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ORIGINAL ARTICLE

Real-world prognostic assessment of the HERO score in metastatic urothelial carcinoma treated with enfortumab vedotin (ARON-2EV study)

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Background: Enfortumab vedotin (EV) is a standard treatment for metastatic urothelial carcinoma (mUC) after platinum-based chemotherapy and immune checkpoint inhibitors. However, reliable and clinically accessible prognostic tools for patients treated with EV remain limited. We evaluated the clinical prognostic performance of the HERO score in a large real-world cohort of EV-treated patients.

Patients and methods: ARON-2EV is a retrospective multicenter cohort study including patients with mUC treated with EV after platinum-based chemotherapy and immune checkpoint inhibitors. The association between the HERO score, based on hemoglobin level and neutrophil-to-lymphocyte ratio, and survival outcomes (overall survival and progression-free survival) was assessed. Response analyses were considered exploratory.

Results: A total of 548 patients with mUC treated with EV were included in the analysis. Median overall survival was 12.4 months and median progression-free survival was 6.8 months. The HERO score was associated with survival and response outcomes, with patients with a score of 2 experiencing the most favorable outcomes. These associations remained consistent across multivariable analyses.

Conclusions: In this large international real-world cohort, the HERO score was associated with survival and response outcomes in patients with mUC treated with EV, particularly through identification of a subgroup with a more favorable prognosis (score 2). However, discrimination between lower score categories was less pronounced. Further prospective refinement and evaluation of the HERO score are warranted, particularly in contemporary EV-based treatment strategies.

Key words: enfortumab vedotin, HERO score, prognostic factors, real-world study, urothelial carcinoma

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INTRODUCTION

Urothelial carcinoma (UC) represents the most common histological subtype of bladder cancer and remains a major cause of cancer-related morbidity and mortality worldwide.[1] Despite advances in systemic therapy, the prognosis of patients with metastatic urothelial carcinoma (mUC)

remains poor, with limited long-term survival.[2] Platinum-based chemotherapy has historically represented the standard first-line treatment, but responses are often short-lived.[2] More recently, immune checkpoint inhibitors (ICIs) have changed the therapeutic landscape across multiple disease settings, including first-line combinations with antibody-drug conjugates, maintenance with avelumab and post-platinum disease.[3-6] However, a substantial proportion of patients do not respond to ICIs or develop disease progression, highlighting the need for effective subsequent treatment options.

Enfortumab vedotin (EV), an antibody—drug conjugate targeting Nectin-4, has emerged as a key therapeutic option in this setting.[7,8] By delivering the cytotoxic agent monomethyl auristatin E directly into tumor cells, EV disrupts microtubule dynamics and induces apoptosis. Clinical trials such as EV-201 and EV-301 have demonstrated significant improvements in response rates and overall survival (OS) in patients previously treated with both platinum-based chemotherapy and ICIs, leading to their widespread adoption in clinical practice.[7,8] Nevertheless, clinical trial populations are highly selected and may not fully reflect the heterogeneity of patients treated in routine clinical practice, who are often older, more comorbid, and characterized by broader variability in performance status (PS) and disease burden. In this context, real-world cohorts represent an important setting not only to evaluate treatment outcomes outside clinical trials but also to validate the robustness and generalizability of prognostic models in contemporary patients receiving EV.

Traditional prognostic models in mUC, such as the Bellmunt and Bajorin scores,[9,10] were developed in earlier therapeutic eras and may not fully capture outcomes in patients exposed to ICIs and antibody—drug conjugates. In addition, these models are often relatively complex and less practical for everyday clinical use, highlighting the need for simple and accessible prognostic tools applicable in routine practice.

Among readily available host-related biomarkers, hemoglobin levels and the neutrophil-to-lymphocyte ratio (NLR) have consistently demonstrated prognostic value across multiple malignancies, including UC.[10,11] Anemia has been associated with tumor hypoxia and aggressive disease biology,[12] whereas an elevated NLR may reflect a proinflammatory state associated with tumor progression and impaired antitumor immunity.[11] These parameters are inexpensive, routinely measured, and easily transferable across clinical settings.

