



Endothelial Activation and Stress Index (EASIX) as a Prognostic Tool for Predicting Survival in Advanced-Stage Classical Hodgkin Lymphoma

İleri Evre Klasik Hodgkin Lenfomada Sağkalımın Öngörülmesinde Prognostik Bir Araç Olarak Endotelyal Aktivasyon ve Stres İndeksi (EASIX)

Murat Kaçmaz¹ | Şengül Baran Yerlikaya¹ | Cihan Ural² | Ali Doğan²
Cengiz Demir¹

¹ Diyarbakır Gazi Yaşargil Training and Research Hospital, Department of Hematology, Diyarbakır, Türkiye

² Van Yüzüncü Yıl University, Faculty of Medicine, Department of Hematology, Van, Türkiye

ORCID: MK: 0000-0003-1111-8605 **ŞBY:** 0000-0001-9624-8091 **CU:** 0000-0003-1209-4668 **AD:** 0000-0003-0207-3505
CD: 0000-0001-9856-184X

Sorumlu Yazar | Correspondence Author

Murat Kaçmaz

dr_muratkaçmaz@hotmail.com

Address for Correspondence: Diyarbakır Gazi Yaşargil Training and Research Hospital, Department of Hematology, Diyarbakır, Türkiye

Makale Bilgisi | Article Information

Makale Türü | Article Type: Araştırma Makalesi | Research Article

Doi: <https://doi.org/10.52827/hititmedj.1846588>

Geliş Tarihi | Received: 21/12/2025

Kabul Tarihi | Accepted: 27/04/2026

Yayın Tarihi | Published: 29/06/2026

Atıf | Cite As

Kaçmaz M, Baran Yerlikaya Ş, Ural C, Doğan A, Demir C. Endothelial Activation and Stress Index (EASIX) as a Prognostic Tool for Predicting Survival in Advanced-Stage Classical Hodgkin Lymphoma. Hitit Medical Journal 2026;8(2):386-395. <https://doi.org/10.52827/hititmedj.1846588>

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.

Etik Beyanı: Çalışma için 26/04/2024 tarihinde Gazi Yaşargil Eğitim Araştırma Hastanesi Etik Kurulu'ndan onay alınmıştır. Karar no: 26/04/2024-21.

İntihal Kontrolleri: Evet (iThenticate)

Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.

Şikayetler: hmj@hitit.edu.tr

Katkı Beyanı: Fikir/Hipotez: MK, ŞBY; Tasarım: MK, CD; Veri Toplama/Veri İşleme: MK, CU, AD; Veri Analizi: MK, ŞBY; Makalenin Hazırlanması: MK, AD, CD

Hasta Onamı: Çalışma retrospektif bir çalışma olduğundan bilgilendirilmiş onam formu gerekli değildir.

Finansal Destek: Çalışma için finansal destek alınmamıştır.

GenAI Statement: Bu çalışmanın hazırlanması sırasında yazar(lar) yapay zeka araçlarını yalnızca dilbilgisi, yazım hataları ve üslup tutarlılığını kontrol etmek için kullanmıştır.

Telif Hakkı & Lisans: Dergi ile yayın yapan yazarlar, CC BY-NC 4.0 kapsamında lisanslanan çalışmalarının telif hakkını elinde tutar.

Peer Review: Evaluated by independent reviewers working in at least two different institutions appointed by the field editor.

Ethical Statement: Approval for the study was obtained from the Gazi Yaşargil Training and Research Hospital Ethics Committee on 26/04/2024. Decision no: 26/04/2024-21.

Plagiarism Check: Yes (iThenticate)

Conflict of Interest: The authors declared that they have no conflict of interest.

Complaints: hmj@hitit.edu.tr

Authorship Contribution: Idea/Hypothesis: MK, ŞBY; Design: MK, CD; Data Collection/Data Processing: MK, CU, AD; Data Analysis: MK, ŞBY; Manuscript Preparation: MK, AD, CD

Informed Consent: Since the study was designed as a retrospective study, obtaining an informed consent form was not required.

Financial Disclosure: No financial support was received for the conduct of this study.

GenAI Statement: During the preparation of this work, the author(s) used artificial intelligence tools solely to check grammar, spelling errors, and stylistic consistency.

Copyright & License: Authors publishing with the journal retains the copyright of their work licensed under CC BY-NC 4.0.

Endothelial Activation and Stress Index (EASIX) as a Prognostic Tool for Predicting Survival in Advanced-Stage Classical Hodgkin Lymphoma

ABSTRACT

Objective: The Endothelial Activation and Stress Index (EASIX) score has been demonstrated to be prognostically significant in a variety of hematologic malignancies. The purpose of this study was to evaluate the EASIX score's predictive value for survival outcomes in patients with advanced-stage classical Hodgkin lymphoma (cHL).

Material and Method: Patients with advanced-stage cHL (stages IIB–IV) who received first-line treatment with ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) were included in this retrospective study. The formula used to calculate EASIX scores at diagnosis was serum creatinine (mg/dL) $\times$ LDH (U/L)/platelet count ($10^9/L$).

