during the course of treatment were not assessed. Third, infection was not a baseline variable and may have been influenced by treatment course, disease progression, and survival duration; therefore, its association with survival outcomes should be interpreted with caution. Finally, detailed data regarding salvage therapies and transplantation were not available for all patients, and their potential effect on OS cannot be excluded.

CONCLUSION

As a result, our findings support an association between IgG-defined hypogammaglobulinemia at diagnosis and inferior survival outcomes in patients with DLBCL. However, patients with IgG-defined hypogammaglobulinemia also exhibited a higher frequency of adverse baseline clinical characteristics, and our multivariable analyses did not consistently support its role as an independent prognostic factor. Therefore, larger prospective multicenter studies with more comprehensive adjustment for established prognostic variables are needed to clarify its independent prognostic significance and potential role in risk stratification.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Clinical Researches Ethics Committee of Akdeniz University Faculty of Medicine (Date: 04.03.2020, Decision No: 245).

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

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

Author Contributions

Concept: SÖ, OS, LÜ; Design: SÖ, ÜA, UI, OS; Control: ÜA, UI, OKY, OS; Data Collection and/or Processing: SÖ, ÜA, UI; Analysis and/or Interpretation: SÖ, ÜA, UI, OKY; Literature Review: SÖ, ÜA, UI; Article Writing: SÖ, ÜA, UI; Critical Review: OKY, OS, LÜ.

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Journal of Current Hematology & Oncology Research

Original Article

DOI: 10.51271/JCHOR-0090

Association of ABO and Rh blood groups with survival and clinicopathological characteristics in patients with gastric adenocarcinoma: a single-center retrospective cohort study

Erdoğan Şeyran*, Azer Gökmen

Department of Medical Oncology, Van Training and Research Hospital, University of Health Sciences, Van, Turkiye

Cite this article: Şeyran E, Gökmen A. Association of ABO and Rh blood groups with survival and clinicopathological characteristics in patients with gastric adenocarcinoma: a single-center retrospective cohort study. *J Curr Hematol Oncol Res.* 2026;4(3):99-104. doi:10.51271/JCHOR-0090

***Corresponding Author:** Erdoğan Şeyran, erdogan.seyran@gmail.com

Received: 16/04/2026 ◆ **Accepted**: 06/07/2026 ◆ **Published**: 08/08/2026

ABSTRACT

Aims: Identifying factors affecting the prognosis of gastric cancer is clinically important. Although ABO and Rh blood groups have been suggested to have a prognostic role in various malignancies, their impact in gastric cancer remains unclear. This study aimed to evaluate the association of ABO and Rh blood groups with clinicopathological characteristics and overall survival in patients with gastric adenocarcinoma.

Methods: In this retrospective single-center study, 320 patients diagnosed with gastric adenocarcinoma were included. Demographic and clinical data were obtained from electronic medical records. Overall survival was analyzed using the Kaplan-Meier method, and differences between groups were compared using the log-rank test. Cox regression analysis was performed to identify prognostic factors.

Results: The mean age of the patients was 70.2±9.5 years, and 68.4% were male. Among clinicopathological characteristics, only surgical treatment showed a statistically significant association with ABO blood groups (p=0.047). The median overall survival was 15.8 months. No statistically significant association was found between ABO blood groups (p=0.223) or Rh factor (p=0.850) and overall survival. The presence of metastasis was significantly associated with overall survival (p<0.001). A statistically significant difference in overall survival was observed according to primary surgical treatment status (p<0.001). In multivariate analysis, only surgical treatment was identified as an independent prognostic factor (HR: 0.58; 95% CI: 0.40-0.85; p=0.005).

Conclusion: ABO and Rh blood groups may not have a significant independent prognostic impact on overall survival in patients with gastric adenocarcinoma. In contrast, clinical factors such as metastasis and surgical treatment were identified as key determinants of survival. These findings suggest that prognosis in gastric cancer is more closely related to disease extent and treatment strategies rather than blood group characteristics.

Keywords: ABO blood group, gastric cancer, prognostic factors, Rh factor, survival

INTRODUCTION

Gastric cancer remains one of the leading causes of cancer-related mortality worldwide. According to recent global cancer statistics, gastric cancer ranks among the most common malignancies and constitutes a major public health problem, particularly in developing countries.[1,2] The fact that a substantial proportion of patients are diagnosed at an advanced or metastatic stage negatively affects survival outcomes.[3] Therefore, a better understanding of prognostic factors in gastric cancer and their integration into clinical practice is of great importance.

In recent years, there has been increasing interest in potential biomarkers that may influence tumor biology and patient prognosis. In this context, the ABO blood group system has emerged as a potential factor associated with both cancer development and prognosis in various malignancies.[4,5] ABO antigens are thought to play roles in cell adhesion, membrane signaling, inflammation, and immune response processes, which may influence tumor development and progression through these mechanisms.[6] Epidemiological studies investigating the relationship between ABO blood groups and gastric cancer have reported that blood group A may be associated with an increased risk of gastric cancer.[4,7] However, studies evaluating the impact of ABO blood groups on survival have yielded conflicting results. While some studies have shown that certain blood groups are associated with poorer prognosis,[8] others have found no significant association between blood groups and survival.[9,10] These discrepancies may be attributed to heterogeneity in patient populations, sample sizes, and study designs.

The relationship between Rh blood group and cancer prognosis has been evaluated in a limited number of studies, and the available data suggest that its prognostic value remains unclear.[11] Therefore, evaluating ABO and Rh blood groups together may provide a more comprehensive understanding of potential factors influencing prognosis in gastric cancer.

In this study, we aimed to evaluate the association of ABO and Rh blood groups with clinicopathological characteristics and overall survival in patients with gastric adenocarcinoma. In addition, the effects of clinically relevant factors, including metastasis status and primary surgical treatment, were analyzed to identify the major determinants of prognosis. Unlike many previous studies that focused primarily on cancer risk or evaluated ABO blood groups alone, our study simultaneously assessed ABO and Rh blood groups in a relatively large real-world cohort of patients with gastric adenocarcinoma treated over a 15-year period. Therefore, this study provides contemporary real-world evidence regarding the prognostic relevance of blood group systems in routine clinical practice.

METHODS

Ethics

The study was approved by the Van Training and Research Hospital Clinical Researches Ethics Committee (Date: 10.04.2026, Decision No: GOKAEK/2026-04/27). The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was waived by the ethics committee due to the retrospective design and the use of anonymized data.

Study Design and Patient Selection

This retrospective, single-center study was conducted to evaluate the association of ABO and Rh blood groups with clinicopathological characteristics and overall survival in patients with gastric adenocarcinoma. A total of 320 patients diagnosed and treated for gastric adenocarcinoma at the Medical Oncology Clinic of Van Training and Research Hospital, University of Health Sciences, between January 2010 and January 2025 were included in the study. Patients with histopathologically confirmed gastric adenocarcinoma and available ABO and Rh blood group data were included. Patients with missing key clinical data or unavailable baseline information were excluded. Patients who were alive at the last follow-up were censored in survival analyses.

Data Collection and Variables

Demographic and clinical data were retrospectively obtained from the hospital's electronic medical records system. The recorded variables included age, sex, tumor location, histopathological characteristics, presence of metastasis, treatment modalities, and follow-up duration. Metastasis status was determined based on clinical and radiological evaluations at the time of diagnosis. Primary surgical treatment was defined as surgical resection of the primary gastric tumor, including total gastrectomy, subtotal/distal gastrectomy, and gastrectomy combined with regional lymph node dissection (D1 or D2 lymphadenectomy). The majority of surgical procedures were performed with curative intent. Surgical treatment status was recorded as a binary variable (yes/no) for survival analyses. ABO and Rh blood group data were obtained from patient records. Clinical stage information was not available for all patients because of the retrospective study design, the long study period, and incomplete staging documentation in some historical medical records. Therefore, stage data could only be obtained for a subset of patients.

Survival Definitions

Overall survival (OS) was defined as the time from the date of diagnosis to death or last follow-up. Patients who were alive at the last follow-up or had no documented death record were censored at the date of last confirmed contact.

Statistical Analysis

The data analyses were performed using SPSS software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean±standard deviation or median (minimum-maximum), while categorical variables were presented as frequencies and percentages (%). The Chi-square test or Fisher's exact test was used to compare categorical variables between groups. Overall survival was analyzed using the Kaplan–Meier method, and differences between groups were evaluated with the log-rank test. Cox proportional hazards regression analysis was performed to identify prognostic factors. Variables that were statistically significant in univariate analysis or considered clinically relevant were included in the multivariate model. Collinearity between metastasis status and primary surgical treatment was assessed using correlation analysis. A moderate-to-strong inverse correlation was observed between these variables (r=-0.566). Given the close clinical and statistical relationship between metastasis status and surgical treatment, metastasis was not included in the primary multivariable Cox regression model in order to minimize model instability and potential overadjustment. The prognostic impact of metastasis was therefore evaluated in univariate analyses and Kaplan-Meier survival analyses.

Results were reported as hazard ratios (HR) with 95% confidence intervals (CI). All analyses were two-sided, and a p-value of <0.05 was considered statistically significant.

RESULTS

A total of 320 patients were included in the study. The mean age was 70.2±9.5 years, and 68.4% of the patients were male. The clinical and demographic characteristics of the patients are presented in **Table 1**. Stage information was available for 230 patients. Missing stage data were mainly related to incomplete documentation in historical medical records because of the retrospective nature and long study period of the cohort. The majority of cases were at an advanced stage, and metastasis was present in 68.5% of patients.

The associations between ABO blood groups and clinicopathological characteristics are shown in **Table 2**. Among the analyzed variables, only surgical treatment status was significantly associated with ABO blood groups (p=0.047). No significant differences were observed between groups in terms of metastasis status, Lauren classification, differentiation, or survival status (all p>0.05).

Table 1. Demographic and clinical characteristics of patients (n=320)

Variable	n (%)
Age (years), mean±SD	70.2±9.5
Gender	
Female	101 (31.6)
Male	219 (68.4)
Clinical stage*	
Stage I–II	32 (13.9)
Stage III–IV	198 (86.1)
Metastasis status*	
Absent	75 (31.5)
Present	163 (68.5)
Surgical treatment	
No	145 (45.3)
Yes	175 (54.7)
Lauren classification*	
Intestinal	57 (23.6)
Diffuse	179 (74.0)
Differentiation*	
Well/moderate	79 (44.9)
Poor	97 (55.1)
ABO blood group	
O	95 (29.7)
A	153 (47.8)
B	44 (13.8)
AB	28 (8.8)
Rh factor	
Negative	38 (11.9)
Positive	282 (88.1)
Survival status	
Alive	99 (30.9)
Dead	221 (69.1)

*Due to missing data, the total number of patients varies for some variables.
Abbreviations: SD: Standard deviation

In the overall survival analysis, the median survival time for the entire cohort was 15.8 months. The median survival times according to ABO blood groups were 15.6 months for group O, 15.5 months for group A, 13.1 months for group B, and 28.4 months for group AB (Table 3). Kaplan–Meier analysis showed no significant difference in overall survival among ABO blood groups (log-rank p=0.223) (Figure 1).