On this basis, the HERO score was recently developed in a real-world cohort of patients with mUC treated with EV after platinum-based chemotherapy and ICIs.[13] By assigning one point each for hemoglobin $\geq$11 g/dL and NLR $<$4, the score stratifies patients into three groups ranging from 0 to 2. Preliminary evidence suggests that the HERO score may discriminate outcomes in patients treated with EV,[13] but robust external validation in large international real-world cohorts remains limited. To address these gaps, we carried out a real-world clinical prognostic assessment of the HERO score within the ARON-2EV cohort,[14] a large international population of patients with mUC treated with EV after platinum-based chemotherapy and ICIs.

PATIENTS AND METHODS

Study design and patient population

The present analysis was conducted as a retrospective multicenter cohort study within the ARON-2EV collaborative network. The ARON-2EV study was a retrospective, multicenter analysis conducted across 56 oncological centers from 15 countries.[14] Adult patients (age $\geq$18 years) with a histologically and/or cytologically confirmed diagnosis of mUC were eligible for inclusion. Patients were excluded if they had incomplete or missing key clinical data, no available follow-up after treatment initiation, non-urothelial histology, or nonmetastatic disease at baseline. Additional exclusion criteria included treatment exclusively within clinical trials and the presence of concomitant active malignancies requiring systemic therapy.

We analyzed data from patients who received EV between 1 January 2022 and 30 April 2025, after prior treatment with platinum-based chemotherapy and ICIs. Clinical, pathological, and treatment-related data were retrospectively collected from medical records at each participating institution.

EV was administered as monotherapy according to the approved dosing schedule (1.25 mg/kg on days 1, 8, and 15 of a 28-day cycle). Treatment was continued until radiological or clinical disease progression, unacceptable toxicity, withdrawal of consent, or physician decision.

Patients were monitored according to local clinical practice and international guidelines, including regular physical examinations, laboratory assessments, and radiological evaluations using computed tomography and/or magnetic resonance imaging. Given the retrospective real-world design, imaging intervals and response assessment schedules were not centrally standardized across participating centers.

Study objectives

The primary objective of this study was to evaluate the prognostic performance of the HERO score for survival outcomes, specifically OS and progression-free survival (PFS), in patients with mUC treated with EV. Secondary objectives included the assessment of treatment response and survival outcomes in the overall study population receiving EV. Analyses of tumor response according to HERO score were considered exploratory and hypothesis-generating.

The HERO score is a composite index based on two baseline laboratory parameters: hemoglobin level and NLR. Specifically, one point was assigned for hemoglobin $\geq$11 g/dL and one point for NLR $<$4, resulting in a total score ranging from 0 to 2. Patients were stratified into three risk groups (score 0, 1, or 2). These thresholds were selected based on previous evidence.[14] The detailed HERO score calculation is summarized in Supplementary Table S1 (available at https://doi.org/10.1016/j.esmoop.2026.108302).

OS was defined as the interval between the initiation of EV and death from any cause. PFS was defined as the interval between initiation of EV and progression or death from any cause. Tumor response was evaluated locally at each center according to the RECIST version 1.1 criteria,[15] classifying outcomes as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).

Importantly, the present study was designed as a retrospective clinical prognostic assessment of the HERO score in EV-treated patients, rather than as a formal prognostic model validation study according to dedicated methodological frameworks.

Statistical analysis

Time-to-event endpoints, including OS and PFS, were estimated using the Kaplan—Meier method, with median values reported together with corresponding 95% confidence intervals (CIs). Patients without documented events at the time of analysis were censored at their last follow-up.

Survival curves were compared using the log-rank test. Median follow-up duration was estimated using the reverse Kaplan—Meier method, considering patients without events as censored observations.

Categorical variables were compared using the Fisher exact test or chi-square test, as appropriate. Associations between continuous variables were evaluated using the Pearson correlation coefficient.

Univariable Cox proportional hazards analyses were carried out to explore associations between baseline clinicopathologic variables and survival outcomes. Analyzed variables included demographic, clinical, and disease-related variables such as age, sex, smoking status, Eastern Cooperative Oncology Group (ECOG) PS, tumor histology, primary tumor location, metastatic burden, specific metastatic sites, and duration of prior immunotherapy. Prior response to ICIs was considered the main variable of interest. Because hemoglobin and NLR are components of the HERO score, analyses of individual laboratory parameters were interpreted as complementary to, rather than independent from, the composite score analysis.