Results: Eighty-five patients were included in the analysis. The median age of the cohort was 36 years, with males accounting for 61.2% of the population. Using an optimal ROC-based cutoff value of 0.66, 47 patients (55%) were assigned to the low-EASIX group, while 38 patients (45%) were categorized as high-EASIX. No statistically significant difference was observed in progression-free survival (PFS) between the two groups ($p=0.405$), and median PFS was not achieved in either group. Likewise, overall survival (OS) did not differ significantly between groups ($p=0.295$). Median OS was reached only in the high-EASIX group at 141.2 months, whereas it was not reached in the low-EASIX group.

Conclusion: The EASIX score was not associated with survival outcomes in patients with advanced stage cHL. Studies conducted with larger patient cohorts are needed to better assess the prognostic significance of the EASIX score in this patient group

Keywords: Creatinine, Hodgkin Disease, Lactate dehydrogenases, Platelet count, Prognosis.

İleri Evre Klasik Hodgkin Lenfomada Sağkalımın Öngörülmesinde Prognostik Bir Araç Olarak Endotelyal Aktivasyon ve Stres İndeksi (EASIX)

ÖZ

Amaç: Endotelyal Aktivasyon ve Stres İndeksi (EASIX) skorunun prognostik önemi, çeşitli hematolojik malignitelerde gösterilmiştir. Bu çalışmanın amacı, ileri evre klasik Hodgkin Lenfomalı (kHL) hastalarda EASIX skorunun sağkalım sonuçlarını öngörmedeki değerini incelemektir.

Gereç ve Yöntem: Bu retrospektif çalışmaya, birinci basamak tedavi olarak ABVD (doksorubisin, bleomisin, vinblastin, dakarbazin) alan ileri evre kHL'lı (evre IIB–IV) hastalar dahil edildi. EASIX skorları tanı anında, şu formül kullanılarak hesaplandı: serum kreatinin (mg/dL) $\times$ LDH (U/L)/trombosit sayısı ($10^9/L$).

Bulgular: Analize 85 hasta dahil edildi. Kohortun medyan yaşı 36 yıl olup, popülasyonun %61,2'sini erkekler oluşturmaktadır. Optimal ROC tabanlı kesme değeri 0,66 kullanılarak, 47 hasta (%55) düşük EASIX grubuna, 38 hasta (%45) ise yüksek EASIX grubuna atandı. İki grup arasında ilerlemesiz sağkalım (PFS) açısından istatistiksel olarak anlamlı bir fark gözlenmedi ($p=0,405$) ve her iki grupta da medyan PFS'ye ulaşılamadı. Benzer şekilde, genel sağkalım (OS) gruplar arasında anlamlı bir farklılık göstermedi ($p=0,295$). Medyan OS'ye yüksek EASIX grubunda 141,2 ayda ulaşıldı, düşük EASIX grubunda ise ulaşılamadı.

Sonuç: EASIX skoru ile ileri evre kHL'lı hastaların sağkalım sonuçları arasında ilişkili bulunmamıştır. Bu hasta grubunda EASIX skorunun prognostik öneminin daha iyi değerlendirilebilmesi için daha büyük ölçekli hasta serileriyle yapılacak çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Hodgkin Hastalığı, Kreatinin, Laktat Dehidrogenaz, Prognoz, Trombosit sayısı.

Introduction

Classical Hodgkin lymphoma (cHL) predominantly affects younger adults and generally presents with favorable outcomes. Despite this, a subset of patients with advanced-stage or high-risk cHL faces challenges in achieving long-term remission (1). Treatment decisions for cHL traditionally rely on disease stage and various risk factors, including age, B symptoms, sedimentation rate, and tumor burden in the mediastinum (1). The mainstay of treatment has been anthracycline-based chemotherapy, with or without concurrent radiation therapy, which has shown significant cure rates, especially for patients with low-risk or early-stage disease (2). However, the survival cure rates decrease to approximately 70% for patients with high-risk or advanced-stage cHL. Autologous stem cell transplantation (ASCT) can be performed after high-dose chemotherapy in patients with recurrent or refractory cHL (3). For patients with advanced-stage cHL, the International Prognostic Score (IPS7), first described by the German Hodgkin Study Group (GHSG) in 1998, remains the most commonly applied prognostic assessment tool (4). A simplified version, IPS3, which considers stage IV disease, age over 45 years, and hemoglobin levels below 10.5 g/dL, has also been proposed and shown to offer comparable prognostic information (5,6). Ongoing research is focused on developing new prognostic indexes better to predict outcomes in advanced-stage cHL (7). Advancements in imaging techniques, particularly fluorodeoxyglucose positron emission tomography/computed tomography (PET-CT), have revolutionized treatment planning in cHL. However, these advancements have also raised concerns about the continued relevance and accuracy of traditional prognostic factors in predicting disease outcomes (8,9).