Table 3. Overall survival analysis according to ABO blood groups

Blood group	n	Events (n)	Median OS (months)	95% CI
O	95	67	15.6	11.9–19.4
A	153	108	15.5	13.7–17.2
B	44	32	13.1	5.1–21.2
AB	28	14	28.4	5.0–51.8
Total	320	221	15.8	14.1–17.5

OS: Overall survival, CI: Confidence interval
Log-rank test p=0.223.

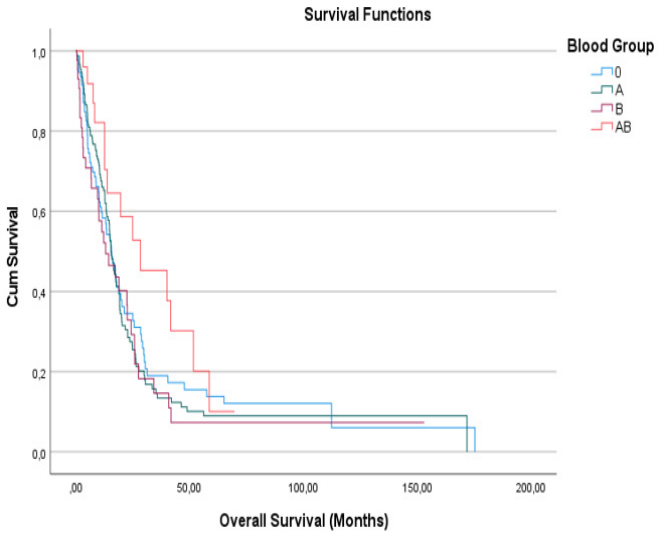

Figure 1. Kaplan–Meier overall survival curves according to ABO blood groups (log-rank p=0.223)

Table 2. Association between ABO blood groups and clinicopathological characteristics

Variable	O (n=95)	A (n=153)	B (n=44)	AB (n=28)	p
Metastasis*					0.91
Absent	23 (31.9)	38 (33.0)	9 (28.1)	5 (26.3)	
Present	49 (68.1)	77 (67.0)	23 (71.9)	14 (73.7)	
Surgical treatment					**0.047**
No	53 (55.8)	60 (39.2)	22 (50.0)	10 (35.7)	
Yes	42 (44.2)	93 (60.8)	22 (50.0)	18 (64.3)	
Lauren classification*					0.77
Intestinal	14 (19.2)	27 (23.5)	12 (34.3)	4 (21.1)	
Diffuse	57 (78.1)	85 (73.9)	23 (65.7)	14 (73.7)	
Differentiation*					0.50
Well/moderate	24 (42.9)	33 (40.2)	12 (52.2)	10 (66.7)	
Poor	32 (57.1)	49 (59.8)	11 (47.8)	5 (33.3)	
Survival status					0.15
Alive	28 (29.5)	45 (29.4)	12 (27.3)	14 (50.0)	
Dead	67 (70.5)	108 (70.6)	32 (72.7)	14 (50.0)	

*Due to missing data, the total number of patients varies for some variables.
p-values were calculated using the chi-square test or Fisher–Freeman–Halton exact test

A statistically significant difference in overall survival was observed according to the presence of metastasis (p<0.001) (**Figure 2**). Similarly, a significant difference in overall survival was found based on primary surgical treatment status (p<0.001) (**Figure 3**). No significant difference in overall survival was observed according to Rh blood group (p=0.850) (**Figure 4**).

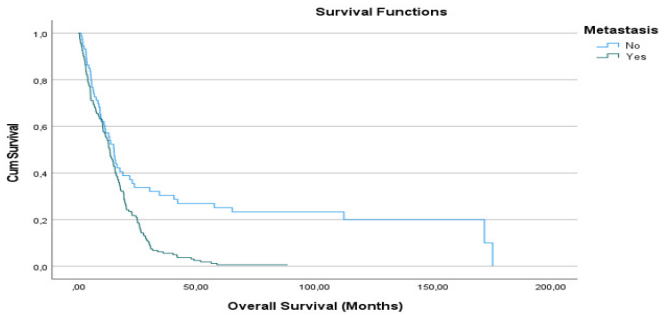

Figure 2. Kaplan–Meier overall survival curves according to metastasis status (log-rank p<0.001)

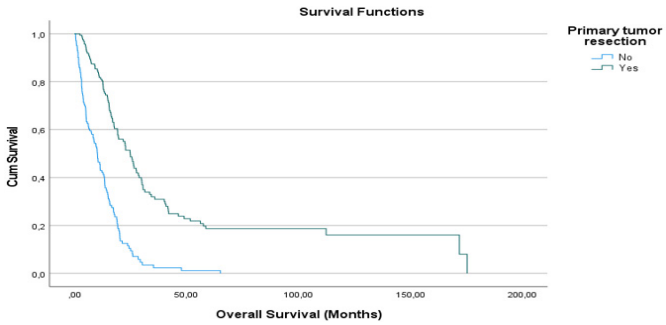

Figure 3. Kaplan–Meier overall survival curves according to primary surgical treatment status (log-rank p<0.001)

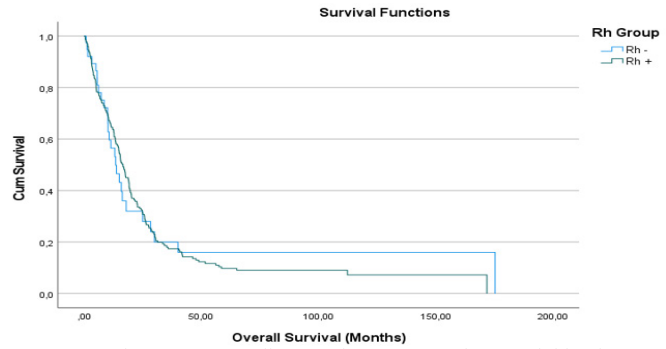

Figure 4. Kaplan–Meier overall survival curves according to Rh blood groups (log-rank p=0.850)

In univariate Cox regression analysis, the presence of metastasis was significantly associated with survival (HR: 1.90; 95% CI: 1.30-2.80; p=0.001). In multivariate analysis, only surgical treatment was identified as an independent prognostic factor (HR: 0.58; 95% CI: 0.40–0.85; p=0.005). Collinearity assessment demonstrated a moderate-to-strong inverse correlation between metastasis status and primary surgical treatment (r=-0.566). Because these variables were closely related both clinically and statistically, metastasis was excluded from the primary multivariable model. Nevertheless, metastasis remained a significant prognostic factor in univariate Cox regression analysis (HR: 1.90; 95% CI: 1.30–2.80; p=0.001) and Kaplan–Meier survival analysis (log-rank p<0.001). ABO and Rh blood groups were not found to have a significant impact on survival (**Table 4**).

DISCUSSION

In this study, we evaluated the impact of ABO and Rh blood groups on overall survival in patients with gastric adenocarcinoma and demonstrated that neither blood group system was a significant prognostic factor for survival. In contrast, clinical factors such as the presence of metastasis and the application of primary surgical treatment were found to be key determinants of survival.

The relationship between ABO blood groups and gastric cancer has been extensively investigated. Several epidemiological and meta-analysis studies have reported that blood group A is associated with an increased risk of gastric cancer.[4,7,12] However, findings regarding the impact of ABO blood groups on survival have been inconsistent. While some studies have reported an association between certain blood groups and poor prognosis,[8,13] others have found no significant relationship between blood groups and survival outcomes.[9,10,14] The lack of a significant association between ABO blood groups and overall survival in our study is consistent with studies involving larger patient cohorts that have reported no prognostic impact. Although patients with blood group AB demonstrated the longest median overall survival in our cohort (28.4 months), this difference did not reach statistical significance. One possible explanation is the relatively small number of patients in the AB subgroup (n=28), which may have limited the statistical power to detect modest survival differences between blood groups. Therefore, the observed numerical survival advantage in the AB group should be interpreted cautiously and requires confirmation

Table 4. Univariate and multivariate Cox regression analysis for overall survival

Variable	Univariate HR	95% CI	p	Multivariate HR	95% CI	p
Age	1.01	0.99–1.02	0.320	1.00	0.97–1.02	0.844
Gender (male vs female)	0.75	0.50–1.12	0.158	0.70	0.42–1.16	0.164
Metastasis (present vs absent)	1.90	1.30–2.80	0.001	—	—	—
Surgery (yes vs no)	0.45	0.32–0.64	<0.001	0.58	0.40–0.85	0.005
ABO blood group			0.820			0.822
A vs O	1.20	0.80–1.80	0.350	1.25	0.76–2.04	0.374
B vs O	1.15	0.70–1.90	0.580	1.02	0.52–2.01	0.959
AB vs O	0.85	0.45–1.60	0.620	1.11	0.43–2.86	0.827
Rh (positive vs negative)	1.05	0.65–1.70	0.850	1.02	0.51–2.02	0.959

Reference category: Blood group O. HR: Hazard ratio, CI: Confidence interval, Variables that were statistically significant in univariate analysis or considered clinically relevant were included in the multivariate model. Metastasis was excluded from the primary multivariable model because of its moderate-to-strong inverse correlation with surgical treatment (r=-0.566).

in larger multicenter cohorts with a greater representation of less common blood groups.

From a biological perspective, ABO antigens are known to play roles in cell adhesion, tumor cell migration, angiogenesis, and immune response.[6,15] Additionally, the ABO gene locus has been shown to interact with molecular pathways related to inflammation and thrombosis.[16] However, the limited reflection of these biological mechanisms on clinical survival outcomes highlights the multifactorial nature of prognosis in gastric cancer. Indeed, factors such as molecular subtypes, genetic alterations, and the tumor microenvironment are considered to have a more substantial impact on prognosis.[3,17] One possible explanation for this discrepancy is that the biological effects of ABO antigens may be more relevant to cancer susceptibility and early tumor development than to disease progression after diagnosis. Once gastric adenocarcinoma has developed, survival outcomes are likely driven predominantly by established clinical and tumor-related factors such as disease stage, metastatic burden, treatment response, molecular characteristics, and patient performance status. Consequently, any potential biological influence of ABO antigens may be overshadowed by these stronger determinants of prognosis.