Exploratory multivariable Cox regression analyses were carried out, including selected clinically relevant variables in order to assess the consistency of associations between HERO score components and survival outcomes after adjustment for major baseline clinical factors. Results from multivariable analyses are presented as hazard ratios (HRs) with 95% CIs.

All statistical tests were two-sided and a P-value <0.05 was considered statistically significant. RStudio software (version 4.5.1 RStudio, PBC: Boston, MA) was used for the statistical analyses.

Ethics approval

The study protocol was approved by the ethics committee of the coordinating center (Marche Region, Italy; reference 2022 39/7875, ARON-2 study, NCT05290038) as well as by the institutional review boards of all participating centers.

The study was conducted in accordance with Good Clinical Practice guidelines and the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all patients before inclusion.

RESULTS

Baseline characteristics according to HERO score

A total of 548 patients treated with EV were included in the analysis and stratified according to the HERO score (score 0: $n = 53$, 9.7%; score 1: $n = 210$, 38.3%; score 2: $n = 285$, 52.0%).

These patients were derived from a total of 578 patients registered across participating centers; 30 patients (5.2%) were excluded from the present analysis because of missing or incomplete baseline data required for HERO score calculation.

Baseline characteristics were overall comparable across the three HERO groups (Table 1). No statistically significant differences were observed in terms of sex distribution, tumor histology, primary tumor location, age, or body mass index (BMI). Median age was similar across groups (~70-72 years) and more than half of the patients in each group were aged ≥70 years.

Similarly, prior exposure to ICIs, including avelumab, pembrolizumab, and atezolizumab/nivolumab, was evenly distributed among the groups, suggesting a homogeneous pretreatment background. The proportion of patients receiving a reduced starting dose of EV was low and comparable across groups.

In contrast, ECOG PS differed significantly across HERO categories ($P = 0.001$). Patients with a HERO score of 2 were more likely to have ECOG PS 0, whereas poorer PS (ECOG PS 2) was more frequently observed in lower score groups.

Most metastatic sites, including nonregional lymph nodes, lung, and bone metastases, were similarly distributed across groups. However, liver metastases were significantly more frequent in the score 1 group (38.1%) compared with score 0 (30.2%) and score 2 (25.6%) ($P = 0.012$); and brain metastases were more common among patients with lower HERO scores (9.4% in score 0 versus 1.8% in score 2; $P = 0.011$).

Treatment response according to HERO score

Response to EV significantly differed across HERO score categories ($P < 0.001$) (Table 2; Figure 1). Patients with higher HERO scores had more favourable response outcomes. The CR increased from 4.3% in the score 0 group to 12.9% in the score 2 group. Similarly, PR rates were higher in the score 2 group (39.8%) compared with the score 1 (36.3%) and score 0 (28.3%) groups.

Conversely, PD was more frequent among patients with lower HERO scores, occurring in 41.3% of patients with score 0, 35.8% of those with score 1, and 16.9% of those with score 2. SD rates were broadly similar across groups, although slightly higher in the score 2 group. Overall, response outcomes differed according to HERO score