In recent years, endothelial dysfunction has gained increasing attention as a key contributor to complications observed after allogeneic stem cell transplantation (alloSCT) (10-13). Impaired endothelial dysfunction may result in serious clinical conditions such as graft-versus-host

disease (GvHD), transplant-associated thrombotic microangiopathy (TMA), and sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) (10-13). The recognition of TMA as a potential terminal manifestation of endothelial injury has led to the introduction of the Endothelial Activation and Stress Index (EASIX). This index is calculated using serum creatinine (mg/dL), lactate dehydrogenase (U/L), and platelet count ($10^9/L$), and has been suggested both as a diagnostic tool for TMA and as a surrogate marker of endothelial activation and stress (14). Subsequent studies have highlighted the prognostic relevance of EASIX across a range of hematologic malignancies and alloSCT-related conditions, including myelodysplastic syndromes (MDS), multiple myeloma (MM), diffuse large B-cell lymphoma (DLBCL) and acute GvHD (15-19).

Cytokine-mediated interactions between the tumor microenvironment (TME) and Hodgkin Reed–Sternberg (HRS) cells play a pivotal role in the pathobiology of classical Hodgkin lymphoma (cHL), with endothelial activation constituting a critical component of this process. In this context, the present study aims to assess the prognostic relevance of the EASIX in predicting survival outcomes among patients with advanced-stage cHL.

Material and Method

This research was conducted as a retrospective, observational, cross-sectional study and included patients with advanced-stage classical Hodgkin lymphoma (cHL) whose data were retrieved from Gazi Yaşargil Training and Research Hospital and Van Yüzüncü Yıl University Faculty of Medicine archives between 2008 and 2023. In addition to the demographic and laboratory data of the cases, diagnosis dates, cHL subtypes, stages, presence of B symptoms, extranodal disease states, bulky diseases, mediastinal masses, bone marrow involvements, prognostic scores (IPS7 and IPS3), Eastern Cooperative Oncology Group (ECOG) performance status, treatment characteristics, relapse dates, and survey

information were recorded. Bulky disease was considered present when the nodal mass exceeded 7.5 cm in diameter, while mediastinal involvement was defined as a mass occupying more than one-third of the maximum intrathoracic diameter. The EASIX score of the cases was calculated with the creatinine, LDH, and platelet counts before the start of treatment. EASIX score was calculated using the following formula: serum creatinine (mg/dL) x LDH (U/L) / platelet count ($10^9/L$). The duration of progression-free survival (PFS) was measured from treatment onset to the occurrence of disease progression, death, or last confirmed follow-up. Overall survival (OS) was defined as the time from treatment initiation to death from any cause. The study was performed in accordance with the principles outlined in the Declaration of Helsinki, and the study protocol was reviewed and approved by the relevant local ethics committee of Gazi Yaşargil Training and Research Hospital (Approval No: 26/04/2024-21).

The study included patients aged 18 years or older with advanced-stage cHL (Ann Arbor stage IIB or higher) who had completed first-line therapy. All participants received ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, and dacarbazine) as initial treatment. Patients with early-stage disease (below Ann Arbor stage IIB), nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), or those who had not completed first-line therapy were excluded.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Categorical variables were summarized as frequencies and percentages, whereas continuous variables were reported as mean $\pm$ standard deviation or median with interquartile range, as appropriate. Data distribution was evaluated using the Kolmogorov–Smirnov test. Comparisons between two independent groups were carried out using the independent t-test for normally distributed variables and the Mann–Whitney U

test for non-normally distributed variables. The ability of the EASIX score to predict mortality was assessed through receiver operating characteristic (ROC) curve analysis. PFS and OS were compared among groups using the Kaplan–Meier method. Univariate and multivariate Cox proportional hazards regression models were applied to identify clinical factors associated with PFS and OS. Statistical significance was defined as a two-sided p value <0.05 .

Results

A total of 85 patients were included in the analysis, with a median age of 36 years (IQR: 24); most of the cohort were male ($n=52$, 61.2%). As illustrated in Figure I, the prognostic performance of the EASIX score for survival was assessed using ROC curve analysis, yielding an area under the curve (AUC) of 0.706 (95% CI: 0.575–0.842; $p<0.003$), which reflects a moderate discriminative ability. The optimal EASIX cut-off value was identified as 0.66, corresponding to a sensitivity of 60.9% and a specificity of 61.3%. Based on this threshold, 47 patients (55%) were categorized into the low EASIX group, while 38 patients (45%) were assigned to the high EASIX group. Comparative analyses demonstrated that white blood cell counts ($p=0.001$), neutrophil counts ($p<0.001$), and platelet counts ($p<0.001$) were significantly higher in the low EASIX group. In contrast, patients with high EASIX scores were older ($p=0.028$), more frequently male ($p=0.010$), and exhibited significantly elevated levels of creatinine ($p<0.001$), lactate dehydrogenase ($p<0.001$), and ferritin ($p=0.028$). Detailed baseline characteristics stratified by EASIX category are summarized in Table I.