The relationship between Rh blood group and cancer prognosis has been less extensively studied, and available data are limited. Some population-based studies have reported no significant association between Rh factor and cancer risk or prognosis.[11,18] Consistent with these findings, our study also demonstrated no significant impact of Rh blood group on overall survival.

The finding of a significant association between the presence of metastasis and overall survival in our study is expected and is consistent with previous studies demonstrating that disease stage is one of the strongest prognostic determinants in gastric cancer.[3,9,19] Tumor burden and the pattern of dissemination directly affect survival in metastatic disease. This observation underscores that prognosis in advanced gastric cancer is largely determined by the extent of disease. Because metastasis status was strongly associated with the likelihood of undergoing primary surgical treatment, both variables could not be interpreted entirely independently within the same prognostic framework. This relationship should be considered when interpreting the multivariable results.

The significantly better survival observed in patients who underwent primary surgical treatment is another important finding. Previous studies have shown that surgery, when applied to appropriately selected patients, may provide a survival benefit.[11,20] In the present cohort, primary surgical treatment mainly consisted of gastrectomy-based procedures with regional lymph node dissection, reflecting routine surgical management strategies for gastric adenocarcinoma. However, because metastasis status was closely associated with surgical treatment in our cohort and detailed data regarding metastatic burden were not available, the independent contribution of surgery should be interpreted with caution. Therefore, our findings should not be considered evidence supporting surgical treatment in oligometastatic disease, but rather as an observation derived from a retrospective real-world cohort.

In multivariate analysis, only surgical treatment was identified as an independent prognostic factor, highlighting the prognostic importance of treatment-related interventions. This finding emphasizes the importance of individualized treatment strategies in clinical practice. Careful patient selection and appropriate treatment planning play a crucial role in determining survival outcomes.

Although the association between ABO blood groups and gastric cancer has been investigated previously, most available studies have focused on cancer susceptibility rather than long-term survival outcomes. Furthermore, data evaluating ABO and Rh blood groups simultaneously in real-world gastric adenocarcinoma cohorts remain limited. By including a relatively large cohort with long-term follow-up and comprehensive clinicopathological evaluation, our study provides additional evidence suggesting that blood group systems have limited prognostic utility compared with established clinical factors such as metastasis and surgical treatment.

Limitations

The strengths of our study include a relatively large patient cohort and the use of real-world data. However, several limitations should be acknowledged. Missing data for certain clinical variables (such as incomplete staging information) may have limited the statistical power of the analyses. Furthermore, stage information was unavailable for a proportion of patients, which may have reduced the precision of prognostic analyses and limited the evaluation of stage-adjusted survival outcomes. Additionally, the retrospective and single-center design may introduce selection bias and unmeasured confounding factors. In addition, detailed information regarding performance status (ECOG PS), metastatic sites, treatment regimens, and laboratory-based prognostic biomarkers was not consistently available for all patients. Therefore, the potential impact of these established prognostic factors on survival outcomes could not be fully evaluated.

Nevertheless, our findings are clinically relevant as they reflect a patient population commonly encountered in routine practice. Overall, our results suggest that prognosis in gastric cancer is more strongly influenced by disease extent and treatment strategies rather than blood group characteristics.

CONCLUSION

This study suggests that ABO and Rh blood groups may not have a significant prognostic impact on survival in patients with gastric adenocarcinoma. These findings indicate that the prognostic value of blood groups, despite being easily accessible biomarkers in clinical practice, may be limited. In contrast, clinical factors such as the presence of metastasis and surgical treatment were confirmed to be key determinants of survival. Overall, our results suggest that disease extent and treatment strategies should be prioritized over blood group characteristics in prognostic evaluation in clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Van Training and Research Hospital Clinical Researches Ethics Committee (Date: 10.04.2026, Decision No: GOKAEK/2026-04/27).

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

Author Contributions
Concept: EŞ, AG; Design: EŞ, AG; Control: EŞ, AG; Data Collection and/or Processing: EŞ, AG; Analysis and/or Interpretation: EŞ, AG; Literature Review: EŞ, AG; Article Writing: EŞ, AG; Critical Review: EŞ, AG.

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Journal of Current Hematology & Oncology Research

Original Article

DOI: 10.51271/JCHOR-0091

Real world data of carfilzomib once weekly dosing in patients with relapsed and refractory multiple myeloma: single center experience

Meral Uluköylü Mengüç*[1], İbrahim Talha Şişman[2], Fatma Arıkan[3], Seçil Salim[3], Ahmet Mert Yanık[4], Özlem Candan[5], Derya Demirtaş[6], Hatice Gizem Günhan[7], Asu Fergün Yılmaz[3], Tayfur Toptaş[3], Işık Atagündüz[3], Ayşe Tülin Tuğlular[8]

[1]*Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Yeditepe University, İstanbul, Turkiye*
[2]*Department of Internal Medicine, Faculty of Medicine, Marmara University, İstanbul, Turkiye*
[3]*Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Marmara University, İstanbul, Turkiye*
[4]*Depatment of Hematology, Bursa City Hospital, Bursa, Turkiye*
[5]*Depatment of Hematology, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkiye*
[6]*Department of Hematology, Adana City Hospital, Adana, Turkiye*
[7]*Department of Internal Medicine, Marmara University Pendik Training and Research Hospital, İstanbul, Turkiye*
[8]*Department of Hematology, Acıbadem Fulya Hospital, İstanbul, Turkiye*

Cite this article: Uluköylü Mengüç M, Şişman İT, Arıkan F, et al. Real world data of carfilzomib once weekly dosing in patients with relapsed and refractory multiple myeloma: single center experience. *J Curr Hematol Oncol Res.* 2026;4(3):105-109. doi:10.51271/JCHOR-0091

***Corresponding Author:** Meral Uluköylü Mengüç, u_meral@hotmail.com

Received: 04/06/2026 ◆ **Accepted**: 10/07/2026 ◆ **Published**: 08/08/2026

ABSTRACT

Aims: Relapsed or refractory multiple myeloma (RRMM) remains a therapeutic challenge due to treatment resistance, comorbidities, and limited options after multiple therapy lines. Carfilzomib, a second-generation proteasome inhibitor, has demonstrated efficacy when administered once weekly at 70 mg/m² in combination with dexamethasone (wKd70), offering a convenient and effective alternative to twice-weekly schedules. We conducted a retrospective analysis of 32 RRMM patients treated with wKd70 between 2018 and 2023 at a single referral center.

Methods: Thirty-two RRMM patients were analyzed retrospectively. Patients with RRMM who received at least one course of carfilzomib at a dose of 70 mg/m² (administered on days 1, 8, and 15 of 28-day cycles) in combination with dexamethasone 40 mg/week were included in the study.

Results: The median age was 57.5 years (range: 43-75), and patients had received a median of three prior therapy lines. The overall response rate (ORR) was 62.1%. Median progression-free survival (PFS) was 16 months, and median overall survival (OS) was 51 months. Prior autologous stem cell transplantation was associated with significantly improved PFS and OS. Adverse events were common but mostly mild (grades 1-2) forms.

Conclusion: Our findings support wKd70 as an effective and well-tolerated treatment option for RRMM, even in heavily pretreated patients. The favorable survival outcomes compared to historical trials suggest a role for earlier use of this regimen.

Keywords: RRMM, carfilzomib , dexamethasone, progression free survival, autologous stem cell transplantation

INTRODUCTION

Quadruplet therapies, including an anti-CD38 monoclonal antibody, are the standard of care for patients with newly diagnosed, transplant-eligible or ineligible multiple myeloma (MM). In the relapsed refractory setting, the situation is more complex and depends on various factors, including prior therapies, the patient's performance status, comorbidities, and access to novel drugs or cellular therapies.[1]

Carfilzomib is an irreversible proteasome inhibitor approved both as a single agent and in combination with dexamethasone or lenalidomide for relapsed refractory MM (RRMM).[2] In the phase Ib/II CHAMPION trial, the maximum tolerated dose of once-weekly carfilzomib was established at 70 mg/m², resulting in an overall response rate (ORR) of 77 % and a median progression-free survival (PFS) of 12.6 months.[3] The phase III ARROW trial demonstrated that once-weekly carfilzomib at 70 mg/m² was superior to twice-weekly carfilzomib at 27 mg/m² regarding PFS and ORR, without increased toxicity.[4] Once-weekly dosing offers fewer hospital visits without sacrificing efficacy, making it a popular regimen, especially during the COVID-19 pandemic and thereafter.[5,6]

In this study, we analyzed the retrospective outcomes of RRMM patients treated with once-weekly carfilzomib at 70 mg/m² in combination with dexamethasone (wKd70), as followed up in a referral hospital of a faculty of medicine.

METHODS

The research protocol was approved by the Ethics Committee for Non-drug and Non-medical Device Researches at Marmara University Faculty of Medicine (Date: 24.02.2025, Decision No: 09.2024.1292). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Thirty-two RRMM patients followed by the department of hematology between 2018 and 2023 were analyzed retrospectively. Clinical and follow-up data were obtained from medical records. Patients with RRMM who received at least one course of carfilzomib at a dose of 70 mg/m² (administered on days 1, 8, and 15 of 28-day cycles) in combination with dexamethasone 40 mg/week at our institution after 2018 were included in the study. Patients who received carfilzomib at doses other than 70 mg/m² or those who received carfilzomib in combination with lenalidomide and dexamethasone were excluded. Patient demographics, disease characteristics, response to wKd70, and adverse event profiles were analyzed.

Genetic abnormalities, such as t(4;14), t(14;16), and deletion of 17p determined by fluorescence in situ hybridization (FISH), along with a complex karyotype identified through cytogenetics, were categorized as high-risk genetics. PFS was calculated from the date of wKd70 initiation to the date of documented disease relapse/progression or the date of death, whichever occurred first. Overall survival (OS) was calculated from the date of wKd70 initiation to the date of death from any cause or for surviving patients, censored at their last known alive visit. Response to wKd70 was assessed according to the International Myeloma Working Group (IMWG) criteria.[7] Treatment-emergent adverse events (TEAEs) were analyzed from medical records and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical Analysis

All data analyses were performed using IBM SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA). Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the assumption of normality. Continuous variables were presented based on normal distribution as mean±standard deviation or (in cases of non-normal distribution) as median (25^{th}-75^{th} percentile). Categorical variables were summarized as counts (percentages). Comparisons of continuous variables between groups were conducted using the Mann-Whitney U test and the Kruskal-Wallis test, given that the normality assumption did not hold. The Kaplan-Meier method was utilized for survival analysis. Associations between continuous variables were determined using Spearman correlation analysis, while the association between two categorical variables was examined using the Chi-square test. All statistical analyses were carried out with a significance level of 5%, considering a two-sided p-value <0.05 as statistically significant.