Table 1. Patient baseline characteristics according to HERO score

Variables	Total ($N = 548$)	Score 0 ($N = 53$)	Score 1 ($N = 210$)	Score 2 ($N = 285$)	P
Sex, *n* (%)					0.432
Male	419 (76.9)	43 (81.1)	163 (78.7)	213 (74.7)	
Female	126 (23.1)	10 (18.9)	44 (21.3)	72 (25.3)	
Tumor histology, *n* (%)					0.079
Pure urothelial carcinoma	419 (78.3)	35 (67.3)	157 (77.3)	227 (81.1)	
Variants/mixed	116 (21.7)	17 (32.7)	46 (22.7)	53 (18.9)	
Primary tumor location, *n* (%)					0.742
Lower urinary tract	398 (72.6)	39 (73.6)	156 (74.3)	203 (71.2)	
Upper urinary tract	150 (27.4)	14 (26.4)	54 (25.7)	82 (28.8)	
Age, median [range]	70.5 [37.0-88.0]	72.0 [43.0-84.0]	71.0 [45.0-88.0]	70.0 [37.0-87.0]	0.928
Age category, *n* (%)					0.933
<70	252 (46.1)	24 (45.3)	95 (45.2)	133 (46.8)	
≥70	295 (53.9)	29 (54.7)	115 (54.8)	151 (53.2)	
BMI, median [range]	24.3 [14.9-43.4]	24.5 [15.1-40.0]	24.3 [16.1-37.0]	24.2 [14.9-43.4]	0.723
BMI category, *n* (%)					0.587
≤25	338 (62.4)	29 (55.8)	131 (63.0)	178 (63.1)	
>25	204 (37.6)	23 (44.2)	77 (37.0)	104 (36.9)	
ECOG PS (baseline), *n* (%)					0.001
0	146 (26.7)	9 (17.0)	42 (20.0)	95 (33.5)	
1	314 (57.4)	32 (60.4)	123 (58.6)	159 (56.0)	
2	80 (14.6)	11 (20.8)	40 (19.0)	29 (10.2)	
Prior ICI, *n* (%)					0.519
Avelumab	212 (40.9)	21 (42.0)	85 (43.4)	106 (39.0)	
Pembrolizumab	257 (49.6)	23 (46.0)	90 (45.9)	144 (52.9)	
Atezolizumab/nivolumab	49 (9.5)	6 (12.0)	21 (10.7)	22 (8.1)	
Best response, *n* (%)					<0.001
EV dose at first administration, *n* (%)					0.433
Standard	497 (90.7)	48 (90.6)	185 (88.1)	264 (92.6)	
Reduced	49 (8.9)	5 (9.4)	24 (11.4)	20 (7.0)	
Severe G3/G4 adverse events, *n* (%)	111 (20.3)	6 (11.3)	40 (19.0)	65 (22.9)	0.134
Current smoker, *n* (%)	347 (64.4)	41 (78.8)	129 (62.6)	177 (63.0)	0.072
Nonregional lymph nodes, *n* (%)	397 (72.4)	39 (73.6)	154 (73.3)	204 (71.6)	0.894
Lung, *n* (%)	258 (47.1)	31 (58.5)	99 (47.1)	128 (44.9)	0.191
Liver, *n* (%)	169 (30.8)	16 (30.2)	80 (38.1)	73 (25.6)	0.012
Brain, *n* (%)	20 (3.6)	5 (9.4)	10 (4.8)	5 (1.8)	0.011
Bone, *n* (%)	190 (34.7)	20 (37.7)	84 (40.0)	86 (30.2)	0.067
Radiotherapy, *n* (%)	207 (37.8)	22 (41.5)	85 (40.5)	100 (35.2)	0.415
Prior targeted therapy (mainly FGFR inhibitors), *n* (%)	67 (13.2)	7 (14.6)	28 (14.1)	32 (12.2)	0.787

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; EV, enfortumab vedotin; FGFR, fibroblast growth factor receptor; G3/G4, Grade 3/4; ICI, immune checkpoint inhibitor; PS, performance status.

category, with more favorable responses observed among patients with higher scores.

Association between HERO score and survival outcomes

In the overall population, median OS was 12.4 months (95% CI 10.7-14.5), and median PFS was 6.8 months (95% CI 6.1-7.7).

A clear and statistically significant stratification of survival outcomes according to the HERO score was observed. Median OS increased from 7.3 months (95% CI 4.0-10.1) in patients with score 0, to 9.2 months (95% CI 7.5-11.1) in score 1, and to 16.1 months (95% CI 14.0-21.0) in score 2 ($P < 0.001$) (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2026.108302; Figure 2).

At 6, 12, and 24 months, OS rates were 56.5%, 29.7%, and 8.7% in the score 0 group; 68.1%, 39.0%, and 15.5% in the score 1 group; and 87.4%, 66.4%, and 38.5% in the score 2 group, respectively.

Compared with score 0, patients with score 2 had a significantly lower risk of death (HR 0.33, 95% CI 0.22-0.50, $P < 0.001$), while the difference between score 1 and score 0 did not reach statistical significance (HR 0.75, 95% CI 0.52-1.12, $P = 0.156$).

A similar pattern was observed for PFS. Median PFS was 5.3 months (95% CI 3.2-7.1) in patients with score 0, 5.8 months (95% CI 5.1-6.2) in score 1 patients, and 8.3 months (95% CI 7.4-11.4) in score 2 patients ($P < 0.001$) (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2026.108302; Figure 3).