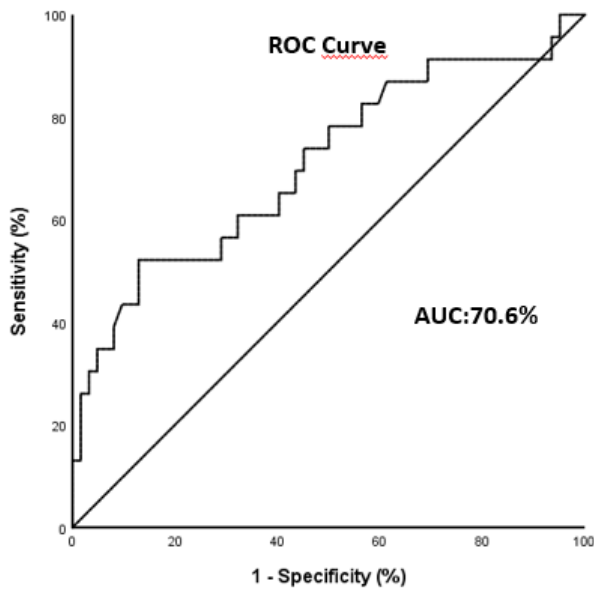


Figure 1. Receiver operating characteristics (ROC) curve analysis indicating a reasonable ability to distinguish survival with EASIX in cHL cases. (AUC: 0.706, 95% CI: 0.575-0.842, $p < 0.003$)

Table 1. Case Demographics and Characteristics According to the EASIX Score

	EASIX score			
Variables	Total n (%)=85 (100)	Low n (%)=47 (55)	High n (%)=38 (45)	<i>p</i>
Age, median (IQR)	36 (24)	30 (25)	38 (28)	0.028 ^c
Gender, n (%)				
Male	52 (61.2)	23 (48.9)	29 (76.3)	0.010 ^b
Female	33 (38.8)	24 (51.1)	9 (23.7)	
ECOG performance, n (%)				
0-1	76 (89.4)	44 (93.6)	32 (84.2)	0.288 ^b
≥2	9 (10.6)	3 (6.4)	6 (15.8)	
cHL subtype, n (%)				
Lymphocyte-depleted	7 (8.2)	3 (6.4)	4 (10.5)	0.276 ^b
Lymphocyte-rich	7 (8.2)	2 (4.3)	5 (13.2)	
Mixed Cellularity	22 (25.9)	15 (31.9)	7 (18.4)	
Nodular Sclerosis	49 (57.6)	27 (57.4)	22 (57.9)	
B symptoms, n (%)				
No	10 (11.8)	4 (8.5)	6 (15.8)	0.331 ^b
Yes	75 (88.2)	43 (91.5)	32 (84.2)	
Mediastinal mass, n (%)				
No	52 (61.2)	27 (57.4)	25 (65.8)	0.433 ^b
Yes	33 (38.8)	20 (42.6)	13 (34.2)	
Bulky disease, n (%)				
No	79 (92.9)	44 (93.6)	35 (92.1)	1.000 ^b
Yes	6 (7.1)	3 (6.4)	3 (7.9)	
Extranodal disease, n (%)				
No	48 (56.5)	29 (61.7)	19 (50)	0.279 ^b
Yes	37 (43.5)	18 (38.3)	19 (50)	

Bone marrow involvement, n (%)				
No	58 (68.2)	34 (72.3)	24 (63.2)	0.366 ^a
Yes	27 (31.8)	13 (27.7)	14 (36.8)	
IPSS3, n (%)				
0	18 (21.2)	12 (25.5)	6 (15.8)	0.123 ^b
1	40 (47.1)	24 (51.1)	16 (42.1)	
2	24 (28.2)	11 (23.4)	13 (34.2)	
3	3 (3.5)	0 (0)	3 (7.9)	
IPSS7, n (%)				
0-2	41 (48.2)	26 (55.3)	15 (39.5)	0.146 ^a
≥3	44 (51.8)	21 (44.7)	23 (60.5)	
Stage				
II	21 (24.7)	16 (34.0)	5 (13.2)	0.077 ^b
III	17 (20.0)	9 (19.2)	8 (21.0)	
IV	47 (55.3)	22 (46.8)	25 (65.8)	
First line treatment response				
CR	55 (64.7)	28 (59.6)	27 (71.0)	0.543 ^b
PR	14 (16.5)	9 (19.1)	5 (13.2)	
PD	16 (18.8)	10 (21.3)	6 (15.8)	
Hb (g/dL), mean±SD	12.0 ± 2.4	11.9 (1.8)	12.2 (2.8)	0.555 ^d
WBC (10 ⁹ /L), mean±SD	9980 ± 4575	11900 ± 4590	8250 ± 4680	0.001 ^d
Neut (10 ⁹ /L), median (IQR)	6700 (6460)	9060 (7600)	4290 (4260)	<0.001 ^c
Lym (10 ⁹ /L), mean±SD	1520 ± 690	1610 ± 729	1410 ± 640	0.203 ^c
PLT (10 ⁹ /L), median (IQR)	306 (163)	380 (160)	243 (99)	<0.001 ^c
Alb (g/dL), mean±SD	3.7 ± 0.6	3.6 ± 0.6	3.7 ± 0.7	0.424 ^d
Crea (mg/dL), median (IQR)	0.7 (0.2)	0.6 (0.1)	0.7 (0.1)	<0.001 ^c
LDH (U/L), median (IQR)	255 (170)	221 (121)	336 (193)	<0.001 ^c
ESR (mm/hour), median (IQR)	52 (59)	54 (59)	43 (58)	0.510 ^c
FER (ng/mL), median (IQR)	402 (410)	229 (337)	400 (581)	0.028 ^c