RESULTS

A total of 14 female and 18 male patients with RRMM who received wKd70 were retrospectively analyzed. The median age was 57.5 years (range: 43-75 years). The characteristics of the patients at the initiation of wKd70 are summarized in Table 1. IgG kappa and IgG lambda were the most frequent MM subtypes, respectively. International Staging System (ISS) scores were distributed as follows: 1-37.5%, 2-25%, and 3-37.5%. More than half of the patients exhibited standard-risk genetic abnormalities, while 12.5% were classified in the high-risk group; however, results were missing or not available for 9 patients. Twenty-five patients had at least one comorbid disease. Approximately one-third of the patients presented with extramedullary plasmacytoma, among 9 patients with extramedullary disease, 6 (66.6%) had paraosseous plasmacytoma and 3 had true extramedullary soft tissue involvement. The median number of prior therapy lines was three (range: 1-6). Only 9.7% of patients had received an anti-CD38 monoclonal antibody prior to wKd70. Autologous stem cell transplantation (ASCT) was performed in 87.5% of the patients in previous lines of treatment.

Response assessments were conducted in 22 patients at the time of data analysis; the 10 patients not analyzed were either receiving their first two courses of wKd70 or had discontinued

Table 1. Characteristics of patients at wKD70 initiation

Characteristics	Number (n)	Frequency (%)	Characteristics	Number (n)	Frequency (%)
Age (years)	**Median 57.5 (43-75)**		**Number of previous lines**	**Median 3 (1-6)**	
Gender			**Previous antiCD38 exposure**		
Male	18	56.3	Absent	28	90.3
Female	14	43.7	Present	3	9.7
MM type			**ISS**		
Ig G kappa	15	46.9	Stage I	12	37.5
Ig G lambda	4	12.5	Stage II	8	25
Ig A kappa	3	9.4	Stage III	12	37.5
Ig A lambda	3	9.4	**Lenalidomide refractorines**		
Kappa light	5	15.6	Absent	7	21.9
Lambda light	2	6.3	Present	25	78.1
Extramedullary disease			**Genetics**		
Absent	23	71.9	Missing	9	28.1
Present	9	28.1	Standard risk	19	59.4
			High risk	4	12.5
Comorbidity			**Previous ASCT**		
Absent	7	21.9	Yes	28	87.5
Present	25	78.1	No	4	12.5
Total	32	100	Total	32	100

ASCT: Autologous stem cell transplantation, Ig: Immunglobulin, MM: Multiple myeloma, ISS: International Staging System

therapy for various reasons. Response to wKd70 was available in 22 patients, with a median duration of wKd70 treatment of 12 months. Half of the patients exhibited a partial or greater response (see **Table 2**). Cytogenetic factors, lenalidomide refractoriness, the number of previous lines of therapy, and the presence of extramedullary disease were not associated with wKd70 response. Patients with a complex karyotype or those lacking cytogenetic data showed more progressive disease compared to patients with standard cytogenetics, though this difference was not statistically significant.

The majority of patients experienced both hematological and non-hematological adverse events with wKd70, though the severity was primarily mild (grades 1-2). Thrombocytopenia and anemia were the most pronounced hematological adverse events. Three patients discontinued carfilzomib due to toxicities, two of them were due to grade 3 pneumonia, and one was due to grade 3 neuropathy, while 17 patients discontinued due to disease progression. The median duration of follow-up was 20 months (range: 3-85 months), and 19 patients were alive at the time of data analysis. The median PFS was 16 months, with PFS rates at 2 and 5 years being 27.3% and 7.8%, respectively. The median OS was 51 months, with OS rates at 2 and 5 years being 62.6% and 33.7%, respectively. There was no association between gender, ISS stage, cytogenetic status, the number of previous lines of therapy, and PFS or OS. Only patients who had received ASCT exhibited longer PFS and OS compared to those who had not (**Table 3**).

DISCUSSION

This retrospective analysis of patients with RRMM receiving wKd70 therapy contributes valuable insights into the treatment's effectiveness and safety profile. Our cohort, comprising 14 female and 18 male patients with a median age of 57.5 years, presents characteristics consistent with the typical RRMM population, including a significant proportion of individuals with standard-risk genetic abnormalities. Notably, the ISS scores were evenly distributed between stages 1 and 3, with 37.5% of patients falling into each category. These demographic and clinical traits highlight the heterogeneity of RRMM and underscore the importance of personalized treatment approaches.

The study demonstrated that patients received a median of three prior therapy lines, implying that the cohort had undergone considerable therapeutic interventions. A

Table 2. Efficacy and safety analysis of wKD70

Parameter	Number (n)	Frequency (%)	Parameter	Number (n)	Frequency (%)
Carfilzomib response					
VGPR	10	31.3	Number of carfilzomib cycles	Median 12 (1-84)	
PR	6	18.3			
SD	4	12.5			
PD	2	6.3			
N/A	10	31.3			
Hematological AE			**Non-hematological AE**		
Absent	4	12.5	Absent	5	15.6
Present	28	87.5	Present	27	84.4
Anemia			**Cause of carfilzomib discontinuation**		
Grade 1	13	40.6	Progression	17	53.1
Grade 2	12	37.5	Toxicity	3	9.4
Grade 3	5	15.6	Ongoing	12	37.5
Grade 4	2	6.3			
Thrombocytopenia					
Grade 1	9	28.1	Duration of follow- up on carfilzomib (months)	Median 20 (3-85)	
Grade 2	16	50.0			
Grade 3	5	15.6			
Grade 4	2	6.3			
Total	32	100	Total	32	100

AE: Adverse event, VGPR: Very good partial response, PR: Partial response, SD: Stabil disease, PD: Progressive disease, NA: Not applicable

Table 3. Univariate analysis of association of wKd70 response and subgroups

Parameter	N/A n (%)	VGPR n (%)	PR n (%)	SD n (%)	PD n (%)	p
Cytogenetics						
Unknown	3 (30)	3 (30)	2 (33.7)	0 (0)	1(50)	0.193
Standard	6 (60)	7 (70)	4 (66.7)	2 (50)	0 (0)	
High risk	1 (10)	0 (0)	0 (0)	2 (50)	1 (50)	
Lenalidomide refractoriness						
Absent	1 (10)	4 (40)	1 (16.7)	0 (0)	1 (50)	0.298
Present	9 (90)	6 (60)	5 (83.3)	4 (100)	1 (50)	
Extramedullary disease						
Absent	7 (70)	6 (60)	6 (100)	2 (50)	2 (100)	0.337
Present	3 (30)	4 (40)	0 (0)	2 (50)	0 (0)	
Number of previous line						
1	1 (10)	0 (0)	1 (16.7)	0 (0)	0 (0)	0.868
2	5 (50)	2(20)	1 (16.7)	1 (25)	0 (0)	
3	2 (20)	5 (50)	2 (33.3)	2 (50)	1 (50)	
≥4	2 (20)	3 (30)	2 (33.3)	1 (25)	1 (50)	

Fisher's Exact test, p<0.05 statistical significant. VGPR: Very good partial response, PR: Partial response , SD: Stabil disease, PD: Progressive disease, NA: Not applicable

minority of patients had previously been treated with an anti-CD38 monoclonal antibody, which may indicate the evolving treatment landscape and the potential for leveraging new agents in combination therapies. The high percentage (87.5%) of patients undergoing ASCT prior to wKd70 aligns with established treatment protocols and emphasizes the role of ASCT in managing RRMM.

Regarding treatment responses, we observed that half of the patients achieved at least a partial response to wKd70, with response data available for 22 individuals. This suggests that wKd70 is an effective treatment option for this cohort, despite a relatively high rate of prior therapies. Interestingly, factors such as cytogenetic abnormalities, lenalidomide refractoriness, and extramedullary disease were not significantly associated with response rates. This finding suggests that wKd70 may offer consistent efficacy across diverse patient profiles, although the absence of significant statistical findings calls for further investigation into the influence of these variables. Our cohort exhibited an ORR of 62.1%, similar to the ARROW trial, but the distribution of responses was different.[4] None of our patients achieved CR, while 7% in the ARROW trial did. Most of our patients achieved VGPR, slightly surpassing the original cohort. This discrepancy can be explained by the higher proportion of advanced disease of ISS stage 3 patients in the ARROW trial.[4,8] The Korean group reported higher ORRs of 71.1%, but the intensity of responses was not mentioned.[9] The Japanese group reported an ORR comparable to our cohort, with partial responses comprising the majority of responses, similar to our patients. Despite these differences, the ORR reported in the Japanese study was 66.1%, surpassing our observed response rate of 62.6%.[10] Earlier introduction of carfilzomib in treatment regimens has been linked to better response rates, further supported by various studies.[11,12] While only one patient in our cohort received wKd70 as second-line therapy, 17.5% of patients in the Japanese study received this same treatment as second-line therapy, highlighting potential differences in treatment strategies among regions. Another prospective multicenter observational study of 300 patients with RRMM from Asia Pacific region reported an ORR of 54.5% for patients receiving Kd but dose of carfilzomib was not detailed suggesting biweekly dosing schema that requires discontination of therapy by the 18th cycle. Mean age at carfilzomib initiaition was 66.3 years. Patients with high risk genetic abnormalities constituted 37.7% of total cohort and the frequency of ISS stage 3 patients was 26.3%.[13]

Our cohort exhibited a median PFS of 16 months, which is a notably longer duration compared to the 11.2 months reported in the phase 3 ARROW trial for patients receiving once-weekly carfilzomib.[4] Moreover subgroup analysis of the ARROW trial demonstrated a similar median PFS of 12.2 months in patients younger than 65 years old.[8] This difference in median PFS may be attributed to demographic variations in the patient populations, as a larger proportion of standard-risk patients were included in our study. Specifically, only 20% of participants in the ARROW trial were classified as standard risk, while 59.4% of our retrospective cohort fell into this category. The variance in outcomes may also be influenced by the age distribution of the studied populations, with a median age of 66 years in the ARROW trial compared to our cohort's median age of 57 years. This younger demographic in our study likely correlates with a better overall performance status, which may lead to improved treatment responses.

Similar trends are observed in other studies involving Kd70 therapy. For instance, a recent evaluation from four referral centers in Korea reported a shorter median PFS of 5.6 months, despite also having a median age of 66 years.[9] The dose of carfilzomib was biweekly 56 mg/m^2 in a majority of patients but a subset of patients received wKD70 after May 2021 in this trial. This cohort included a higher proportion of high-risk genetic abnormalities (18.4%), which may explain the decreased survival compared to both the ARROW trial and our cohort. Their definition of high-risk status relied solely on the presence of t(4;14) or t(14;16), while our criteria included additional factors such as deletion 17p by FISH and complex karyotype analyses.