At 6 months, PFS rates were 41.5%, 46.4%, and 65.6% for scores 0, 1, and 2, respectively, whereas at 12 months they were 12.2%, 16.1%, and 38.9%, respectively. The separation between survival curves remained evident also at 24 months. Patients with score 2 had a significantly reduced risk of progression compared with those with score 0 (HR 0.46, 95% CI 0.32-0.66, $P < 0.001$), whereas no significant difference was observed between score 1 and score 0 (HR 0.89, $P = 0.532$).

Cox regression analyses for OS/PFS

In univariate Cox regression analysis, NLR ≥4 was associated with worse PFS (HR 1.43, 95% CI 1.10-1.86, $P = 0.008$), whereas hemoglobin ≥11 g/dL was associated with improved PFS (HR 0.52, 95% CI, 0.42-0.65, $P < 0.001$). Bone metastases (HR 1.27, $P = 0.033$) and ECOG PS ≥1 (HR 1.60, $P < 0.001$) were also associated with shorter PFS

Table 2. Efficacy data of enfotumab vedotin according to HERO score

Variable	Total	Score 0	Score 1	Score 2	*P*
Best response, *n* (%) <0.001					
CR	45 (9.3)	2 (4.35)	11 (5.79)	32 (12.9)	
PR	181 (37.3)	13 (28.3)	69 (36.3)	99 (39.8)	
SD	130 (26.8)	12 (26.1)	42 (22.1)	76 (30.5)	
PD	129 (26.6)	19 (41.3)	68 (35.8)	42 (16.9)	
OS					
M-months (95% CI)	12.4 (10.7-14.5)	7.3 (4.0-10.1)	9.2 (7.5-11.1)	16.1 (14.0-21.0)	<0.001
PFS					
M-months (95% CI)	6.8 (6.1-7.7)	5.3 (3.2-7.1)	5.8 (5.1-6.2)	8.3 (7.4-11.4)	<0.001

CI, confidence interval; CR, complete response; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

(Supplementary Table S4 and Figure S1, available at https://doi.org/10.1016/j.esmoop.2026.108302).

In multivariate analysis, hemoglobin ≥11 g/dL (HR 0.54, 95% CI 0.42-0.69, $P < 0.001$) and ECOG PS 1 versus 0 (HR 1.44, 95% CI 1.08-1.91, $P = 0.013$) remained independently associated with PFS (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2026.108302**)**.

For OS, univariate analysis identified NLR ≥4 (HR 1.72, $P < 0.001$), hemoglobin ≥11 g/dL (HR 0.49, $P < 0.001$), lung metastases (HR 1.30, $P = 0.0387$), and ECOG PS ≥1 (HR 2.06, $P < 0.001$) as significant prognostic factors (Supplementary Table S6 and Figure S2, available at https://doi.org/10.1016/j.esmoop.2026.108302).

In multivariate analysis, hemoglobin ≥11 g/dL (HR 0.48, 95% CI 0.36-0.63, $P < 0.001$), ECOG PS ≥1 (HR 1.84, 95% CI 1.30-2.63, $P < 0.001$), lung metastases (HR 1.44, 95% CI 1.10-1.89, $P = 0.0074$), and NLR ≥4 (HR 1.38, 95% CI 1.01-1.88, $P = 0.0452$) remained independently associated with worse OS (Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2026.108302).

DISCUSSION

In this large international real-world cohort of patients with mUC treated with EV, we observed that the HERO score was consistently associated with survival outcomes and treatment response, supporting its potential role as a pragmatic prognostic stratification tool in routine clinical practice. The efficacy outcomes observed in the ARON-2EV cohort were consistent with those reported in clinical trials and other real-world datasets such as UNITE,[16] supporting the reproducibility of EV activity outside the context of highly selected trial populations. Our cohort also reflects routine clinical practice, including patients who are often underrepresented in clinical trials, such as older patients and those with less favorable PS.