Abbreviations: ECOG, Eastern Cooperative Oncology Group; cHL, Classical Hodgkin Lymphoma; IPS, International Prognostic Score; CR, Complete Response; PR, Partial Response; PD, Progressive Disease; Hb, Hemoglobin; WBC, White blood cell; Neut, Neutrophil; Lym, Lymphocyte; PLT, Thrombocyte; Alb, Albumin; Crea, Creatinine; LDH, Lactate dehydrogenase; ESR, Erythrocyte sedimentation rate; FER, Ferritin; EASIX, endothelial activation and stress index. a: Pearson Chi Square test, b: Fisher's Exact test, c: Mann Whitney U test, d: Independent t test, $p < 0.05$ is statistically significant.

During the follow-up period, relapse was documented in 26 patients (30.6%), including 16

cases (34.0%) in the low EASIX group and 10 cases (26.3%) in the high EASIX group. The difference in relapse rates between the two groups was not statistically significant ($p=0.442$). Overall, 23 patients (27.1%) died over the course of the study. Of these, 9 patients (19.1%) belonged to the low EASIX group, whereas 14 patients (36.8%) were in the high EASIX group. Although mortality was numerically higher among patients with high EASIX group, this difference did not reach statistical significance ($p=0.068$). Survival analyses revealed no significant differences in PFS between the groups ($p=0.405$), and the median PFS was not reached in either group. Similarly, OS did not differ significantly between groups ($p=0.295$). The median OS was 141.2 months (range:109.5–173.0 months) in the high EASIX group, while the median OS was not reached in the low EASIX group. Detailed comparisons of PFS and OS are presented in Table II, and the corresponding survival curves are shown in Figures II and III.

Table II. PFS and OS Comparisons of Cases

		Total n (%)=85 (100)	Low EASIX n (%) =47 (55)	High EASIX n (%)=38 (45)	<i>p</i>
Relapse					
No, n (%)		59 (69,4)	31 (66)	28 (73.7)	0.442 ^a
Yes, n (%)		26 (30.6)	16 (34)	10 (26.3)	
Survival					
Alive, n (%)	n	62 (72.9)	38 (80.9)	24 (63.2)	

Death, n (%)	23 (27.1)	9 (19.1)	14 (36.8)	<i>0.068^a</i>
PFS (months)	2 years %	5 years %	Median (%95 CI)	<i>p</i>
Overall	73.5	63.3	-	<i>0.405</i>
Low EASIX	68.1	54.9	-	
High EASIX	80.4	68.2	-	
OS (months)	2 years %	5 years %	Median (%95 CI)	
Overall	88.4	73.9	141.2 (123.9-158.5)	<i>0.295</i>
Low EASIX	95.4	79.2	-	
High EASIX	80.2	67.8	141.2 (109.5-173.0)	

Abbreviations: PFS, progression free survival; OS, overall survival; EASIX, endothelial activation and stress index. a: Pearson Chi Square test, Kaplan Meier curve, Long rank test, $p<0.05$ is statistically significant.

In univariate analyses evaluating factors associated with survival outcomes, extranodal involvement, bone marrow involvement, and an IPS7 score ≥ 3 were significantly associated with PFS ($p<0.05$). However, none of these variables retained statistical significance in the multivariate model for PFS. With respect to OS, univariate analysis identified an ECOG performance status ≥ 2 , bone marrow involvement, and an IPS7 score ≥ 3 as significant predictors ($p<0.05$). In multivariate Cox regression analysis, ECOG performance status (HR: 4.54; 95% CI: 1.70–12.10; $p=0.002$) and bone marrow involvement (HR: 5.11; 95% CI: 1.63–15.97; $p=0.005$) remained independently associated with OS ($p<0.001$; $-2 \log \text{likelihood}=142.02$). Comprehensive Cox regression results for the evaluated clinical variables are detailed in Table III.