Moreover, another retrospective study assessing treatment adherence and effectiveness in carfilzomib-based regimens reported a median PFS of 13.4 months among patients receiving Kd, although the specific dosing of carfilzomib was not detailed.[14] In contrast, the Japanese observational study indicated a median PFS of 9.5 months among 120 RRMM patients.[10] The higher percentage of high-risk patients (29.2%) in the Japanese cohort and a median age of 70 years likely contributed to less favorable outcomes compared to our younger cohort, which had a lower proportion of high-risk patients. Furthermore, fewer patients in Japanese study had previously undergone ASCT compared to our cohort, a factor that has been associated with longer PFS and OS in our analysis. Median time to progression was 23.7 months in Kd group in the prospective observational trial from Asia Pacific region.[13]

The median OS of 51 months, along with 2- and 5-year OS rates of 62.6% and 33.7%, reflects favorable long-term outcomes. In the ARROW trial median follow up for OS was 13.2 months and the data was immature at the interim analysis. Median OS was reported to be of 24 months by Park et al.[9] and was 41.6 months by Quach et al.[13] whereas it was not reached in Abe et al.'s[10] study. Notably, patients who had undergone ASCT exhibited considerably longer PFS and OS, reinforcing the established premise that ASCT remains a critical determinant of survival in RRMM patients.

Safety data revealed that while adverse events were common, they were primarily of mild severity (grades 1-2). Thrombocytopenia and anemia were the most frequently reported hematological adverse events, which underscores the need for vigilant monitoring during treatment. The discontinuation of therapy primarily due to disease progression rather than toxicity illustrates the treatment's overall tolerability in this patient population. Any grade adverse events occurred in 93% of our cohort, comparable to the ARROW study.[4] Treatment-related adverse events leading to treatment discontinuation occurred in 9.4% of our patients, whereas it was 8% in the ARROW trial. Anemia and thrombocytopenia were the most frequent hematological adverse events in our group, with anemia being the most prevalent in the ARROW trial. In the Korean study, the total frequency of any grade adverse events was not mentioned, but neutropenia and lymphopenia were the most reported hematological adverse events.[9] The Japanese group reported

an incidence of adverse events leading to discontinuation of 21.7%, which was higher than our rates. The most frequent hematological adverse events in this cohort were thrombocytopenia and anemia, similar to our findings.[10] Asia Pacific group also reported a rate of 7.9% for adverse events leading to discontinuation.[13]

Limitations

Our study has several limitations that should be acknowledged. First, only a small proportion of patients had previously received anti-CD38-based induction therapy, which may limit the generalizability of our findings to contemporary treatment settings where anti-CD38-containing regimens are increasingly used. The relatively low use of anti-CD38-based induction therapy in our cohort largely reflects the treatment landscape and reimbursement policies during the study period. In addition, the retrospective, single-center design and the relatively small sample size may have introduced selection bias and limited the statistical power of the study. Finally, the absence of a direct comparison with the conventional twice-weekly 27 mg/m² carfilzomib regimen precludes definitive conclusions regarding the comparative efficacy and safety of the once-weekly schedule. The retrospective nature of our study also limits the accurate reporting of adverse events, and the lack of standardized records makes comparison difficult. Limited number of patients is also a disadvantage but most of the literature discussed above are composed of multicenter data compared to our single center records.

CONCLUSION

As a result, this study provides compelling evidence that wKd70 therapy is associated with meaningful treatment responses and a manageable safety profile in a diverse cohort of RRMM patients. Future research should aim to validate these findings in larger, multi-center studies and explore the optimally sequencing of wKd70 with other novel therapies, particularly in patients with high-risk disease characteristics.

ETHICAL DECLARATIONS

Ethics Committee Approval

The research protocol was approved by the Ethics Committee for Non-drug and Non-medical Device Researches at Marmara University Faculty of Medicine (Date: 24.02.2025, Decision No: 09.2024.1292).

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

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

Author Contributions

Concept: MUM, ATT; Design: MUM, ITS, ATT; Control: MUM, ITS, FA; Data Collection and Processing: ITS, FA, SS, AMY, OC, DD, HGG, AFY, TT, IA; Analysis and Interpretation: MUM, ITS, FA; Literature Review : MUM, ITS, FA, SS, AMY, OC, DD, HGG, AFY, TT, IA; Article Writing: MUM; Critical Review: MUM, ITS, ATT.

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Journal of Current Hematology & Oncology Research

Original Article

DOI: 10.51271/JCHOR-0092

Safety profile and predictors of procedural complications in automated erythrocytapheresis for sickle cell disease: a single-center retrospective cohort study

Sinan Mersin*[1], Pelin Aytan[1], Mahmut Bakır Koyuncu[1], Seher Yontar[2], Hamit Ünver[2], Aycan Erkenekli[1], Esin Oğuz Kocan[1], Enver Tekin[1], Eyüp Naci Tiftik[1]

[1]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Mersin University, Mersin, Turkiye
[2]Department of Apheresis, Faculty of Medicine, Mersin University, Mersin, Turkiye

Cite this article: Mersin S, Aytan P, Koyuncu MB, et al. Safety profile and predictors of procedural complications in automated erythrocytapheresis for sickle cell disease: a single-center retrospective cohort study. *J Curr Hematol Oncol Res.* 2026;4(3):110-115. doi:10.51271/JCHOR-0092

***Corresponding Author:** Sinan Mersin, sinanmersin86@msn.com

Received: 05/05/2026 ◆ **Accepted**: 13/07/2026 ◆ **Published**: 08/08/2026

ABSTRACT

Aims: Automated erythrocytapheresis (red cell exchange; RCE) is an established therapeutic modality in sickle cell disease (SCD), yet procedural complication data from Turkiye and the Eastern Mediterranean region remain limited. This study evaluated the safety profile of RCE in adult SCD patients at a single tertiary center and identified clinical and procedural predictors of adverse events.

Methods: We conducted a retrospective cohort study of all automated RCE procedures performed in adult patients (≥18 years) with SCD between January 2015 and December 2020. Adverse events were graded according to the World Apheresis Association (WAA) classification (grades 1-4). Procedures with and without complications were compared using the Mann-Whitney U test for continuous variables and Fisher's exact or Chi-square tests for categorical variables.

Results: A total of 274 procedures in 83 patients were analyzed. The overall complication rate was 12.4% (n=34): grade 1 in 4.4%, grade 2 in 5.8%, and grade 3 in 2.2%; no grade 4 events were observed. Vascular and mechanical dysfunction accounted for 67.6% of complications. Complication rates declined from 31.2% in 2015 to 5.5% in 2018, with no severe events after 2016. Higher pre-procedure hemoglobin (9.4 vs. 8.9 g/dl; p=0.021) and hematocrit (27.0% vs. 25.9%; p=0.022) were significantly associated with complication occurrence. MCS® procedures had a substantially higher complication rate (42.9% vs. 10.8%; p=0.003) and severe event rate (28.6% vs. 0.8%; OR=51.4; p=0.0001) versus the Spectra Optia® system. Indication and hydroxyurea use were not significantly associated with outcomes.

Conclusion: Automated RCE is a safe procedure in adult SCD patients with a low rate of severe adverse events. Higher pre-procedure hemoglobin and hematocrit and use of the MCS® device were associated with increased complication risk. The marked temporal decline in complication rates reflects institutional learning and device transition to the Spectra Optia® platform.

Keywords: Hemoglobin S, vaso-occlusive crisis, transfusion medicine, adverse events, apheresis device, fetal hemoglobin

INTRODUCTION

Sickle cell disease (SCD) is one of the most prevalent monogenic disorders worldwide, affecting approximately 300.000 newborns annually and posing a significant public health burden particularly across sub-Saharan Africa, the Middle East, and the Mediterranean basin.[1,2] In Turkiye, SCD is endemic along the southern and southeastern coastal regions, where the carrier frequency reaches up to 10% in certain provinces of the Çukurova and Hatay regions.[3] Mersin province, situated within this high-prevalence belt, represents one of the largest SCD patient populations in the country, making it an important center for the longitudinal study of disease-related complications and treatment outcomes.

SCD is caused by a point mutation in the β-globin gene, resulting in the substitution of valine for glutamic acid at position 6 of the β-globin chain and the production of hemoglobin S (HbS). Under conditions of deoxygenation, HbS polymerizes, leading to erythrocyte sickling, chronic hemolysis, and progressive vaso-occlusion.[4] These pathophysiological processes underlie the broad spectrum of acute and chronic complications that characterize SCD, including painful vaso-occlusive crises, acute chest syndrome (ACS), stroke, pulmonary hypertension, and hepatic dysfunction.[5]

Red cell transfusion remains a cornerstone of SCD management. Among the available modalities, automated

erythrocytapheresis—also termed red cell exchange (RCE)—has emerged as the preferred approach in many centers given its ability to rapidly reduce the circulating HbS fraction while minimizing iron overload.[6,7] The American Society for Apheresis (ASFA) classifies RCE as a category I indication for stroke prevention in SCD, and its use has expanded to encompass additional indications including ACS, recurrent painful crises, preoperative preparation, and intrahepatic cholestasis.[8] The STOP and STOP 2 randomized trials established the efficacy of chronic RCE programs in reducing primary and recurrent stroke risk.[9,10]

Despite its clinical advantages, RCE is not without procedural risks. Complications include vascular access problems, catheter-related thrombosis, allergic reactions, hemodynamic instability, and—less frequently—hemolysis.[11,12] Adverse events are graded using standardized scales such as the World Apheresis Association (WAA) classification system.[13] Although several Western studies have described complication profiles of RCE in SCD, data from Turkiye and the Eastern Mediterranean region remain limited.[14,15] The present study aimed to evaluate the safety profile of automated erythrocytapheresis in adult SCD patients at a single tertiary center over a five-year period (2015–2020) and to identify clinical and procedural predictors of adverse events.

METHODS

Ethics

The study was approved by the Health Sciences Researches Ethics Committee of Mersin University Rectorate (Date: 28.04.2026, Decision No: 2026/248). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The requirement for individual informed consent was waived given the retrospective nature of data collection.

Study Design and Setting

This was a retrospective cohort study conducted at the Department of Hematology, Mersin University Faculty of Medicine, Mersin, Turkiye. All automated RCE procedures performed in adult patients with SCD between January 2015 and December 2020 were identified from the departmental apheresis registry and included in the analysis.

Patient Population

Adult patients (aged ≥18 years) with a confirmed diagnosis of SCD who underwent at least one automated RCE procedure during the study period were eligible for inclusion. Procedures were the primary unit of analysis; where a single patient underwent multiple procedures, each session was treated as a separate observation. As this approach does not account for potential within-patient clustering, the resulting limitation is addressed in the discussion.