A central finding of our study is the clinical prognostic relevance of the HERO score in this large international real-world cohort. We observed a clear gradient in both OS and PFS across score categories, with the most favorable outcomes seen in patients with a score of 2. In addition, response outcomes also differed according to HERO score,

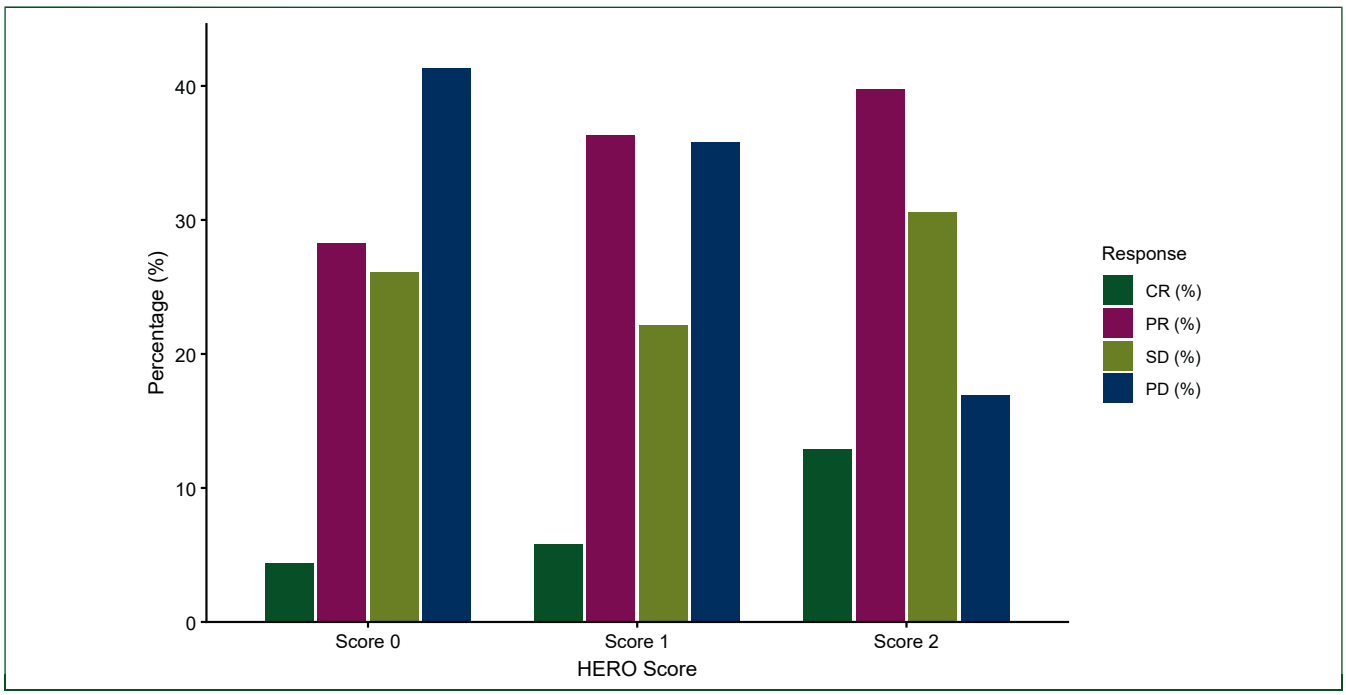

Figure 1. Treatment response according to HERO score.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