Table III. Cox Regression Results for Clinical Variables

Variables	PFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95%CI)	<i>p</i>	HR (95%CI)	<i>p</i>	HR (95%CI)	<i>p</i>	HR (95%CI)	<i>p</i>
Age	1.00 (0.98-1.03)	<i>0.549</i>	-		1.02 (0.99-1.04)	<i>0.079</i>	-	
Gender (ref: male)	0.75 (0.33-1.78)	<i>0.550</i>	-		1.43 (0.60-3.41)	<i>0.417</i>	-	
ECOG (ref: 0-1)	0.55 (0.07-4.08)	<i>0.560</i>	-		8.01 (3.19-20.10)	<i><0.001</i>	4.54 (1.70-12.10)	<i>0.002</i>
B Symptoms (ref: no)	0.91 (0.27-3.06)	<i>0.891</i>	-		1.87 (0.43-8.14)	<i>0.402</i>	-	
Mediastinal mass (ref: no)	1.06 (0.48-2.31)	<i>0.880</i>	-		0.67 (0.27-1.65)	<i>0.395</i>	-	

Bulky disease (ref: no)	1.20 (0.28-5.18)	0.800	-		2.36 (0.68-8.09)	0.172	-	
Extranodal disease (ref: no)	2.38 (1.06-5.34)	0.036	1.75 (0.74-4.12)	0.197	2.03 (0.86-4.80)	0.106	-	
Bone marrow involvement (ref: no)	3.28 (1.49-7.21)	0.003	2.37 (0.97-5.82)	0.058	8.13 (2.94-22.48)	<0.001	5.11 (1.63-15.97)	0.005
IPS7 (ref: 0-2)	2.34 (1.01-5.39)	0.045	1.51 (0.59-3.87)	0.388	3.39 (1.26-9.15)	0.016	1.72 (0.57-5.19)	0.331
EASIX (ref: <0,66)	0.71 (0.32-1.57)	0.407	-		1.56 (0.67-3.67)	0.299	-	
				$p=0.005$; -2 Log Likelihood=188.20		$p<0.001$; -2 Log Likelihood=142.02		

Abbreviations: PFS, progression free survival; OS, overall survival; ECOG, Eastern Cooperative Oncology Group; IPS, International Prognostic Score; EASIX, endothelial activation and stress index.

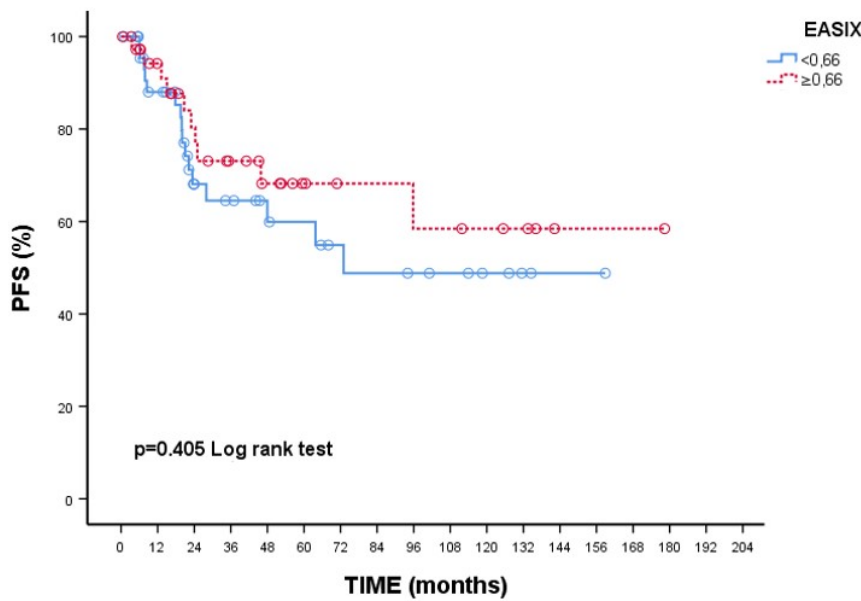


Figure II. Progression-Free Survival Curves (PFS)

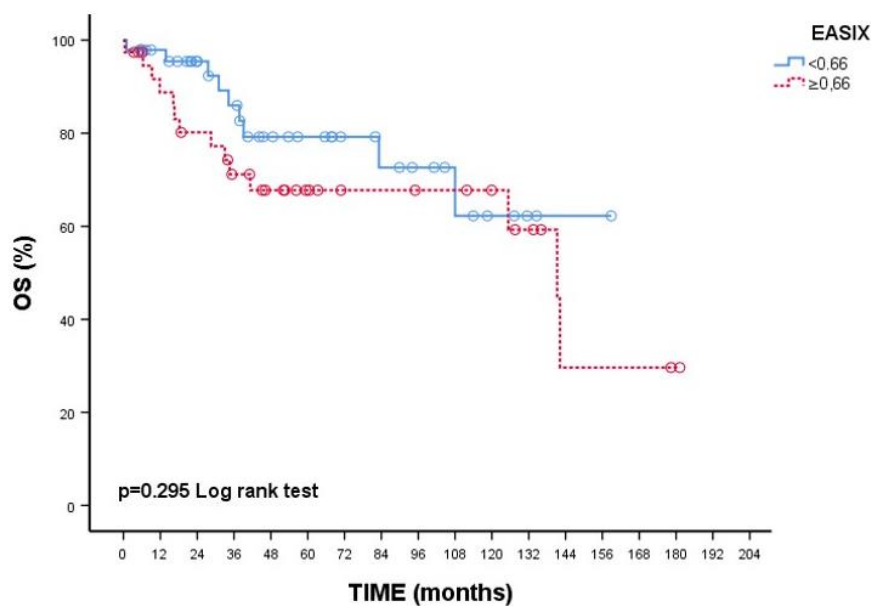


Figure III. Overall survival curves (OS)

Discussion

Accurate prognostic assessment in patients with advanced-stage cHL is essential for guiding therapeutic strategies and post-treatment surveillance. Although the IPS7 continues to serve as a fundamental prognostic tool in this setting, additional markers may further refine risk stratification. In this context, the present study sought to investigate the prognostic value of the EASIX score for predicting survival outcomes in advanced-stage cHL.