Apheresis Procedure

All RCE procedures were performed using automated cell separators, predominantly the Spectra Optia® apheresis system (Terumo BCT, Lakewood, CO, USA) and, in a minority of early procedures, the MCS® device (Haemonetics, Boston, MA, USA). Anticoagulation was achieved with acid citrate dextrose solution A (ACD-A). Vascular access was established via peripheral venous catheterization in the majority of procedures; central venous catheterization was employed when peripheral access was inadequate.

Data Collection

Procedural and clinical data were extracted from the institutional apheresis registry and electronic medical records. Variables collected included patient demographics (age, gender, body weight), clinical characteristics (diagnosis, indication for RCE, referring department), pre- and post-procedure laboratory values (hemoglobin [Hb], hematocrit [Hct], white blood cell count [WBC], platelet count [PLT]), procedural parameters (device type, vascular access type, inlet flow rate, donor erythrocyte volume [DEV], total exchange volume [TEV], procedure duration), and concomitant hydroxyurea use. Where individual data fields were missing in the registry or medical records, the affected variable was recorded as missing for that procedure; the number of available observations is reported for each variable in the corresponding table.

Complication Classification

Adverse events were graded according to the WAA classification: grade 1 (mild, no intervention required), grade 2 (moderate, medical intervention required), grade 3 (severe), and grade 4 (life-threatening or fatal).[13] Three composite outcome variables were defined: (i) any complication (grade 1-4); (ii) severe complication (grade 3-4); and (iii) complication type, categorized as vascular/mechanical, allergic/systemic, hemodynamic, or other.

Statistical Analysis

Continuous variables are expressed as median and interquartile range (IQR). Categorical variables are presented as counts and percentages. Comparisons between groups were performed using the Mann–Whitney U test for continuous variables and Fisher's exact test or Pearson Chi-square for categorical variables. A two-tailed p value of less than 0.05 was considered statistically significant. No imputation was performed for missing data. All analyses were performed using Python (version 3.12; Python Software Foundation, Wilmington, DE, USA) with the SciPy and pandas libraries.

RESULTS

Study Population and Procedural Characteristics

A total of 274 RCE procedures performed in 83 adult patients with SCD were included. Three procedures were excluded due to patient age below 18 years. The median number of procedures per patient was 1 (IQR 1-2; range 1-38). Of the 274 procedures, 151 (55.1%) were performed in male patients. Median patient age was 31 years (IQR 23-44) and median body weight was 63 kg (IQR 54-72). Baseline and procedural characteristics are summarized in **Table 1**.

The most frequent indication was stroke prophylaxis/treatment (153 procedures, 55.8%), followed by painful vaso-occlusive crisis (40, 14.6%), hepatic or intrahepatic cholestasis (35, 12.8%), preoperative preparation or pregnancy-related indications (19, 6.9%), and ACS (18, 6.6%). The Spectra Optia® system was used in 259 procedures (94.5%), with the MCS® device employed in 14 (5.1%). Peripheral venous access was established in 236 procedures (86.1%) and central venous catheterization in 28 (10.2%).

Table 1. Baseline and procedural characteristics of the study population

Characteristic	Median (IQR) or n (%)	Available/range
General		
Total procedures	274	83 patients
Procedures per patient	1 (1–2)	range 1–38
Gender—male	151 (55.1%)	
Age (years)	31 (23–44)	range 18–87
Body weight (kg)	63 (54–72)	
Indication for RCE		
Stroke prophylaxis/treatment	153 (55.8%)	
Painful crisis	40 (14.6%)	
Hepatic/intrahepatic cholestasis	35 (12.8%)	
Preoperative/pregnancy-related	19 (6.9%)	
Acute chest syndrome	18 (6.6%)	
Other	9 (3.3%)	
Device and vascular access		
Spectra Optia® system	259 (94.5%)	
MCS® device	14 (5.1%)	
Peripheral venous access	236 (86.1%)	
Central venous access	28 (10.2%)	
Hydroxyurea use	206/227 (90.7%)	47 unknown
Pre-procedure laboratory values		
Hemoglobin (g/dl)	8.9 (7.8–9.9)	n=271
Hematocrit (%)	26.0 (22.0–29.0)	n=272
WBC ($\times 10^3/\mu L$)	10.8 (7.1–14.9)	n=269
Platelet ($\times 10^3/\mu L$)	359 (251–475)	n=272
Post-procedure laboratory values		
Hemoglobin (g/dl)	9.3 (8.8–9.9)	n=257
Hematocrit (%)	27.0 (26.0–29.0)	n=259
Procedural parameters		
Duration (min)	85 (68–102)	n=263
Inlet flow rate (ml/min)	40 (35–45)	n=260
Donor erythrocyte volume—DEV (ml)	902 (733–1067)	n=270
Total exchange volume—TEV (ml)	1057 (926–1272)	n=271

Data are presented as median (interquartile range) for continuous variables and n (%) for categorical variables. IQR: Interquartile range, RCE: Red cell exchange, WBC: White blood cell count, Min: Minute, DEV: Donor erythrocyte volume, TEV: Total exchange volume

Complication Incidence and Grade Distribution

Procedural complications were recorded in 34 of 274 procedures (12.4%). Of these, 12 events (4.4%) were grade 1, 16 (5.8%) were grade 2, and 6 (2.2%) were grade 3. No grade 4 events were observed. Annual complication rates declined from 31.2% in 2015 (10/32 procedures) to 5.5% in 2018 (3/55), with no severe events recorded after 2016.

Types of Complications

Among the 34 complicated procedures, vascular or mechanical dysfunction was the predominant category (23 events, 67.6%), comprising insufficient blood flow during the procedure (n=14), catheter-related thrombosis or fibrin formation (n=7), and circuit or set errors (n=2). Allergic or systemic reactions accounted for 6 events (17.6%), comprising urticaria (n=5) and chills or rigors (n=1); hemodynamic instability (hypotension) accounted for 2 events (5.9%); and the remaining 3 events (8.8%) comprised one patient-initiated discontinuation and two other or mixed events. Full grade and type distributions are presented in Table 2.

Table 2. Distribution of complication grades and types

Category	n	% of all procedures
Complication grade distribution (n=274 procedures)		
No complication	240	87.6%
Any complication	34	12.4%
Grade 1—mild	12	4.4%
Grade 2—moderate	16	5.8%
Grade 3—severe	6	2.2%
Grade 4—life-threatening	0	0.0%
Severe complications (grade 3–4)	6	2.2%
Complication type (among n=34 procedures with complications)		
Category	**n**	**% of all complications**
Vascular/mechanical	23	67.6%
Insufficient blood flow	14	41.2%
Circuit thrombosis/fibrin formation	7	20.6%
Circuit/set error	2	5.9%
Allergic/systemic reaction	6	17.6%
Urticaria	5	14.7%
Chills/rigors	1	2.9%
Hemodynamic (hypotension)	2	5.9%
Patient-initiated discontinuation	1	2.9%
Other/mixed	2	5.9%

WAA grades: Grade 1, mild; Grade 2, moderate; Grade 3, severe; Grade 4, life-threatening. Upper panel: % of all 274 procedures. Lower panel: % of the 34 complicated procedures

Factors Associated with Complications

Comparisons between procedures with and without complications are presented in Table 3. Pre-procedure Hb was significantly higher in the complication group (9.4 vs. 8.9 g/dl; p=0.021), as was pre-procedure Hct (27.0% vs. 25.9%; p=0.022) and post-procedure Hct (28.0% vs. 27.0%; p=0.039). No significant differences were observed for age, body weight, WBC, PLT, procedure duration, inlet flow rate, DEV, or TEV. Among categorical variables, gender (p=1.000), vascular access type (p=0.763), clinical indication (p=0.466), and hydroxyurea use (p=0.455) were not significantly associated with complication occurrence.

Severe vs. Mild Complications

Comparison of procedures with severe (grade 3, n=6) versus mild-to-moderate (grade 1-2, n=28) complications revealed no statistically significant differences for any variable examined, including age (40 vs. 31.5 years; p=0.331), DEV (700 vs. 973 ml; p=0.139), and pre-procedure Hb (9.3 vs. 9.4 g/dl; p=0.482). These analyses should be interpreted with caution given the small number of severe events (n=6).

Device Type, Indication, and Hydroxyurea Use

Device type was significantly associated with complication occurrence. MCS® procedures had a substantially higher complication rate compared with Spectra Optia® (42.9% vs. 10.8%; p=0.003). This difference was even more pronounced for severe events (28.6% vs. 0.8%; OR=51.4; p=0.0001). Clinical indication (p=0.466) and hydroxyurea use (p=0.455) were not significantly associated with complications. The high HU utilization rate (90.7% of procedures with available medication data) substantially limited statistical power to detect an HU-related effect.

Table 3. Comparison of clinical and procedural variables between procedures with and without complications

Variable	Complication+ (n=34)	Complication– (n=240)	p value	Test
	Median (IQR) or n (%)	Median (IQR) or n (%)		
Continuous variables				
Age (years)	37.0 (23.0–43.0)	30.0 (23.0–44.0)	0.877	MWU
Body weight (kg)	61.0 (55.0–73.5)	63.0 (54.0–72.0)	0.966	MWU
Pre-procedure Hb (g/dl)	9.4 (8.8–10.5)	8.9 (7.8–9.8)	**0.021**	MWU
Post-procedure Hb (g/dl)	9.5 (9.1–9.9)	9.3 (8.8–9.9)	0.133	MWU
Pre-procedure Hct (%)	27.0 (24.0–31.0)	25.9 (21.6–29.0)	**0.022**	MWU
Post-procedure Hct (%)	28.0 (27.0–29.0)	27.0 (26.0–29.0)	**0.039**	MWU
WBC ($\times 10^3/\mu L$)	9.5 (7.1–13.1)	10.9 (7.2–15.3)	0.389	MWU
Platelet ($\times 10^3/\mu L$)	336 (246–447)	361 (253–478)	0.474	MWU
Duration (min)	91 (78–100)	84 (67.5–103.5)	0.157	MWU
Inlet flow rate (ml/min)	40 (35–50)	40 (35–45)	0.604	MWU
DEV (ml)	911 (693–1274)	900 (762–1066)	0.655	MWU
TEV (ml)	1100 (904–1357)	1051 (932–1264)	0.548	MWU
Categorical variables				
Male gender	19 (55.9%)	132 (55.0%)	1.000	Fisher
Central vascular access	4 (11.8%)	24 (10.0%)	0.763	Fisher
MCS® device	6 (17.6%)	8 (3.3%)	**0.003**	Fisher
Stroke prophylaxis indication	17 (50.0%)	136 (56.7%)	0.466	χ^2
Hydroxyurea use[a]	20 (87.0%)	186 (91.2%)	0.455	Fisher

Bold p values indicate statistical significance ($p<0.05$). Continuous variables expressed as median (IQR), compared by Mann–Whitney U test (MWU). Categorical variables expressed as n (%), compared by Fisher's exact test or Pearson Chi-square (χ^2). Hb: Hemoglobin, Hct: Hematocrit, WBC: White blood cell count, Min: Minute, DEV: Donor erythrocyte volume, TEV: Total exchange volume. [a] Hydroxyurea analysis restricted to 227 procedures with available medication data.