The interaction between HRS cells and the surrounding TME is a key driver in the development of cHL. Although HRS cells represent only a minor proportion of the total tumor burden, the TME is composed of various supporting elements, including fibroblasts, immune and endothelial cells, along with an abundant extracellular matrix. Moreover, chemokines and cytokines released from HRS cells and the TME significantly influence tumor growth and survival (21,22). Previous studies have demonstrated a close relationship among HRS cells, TME, and endothelial activation-stimulation in cHL, clearly showing its correlation with prognosis (20,23-25). Despite the apparent significance of endothelial activation in cHL, the IPS7 scoring criteria do not include parameters that detect endothelial activity. Accordingly, this study was designed to assess the prognostic relevance of endothelial activation, as quantified by the EASIX score, in patients with advanced-stage cHL. A study with a design similar to ours was recently published. This study, which included patients with all stages of cHL, evaluated the prognostic impact of the EASIX score. The results demonstrated a strong association between EASIX and prognosis in patients with cHL. In contrast, in our study, which included only patients with advanced-stage cHL, we were unable to demonstrate a significant prognostic impact of the EASIX score. This discrepancy may be attributable to the relatively smaller sample size of our study and the restriction of our cohort to patients with advanced-stage disease (26).

The EASIX score has also been reported to correlate with prognosis in other hematological malignancies, including MM and DLBCL (18,19). However, given the well-established prognostic significance of creatinine and LDH in both MM and DLBCL, the observed association between the EASIX score and prognosis in these diseases is not unexpected (27-29). In contrast, the lack of a prognostic association between the EASIX score and cHL is surprising, particularly considering the complex interactions among Hodgkin and Reed–Sternberg (HRS) cells, the tumor microenvironment (TME), and endothelial cells in this disease. One might have expected that a score reflecting endothelial dysfunction, as EASIX does, would correlate with prognosis given the importance of the endothelium in cHL pathogenesis. The absence of such an association in our study underscores the biological complexity of cHL and highlights the need for further research to better elucidate the mechanisms underlying disease progression and treatment response. Notably, although no significant relationship was observed between the EASIX score and prognosis in patients with advanced-stage cHL in our cohort, established prognostic factors—including IPS7, the presence of extranodal disease, bone marrow involvement, and ECOG performance status—retained their prognostic significance.

There are several limitations to this study. First, it was designed as a retrospective study. Second, the assessment of chemokine and cytokine profiles associated with endothelial activation, which could have strengthened the evaluation of the EASIX score in cHL, was not possible because of the study's retrospective nature. Finally, the relatively small sample size may have reduced the statistical power to detect a meaningful prognostic impact of the EASIX score on survival outcomes.

Conclusion

While our study confirmed the prognostic significance of established parameters in advanced-stage cHL, including IPS7, extranodal disease, bone marrow involvement, and ECOG

performance status, it did not reveal a demonstrable effect of the EASIX score on survival. These results highlight the importance of conducting larger, prospective studies to more clearly define the prognostic value of the EASIX score in patients with advanced-stage cHL.

References

1. Ansell SM. Hodgkin lymphoma: 2023 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2022;97(11):1478-1488.
2. Engert A, Raemaekers J. Treatment of early-stage Hodgkin lymphoma. *Semin Hematol*. 2016;53(3):165-170.
3. von Tresckow B, Moskowitz CH. Treatment of relapsed and refractory Hodgkin Lymphoma. *Semin Hematol*. 2016;53(3):180-185.
4. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. *N Engl J Med*. 1998;339(21):1506-1514.
5. Diefenbach CS, Li H, Hong F, et al. Evaluation of the International Prognostic Score (IPS-7) and a Simpler Prognostic Score (IPS-3) for advanced Hodgkin lymphoma in the modern era. *Br J Haematol*. 2015;171(4):530-538.
6. Ganesan P, Dhanushkodi M, Ganesan TS, et al. Prognostic Utility of the IPS 3 Score for Predicting Outcomes in Advanced Hodgkin Lymphoma. *Clin Lymphoma Myeloma Leuk*. 2019;19(2):116-122.
7. Rodday AM, Parsons SK, Upshaw JN, et al. The Advanced-Stage Hodgkin Lymphoma International Prognostic Index: Development and Validation of a Clinical Prediction Model From the HoLISTIC Consortium. *J Clin Oncol*. 2023;41(11):2076-2086.
8. Hutchings M, Loft A, Hansen M, et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. *Blood*. 2006;107(1):52-59.
9. Bari A, Marcheselli R, Sacchi S, et al. The classic prognostic factors in advanced Hodgkin's lymphoma patients are losing their meaning at the time of Pet-guided treatments. *Ann Hematol*. 2020;99(2):277-282.
10. Corbacioglu S, Carreras E, Ansari M, et al. Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in pediatric patients: a new classification from the European society for blood and marrow transplantation. *Bone Marrow Transplant*. 2018;53(2):138-145.
11. Dietrich S, Falk CS, Benner A, et al. Endothelial vulnerability and endothelial damage are associated with risk of graft-versus-host disease and response to steroid treatment. *Biol Blood Marrow Transplant*. 2013;19(1):22-27.
12. Luft T, Dietrich S, Falk C, et al. Steroid-refractory GVHD: T-cell attack within a vulnerable endothelial system. *Blood*. 2011;118(6):1685-1692.
13. Nassereddine S, Alsubait S, Tabbara I. Sinusoidal Obstruction Syndrome (Veno-occlusive Disease) Following Hematopoietic Stem Cell Transplant: Insights and Therapeutic Advances. *Anticancer Res*. 2018;38(5):2597-2605.
14. Luft T, Benner A, Jodele S, et al. EASIX in patients with acute graft-versus-host disease: a retrospective cohort analysis. *Lancet Haematol*. 2017;4(9):e414-e423.
15. Luft T, Benner A, Terzer T, et al. EASIX and mortality after allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2020;55(3):553-561.
16. Kordelas L, Terzer T, Gooley T, et al. EASIX-1year and late mortality after allogeneic stem cell transplantation. *Blood Adv*. 2023;7(18):5374-5381.
17. Merz A, Germing U, Kobbe G, et al. EASIX for prediction of survival in lower-risk myelodysplastic syndromes. *Blood Cancer J*. 2019;9(11):85.
18. Song GY, Jung SH, Kim K, et al. Endothelial activation and stress index (EASIX) is a reliable predictor for overall survival in patients with multiple myeloma. *BMC Cancer*. 2020;20(1):803.
19. Park S, Go SI, Lee GW. The Endothelial Activation and Stress Index (EASIX) score is an independent prognostic factor in patients with diffuse large B-cell lymphoma. *BMC Cancer*. 2022;22(1):816.
20. Ruco LP, Pittiglio M, Dejana E, Baroni CD. Vascular activation in the histopathogenesis of Hodgkin's disease: potential role of endothelial tissue factor in intravascular thrombosis and necrosis. *J Pathol*. 1993;171(2):131-136.
21. Aldinucci D, Borghese C, Casagrande N. Formation of the Immunosuppressive Microenvironment of Classic Hodgkin Lymphoma and Therapeutic Approaches to Counter It. *Int J Mol Sci*. 2019;20(10):2416.
22. Linke F, Harenberg M, Nietert MM, et al. Microenvironmental interactions between endothelial and lymphoma cells: a role for the canonical WNT pathway in Hodgkin lymphoma. *Leukemia*. 2017;31(2):361-372.
23. Estrada-Bernal A, Mendoza-Milla C, Ventura-Gallegos JL, et al. NF-kappaB dependent activation of human endothelial cells treated with soluble products derived from human lymphomas. *Cancer Lett*. 2003;191(2):239-248.
24. Fhu CW, Graham AM, Yap CT, et al. Reed-Sternberg cell-derived lymphotoxin-α activates endothelial cells to enhance T-cell recruitment in classical Hodgkin lymphoma. *Blood*. 2014;124(19):2973-2982.
25. Rueda A, Olmos D, Vicioso L, et al. Role of vascular endothelial growth factor C in classical Hodgkin lymphoma. *Leuk Lymphoma*. 2015;56(5):1286-1294.
26. Hunutlu FÇ, Öztop H, Gürsoy V, et al. Modified Endothelial Activation and Stress Index: A New Predictor for Survival Outcomes in Classical Hodgkin Lymphoma

Treated with Doxorubicin-Bleomycin-Vinblastine-Dacarbazine-Based Therapy. *Diagnostics* (Basel). 2025;15(2):185.

27. Chim CS, Sim J, Tam S, Tse E, Lie AK, Kwong YL. LDH is an adverse prognostic factor independent of ISS in transplant-eligible myeloma patients receiving bortezomib-based induction regimens. *Eur J Haematol*. 2015;94(4):330-335.

28. Dimopoulos MA, Terpos E, Chanan-Khan A, et al. Renal impairment in patients with multiple myeloma: a consensus statement on behalf of the International Myeloma Working Group. *J Clin Oncol*. 2010;28(33):4976-4984.

29. Yadav C, Ahmad A, D'Souza B, et al. Serum Lactate Dehydrogenase in Non-Hodgkin's Lymphoma: A Prognostic Indicator. *Indian J Clin Biochem*. 2016;31(2):240-242.