DISCUSSION

In this retrospective cohort study of 274 RCE procedures in 83 adult SCD patients, the overall procedural complication rate was 12.4%, with severe adverse events occurring in 2.2% of procedures and no grade 4 events recorded. Vascular and mechanical complications predominated (67.6%). Higher pre-procedure Hb and Hct were significantly associated with complication occurrence, and device type was the categorical variable most strongly associated with both any complication and severe adverse events.

Overall Complication Rate in Context

The overall complication rate of 12.4% is broadly consistent with previously published series of therapeutic apheresis in SCD, where reported rates range from approximately 5% to over 20% depending on patient population, grading systems, and era of data collection.[11,12] Studies applying rigorous prospective adverse event capture tend to report higher rates than those relying on retrospective chart review alone.[13] The low rate of severe events (2.2%) and absence of grade 4 complications align with the generally favorable safety profile of modern automated apheresis.[11,12]

Predominance of Vascular and Mechanical Complications

Access-related problems consistently represent the most frequent adverse event category in therapeutic apheresis.[11,16] The high proportion of peripheral venous access use in our cohort (86.1%) is likely a contributing factor: peripheral veins are inherently more susceptible to flow insufficiency during extracorporeal circulation, particularly in SCD patients with compromised peripheral vasculature.[17] Allergic and systemic reactions (17.6%) are consistent with the known immunological burden of chronically transfused SCD patients.[18]

Declining Complication Rates Over Time

The marked temporal decline in complication rates—from 31.2% in 2015 to 5.5% in 2018—and the confinement of all severe complications to 2015–2016 are highly suggestive of a center-level learning curve effect. The early study period coincided with predominant use of the older MCS® device. Institutional factors including growing procedural experience, protocol refinement, and standardization of vascular access management likely also contributed.[19,20]

Pre-Procedure Hemoglobin and Hematocrit as Risk Factors

Higher pre-procedure Hb and Hct were significantly associated with complication occurrence. A plausible mechanistic explanation relates to blood rheology: higher Hct reflects greater red cell mass and increased whole-blood viscosity within the extracorporeal circuit, predisposing to slower flow rates, increased resistance, and circuit clotting—the dominant complication type in our series.[21] SCD patients with higher resting Hb levels may also carry a larger proportion of dense, dehydrated sickle erythrocytes prone to aggregation under shear stress.[21] These findings, if confirmed prospectively, may support individualized pre-procedure Hb targets or preemptive hydration strategies to reduce complication risk.

Device Type as a Major Determinant of Complication Risk

Among the categorical variables examined, device type showed the strongest association with complications. MCS® procedures had a four-fold higher rate of any complication

(42.9% vs. 10.8%; p=0.003) and a markedly higher rate of severe complications (OR=51.4; p=0.0001) compared with the Spectra Optia® system. These findings are consistent with the established technological advantages of the Spectra Optia®, which employs continuous real-time inlet and outlet Hct monitoring and automated flow optimization algorithms.[22,23] An important caveat is the temporal confounding between device type and study period: MCS® procedures were concentrated in 2015–2016, when overall complication rates were highest. Despite this limitation, the magnitude of the association supports a genuine contribution of device technology to patient safety.

Hydroxyurea Use and Indication

Neither clinical indication nor hydroxyurea use was significantly associated with complication rates. Hydroxyurea reduces sickling by increasing fetal Hb levels and has anti-inflammatory and rheological effects that might theoretically influence blood handling in the extracorporeal circuit.[24] However, given that 90.7% of medication-documented procedures were performed in HU-treated patients, our study was severely underpowered to detect any meaningful difference. The null finding should be interpreted accordingly rather than as evidence of absence of effect.

Limitations

This study represents one of the largest single-center adult SCD apheresis series from Turkiye, a high-prevalence region with limited published data. Standardized WAA grading, a five-year observation window, and comprehensive procedural data collection are notable strengths. Several limitations should nonetheless be acknowledged. First, the analytical unit was the individual procedure, and multiple procedures performed in the same patient were treated as separate observations. Because repeated measurements from the same individual are not statistically independent, this approach may introduce a within-patient clustering effect that could influence the observed associations; the results should therefore be interpreted with this potential dependency in mind, and future studies should employ clustered or mixed-effects models to account for it. Second, all comparisons were univariate, and no multivariable analysis was performed to adjust for potential confounders; consequently, the reported associations cannot be considered independent of one another, and the relationship between device type and study period in particular remains confounded. Third, the retrospective design carries a risk of incomplete or inconsistent complication documentation, especially for milder events in the earlier study years. Fourth, the small number of severe adverse events (n=6) markedly limited statistical power for analyses of severe complications. Fifth, hydroxyurea data were missing for 47 procedures (17.2%), which further reduced power for the medication-related analysis. Finally, the single-center design may limit the generalizability of the findings to other settings.

CONCLUSION

Automated RCE is a safe modality for the management of adult patients with SCD, with an overall procedural complication rate of 12.4% and a severe adverse event rate of 2.2%. No life-threatening complications were recorded. Higher pre-procedure Hb and Hct values were significantly associated with increased complication risk—a novel finding warranting prospective validation. The Spectra Optia® apheresis system demonstrated a markedly superior safety profile compared with the MCS® device. The substantial improvement in complication rates over the study period reflects the combined impact of institutional learning, protocol maturation, and device modernization. These findings may support protocol development and quality improvement at centers establishing or expanding erythrocytapheresis programs for patients with SCD.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Health Sciences Researches Ethics Committee of Mersin University Rectorate (Date: 28.04.2026, Decision No: 2026/248).

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

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

Author Contributions

Concept: SM, PA, SY, HÜ, MBK, AE, EOK, ET, ENT; Design: SM; Control: ENT; Data Collection and/or Processing: PA, MBK, AE, EOK, ET; Analysis and/or Interpretation: SM; Literature Review: SM; Article Writing: SM; Critical Review: ENT.

Acknowledgments

The authors wish to thank all physicians, nurses, and healthcare personnel of the Department of Hematology and the Apheresis Unit at Mersin University Faculty of Medicine Hospital for their dedicated contributions to patient care and their meticulous recording of procedural data, without which this study would not have been possible.

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Case Report

DOI: 10.51271/JCHOR-0093

Primary spinal extramedullary diffuse large B–cell lymphoma presenting with initial spinal cord compression: a case report

Ömer Candar*[1], Ömer Ekinci[2], Ali Doğan[3], Mehmet Aslan[2], İbrahim Aras[4], Cengiz Demir[3]

[1]Department of Hematology, Eskişehir City Hospital, Eskişehir, Turkiye
[2]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Fırat University, Elazığ, Turkiye
[3]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Van Yüzüncü Yıl University, Van, Turkiye
[4]Department of Medical Pathology, Faculty of Medicine, Van Yüzüncü Yıl University, Van, Turkiye

Cite this article: Candar Ö, Ekinci Ö, Doğan A, Aslan M, Aras İ, Demir C. Primary spinal extramedullary diffuse large B–cell lymphoma presenting with initial spinal cord compression: a case report. *J Curr Hematol Oncol Res.* 2026;4(3):116-119. doi:10.51271/JCHOR-0093

***Corresponding Author:** Ömer Candar, oeml6365@gmail.com

Received: 04/08/2025 ◆ **Accepted**: 07/10/2025 ◆ **Published**: 08/08/2026

ABSTRACT

Extranodal lymphomas, by definition, can involve any organ or tissue. Brain parenchyma, spinal cord, eyes, cranial nerves, and meninx are extranodal regions that show involvement at much lower rates. It is quite rare for lymphoma patients to present to the hospital with symptoms and findings associated with spinal cord compression as the initial presentation. This condition can lead to irreversible autonomic dysfunction, and motor and sensory loss. Here, we present a rare primary spinal intradural extramedullary diffuse large B–cell lymphoma (DLBCL) case who presented with acute neurological symptoms and no findings of cerebral involvement or involvement at any other site. Magnetic resonance imaging (MRI) was performed for the spinal region. Surgical procedure was performed for the detected mass. Immunohistochemical staining of the excised mass was performed. In the surgical operation, the mass showed partial invasion of the vertebral bone and the surrounding muscle. Considering the rapid progression of the neurological deficit, surgical resection was performed primarily for spinal decompression. Subsequently, 6 courses of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R–CHOP) chemotherapy regimen were given for the residual tissue, and radiotherapy was administered to the involved region. Timely and effective treatment achieved a complete recovery of motor and sensory function. The patient remains in complete remission without clinical or radiological relapse under follow-up after nearly 4 years. Although it is a rare condition, primary spinal intradural extramedullary DLBCL disease should be suspected in patients who present with acute neurological symptoms and have no signs of cerebral involvement or involvement elsewhere, and necessary investigations should be performed by paying attention to this.

Keywords: Epidural, diffuse large B–cell lymphoma, lymphoma, spinal cord compression, spinal non–Hodgkin lymphoma

INTRODUCTION

Primary central nervous system (CNS) lymphomas comprise 4% of all brain tumors and 4-6% of extranodal lymphomas. The extranodal disease typically manifests as intermediate and high-grade non–Hodgkin lymphoma (NHL).[1] Extranodal lymphomas define the involvement of any organ or tissue, while the brain parenchyma, spinal cord, eyes, cranial nerves, and meninx are extranodal regions that show involvement much less commonly. Approximately 90-95% of primary CNS lymphomas are large B–cell lymphomas (DLBCL) and the risk is higher in patients with inherited immunodeficiency syndromes, HIV/AIDS, and in organ transplant recipients.[2,3] Spinal cord lymphoma is the least prevalent form of CNS lymphoma and is associated with a poor prognosis if untreated. It can involve the lower cervical or upper thoracic regions and manifests symptoms associated with the involved region.[4] Magnetic resonance imaging (MRI) examination can demonstrate an expansile mass lesion. The differential diagnosis includes glioma, metastatic tumor, toxoplasma infection, sarcoidosis, abscess, and progressive multifocal leukoencephalopathy. A tissue biopsy is essential for a definitive diagnosis.

As the initial presentation, it is quite unusual for lymphoma patients to present to the hospital with symptoms and findings associated with spinal cord compression. However, spinal cord compression, which can lead to irreversible autonomic dysfunction, and motor and sensory loss, occurs in 0.1-6.5% of NHL patients and can be the presenting problem.[5] Cases of primary spinal DLBCL are quite rare, with only a few reported cases and short case series.[6] Here, we present a rare primary isolated spinal intradural extramedullary DLBCL case who presented with acute neurological symptoms and did not show cerebral involvement or involvement at any other site.

CASE

41–year–old male patient presented to our hospital with thoracic back pain and progressive complaints of weakness, numbness, and difficulty in ambulation in bilateral lower extremities. His history included hypertension controlled by medical treatment. His history was unremarkable for recent diseases and medication and narcotic drug use. Neurological examination revealed 3/5 strength in bilateral legs and a sensory deficit up to the level of the umbilicus. Bilateral lower extremities showed loss of sensation and reduced motor function, with no fecal or urinary incontinence. On other systemic examinations, there were no hepatomegaly, splenomegaly, lymphadenopathy, or palpable masses. On spinal MRI examination, a well–circumscribed intradural extramedullary mass with a craniocaudal extension of 6 cm and an AP diameter of 1 cm that was isointense to the spinal cord on T1–weighted sequences and slightly hyperintense on T2–weighted series, and showed diffuse homogenous contrast enhancement after intravenous contrast agent injection was determined between the vertebral levels T6 and T8. Also, the narrowing of the spinal cord secondary to compression by the lesion was visualized (**Figure 1 A, B**).

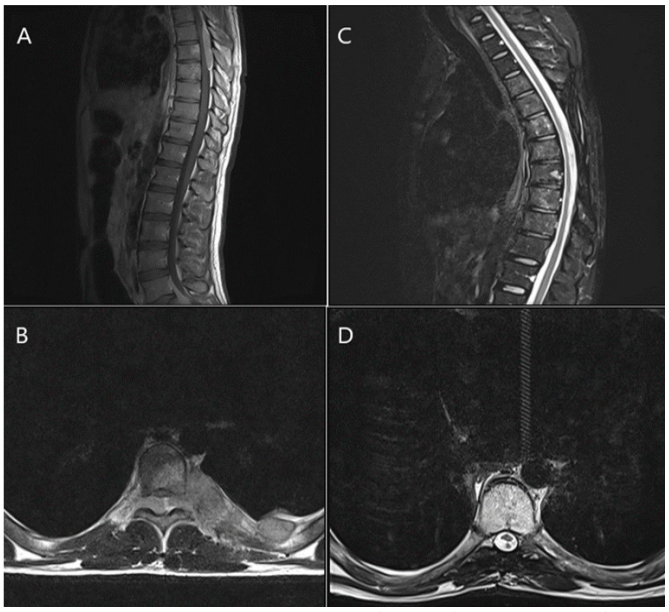

Figure 1. Magnetic resonance images at the initial visit (**A, B**) and post–treatment visit (**C, D**). Sagittal (**A**) plane at T6–8 and axial (**B**) planes at T7 show abnormal lesion located intradural extramedullary space of the thoracic spinal canal. Sagittal (**C**) and axial (**D**) planes had been shown complete disappearance of post–treatment with chemotherapy

Considering the rapid progression of the neurological deficit, resection of the dural mass and spinal decompression were planned. In the surgical operation, the mass showed partial invasion of the vertebral bone and the surrounding muscle. The mass invading the dura was resected and laminectomy was performed at T6–T9. The mass extended to the right and left neural foramina and this section could not be completely resected as it was not anatomically suitable. On histopathological examination of the mass, there was diffuse malignant infiltration by large atypical lymphoid cells with prominent nucleoli and a coarse chromatin structure. On immunohistochemical examination, neoplastic cells showed; CD20 (+, diffuse), CD3 (–), MPO (–), Tdt (–), CD1a (–), S100 (–), ALK (–), CD68 (–), CK (–), actin (–), vimentin (–) staining, and the Ki67 proliferation index was 70% (**Figure 2**). The pathology department reported the mass to be consistent with a diffuse large B cell lymphoma (centroblasts type). Cervical–thoracic–abdominopelvic computed tomography (CT) was performed to determine the extent of the disease, and no masses, organomegaly, or enlarged lymph nodes were detected. Bone marrow aspiration and biopsy did not show bone marrow involvement. Other detailed laboratory examinations did not reveal any pathological results.

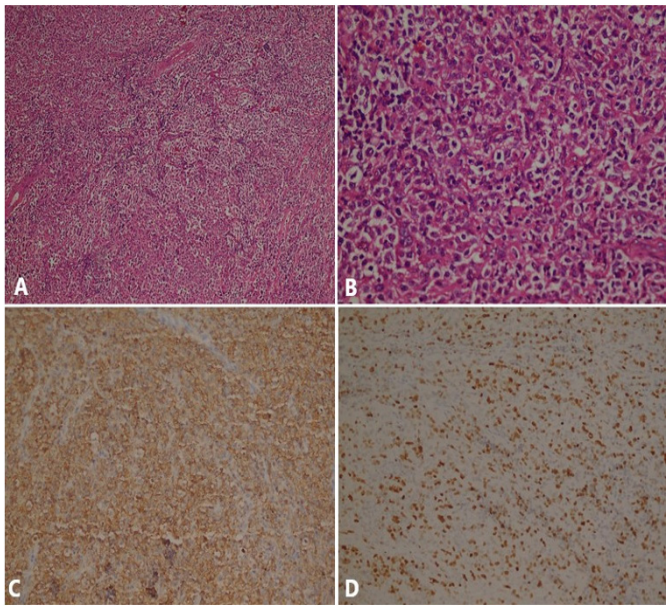

Figure 2. A. Tissue shows diffuse infiltration (Hematoxylin–eosin ×100). **B.** Atypical lymphoid cells with narrow cytoplasm, vesicular nuclei, and occasional prominent nucleoli (Hematoxylin–eosin ×400). **C.** On immunohistochemical examination, diffuse staining with CD20 in neoplastic lymphoid cells (×200). **D.** Ki67 proliferation was evaluated as high (70%) (×200)

After diagnosis, the patient was planned to undergo chemotherapy and radiotherapy. The patient received chemotherapy consisting of rituximab cyclophosphamide, doxorubicin, vincristine, and prednisone (R–CHOP) and was administered with six cycles. After chemotherapy, radiotherapy was given at a total dose of 40 Gy as 2 Gy per fraction. The strength of the bilateral lower extremity muscle groups showed daily improvement and the patient was able to walk normally with two courses of chemotherapy, after approximately six weeks. The neurological examination performed at the end of the patient's treatment revealed no sensory or motor deficits. Follow-up spinal MRI showed no evidence of any mass. The patient remains in remission without clinical or radiological relapse under follow-up after nearly 3 years.

DISCUSSION

A substantial portion of spinal compression cases is linked to metastatic tumors (lung carcinoma, prostate carcinoma, multiple myeloma, etc.), with a rate as large as 85%. The annual incidence of spinal cord compression among patients who showed cancer–related death was 3.4%, and approximately 15% of these cases were of Hodgkin's lymphoma and non–Hodgkin lymphoma.[5]

Compression associated with primary NHL is a condition of infrequent occurrence in clinical practice. Patients in

this group typically receive a diagnosis by presenting with neurological deficits arising from the local effect of the mass, or, although rarely, with back pain. Primary spinal lymphomas may not be clinically and radiologically distinct from other spinal lesion. Spinal intramedullary lymphomas are not associated with pathognomonic radiological findings, however, MRI can provide accurate and reliable data for the correct localization of the mass and post–treatment follows–up.[7] Accordingly, our case presented progressive neurological symptoms that resulted from the mass effect. Before the diagnosis, the lesion was detected using MRI, and post–treatment follow–up also utilized MRI for the evaluation of the response and the monitoring of relapse.

Spinal DLBCL is an aggressive form of lymphoma that is linked to rapid progression and mortality if untreated. The importance of early diagnosis is evident from the high morbidity and mortality rates, particularly in older patients. In spinal DLBCLs, aggressive surgical intervention is usually not recommended as the cases are both chemo– and radiosensitive, and as it can lead to a postoperative delay in initiation of chemotherapy and risk of neurological deficits.[8] The optimal treatment of DLBCL with spinal compression is reported to be controversial. Treatments usually include chemotherapy, radiotherapy, surgery, or a combination of these methods. Chemotherapy regimens based on rituximab continue to represent the standard of care in the management of DLBCL. Among these, R-CHOP remains the most widely employed, while polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, prednisone (Pola-R-CHP) and rituximab, etoposide, cyclophosphamide, doxorubicin, vincristine, prednisone (R-EPOCH) are also utilized as alternative frontline therapeutic options.[9-12] In these patients, intrathecal therapy is not routinely planned; however, in cases considered high-risk, two cycles of systemic high-dose methotrexate are recommended.[3] Radiotherapy is effective in all CNS lymphomas including DLBCL; however, it must not be employed as the first–line treatment due to neurotoxicity and not offering a survival advantage.[13]

On the other hand, since NHLs are highly chemosensitive and radiosensitive tumors, certain clinicians state that non–surgical treatments involving chemotherapy and radiotherapy can achieve rapid improvement of spinal cord and nerve root compression.[14] However, decompression surgery can be considered a primary option for the improvement of neurological symptoms.[15] Accordingly, our case primarily underwent surgical decompression for both diagnostic and treatment purposes, as there were neurological deficits induced by spinal compression. Subsequently, for the residual mass, first chemotherapy, and then radiotherapy was administered as a combined treatment. As a result of this treatment approach, the patient has now remained relapse–free under follow–up for nearly 3 years.

CONCLUSION

As a result, the differential diagnosis of patients who present with a spinal mass should be made carefully. It must be considered that, although rarely, DLBCLs can present as massive disease-causing spinal compression, and that clinically significant improvement can be achieved by timely and effective treatment. In patients who present with spinal compression, early decompression, particularly using surgery, is of great importance. Considering that spinal DLBCL is a malignant disease, appropriate treatment approaches play a vital role in achieving neurological recovery, longer survival times, and better life quality.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient included in this report. Signed consent forms are retained by the authors and are available upon request.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

This case report did not receive any financial support.

Author Contributions

Concept/Design: ÖC, ÖE, CD; Data Collection and/or Processing: ÖC, AD, MA; Analysis and/or Interpretation: ÖC, ÖE, İA, CD; Literature Search: ÖC, AD, MA; Writing the Manuscript: ÖC, ÖE; Critical Review: CD, AD, İA. All authors read and approved the final manuscript.

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