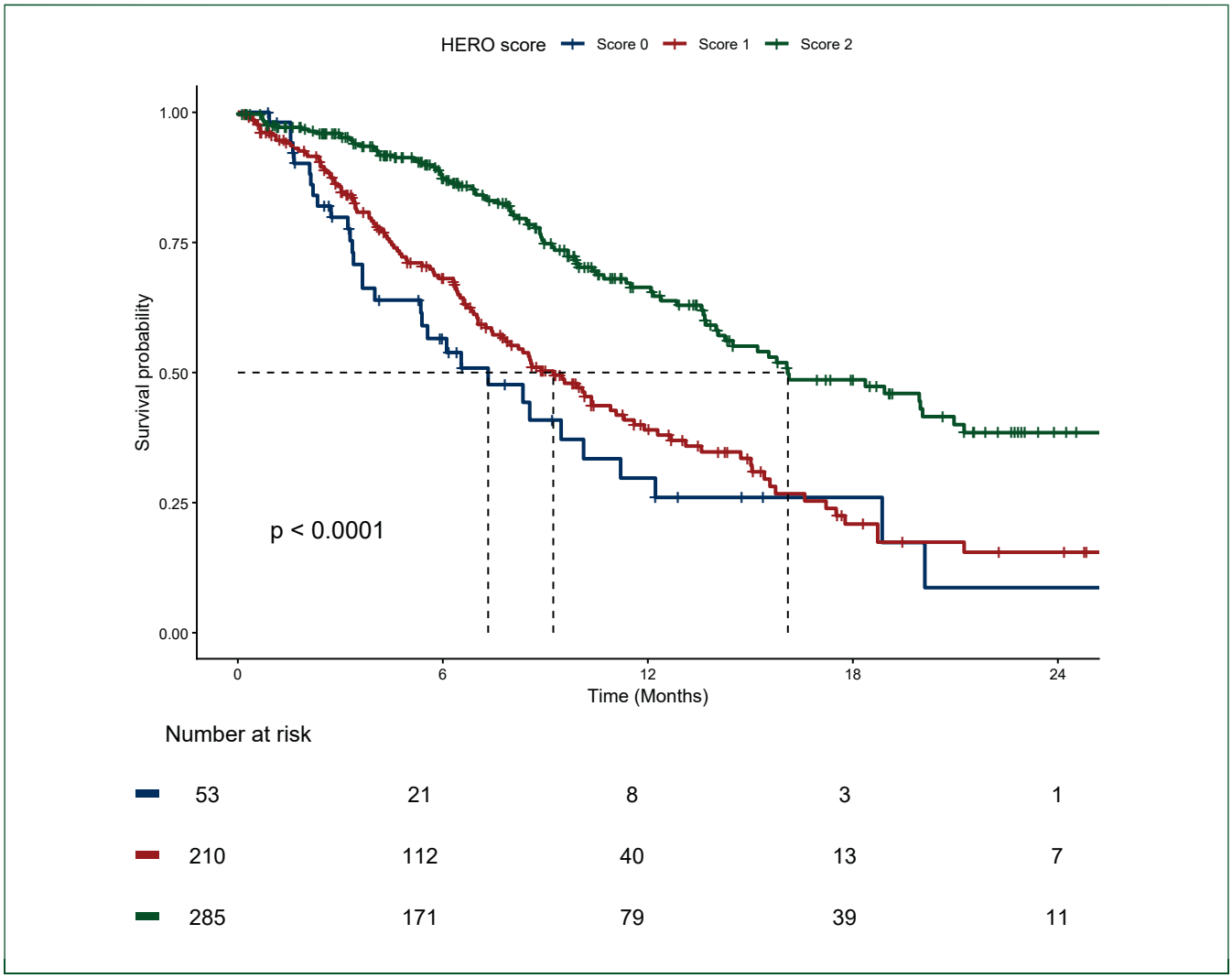

Figure 2. **Kaplan–Meier survival curve of overall survival according to HERO score.**

with more favorable responses observed among patients with higher scores. Taken together, these findings support previous observations suggesting that the HERO score represents a simple yet powerful tool for clinical risk stratification.[13] Notably, our data suggest that the HERO score captures clinically relevant differences not only in baseline prognosis but also in the treatment course during EV therapy. However, these findings should be interpreted with caution given the retrospective single-cohort nature of this analysis. The present study does not allow conclusions regarding treatment-specific predictive value. Rather, the data support the HERO score as a pragmatic prognostic stratification tool in EV-treated mUC.

The biological rationale for the HERO score is supported by the established prognostic role of both hemoglobin level and NLR in UC and other solid tumors. Elevated NLR reflects a systemic proinflammatory state associated with tumor progression and impaired immune surveillance, while anemia has been linked to tumor hypoxia, frailty, and aggressive disease biology. Both factors have been consistently associated with inferior outcomes across malignancies, including UC.[17] By integrating these two routinely available parameters, the HERO score may provide a simple and clinically meaningful summary of both host condition and disease aggressiveness.

An additional relevant observation in our study is the apparent threshold effect of the HERO score. While patients with score 2 consistently experienced significantly better outcomes, the separation between score 0 and score 1 was less pronounced and did not reach statistical significance in survival analyses. These findings suggest that the HERO score may be more effective in identifying a subgroup of patients with a particularly favorable prognosis rather than in providing clear discrimination across all three risk categories. This observation warrants further refinement and prospective evaluation of the score in future studies. Despite recent advances, reliable predictive biomarkers for EV remain lacking. To date, most molecular features, including fibroblast growth factor receptor 2/3 alterations and programmed death-ligand 1 expression, have shown limited or no predictive value for EV response.[17,18] In this context, recent genomic analyses are beginning to shed light on potential molecular determinants of sensitivity.

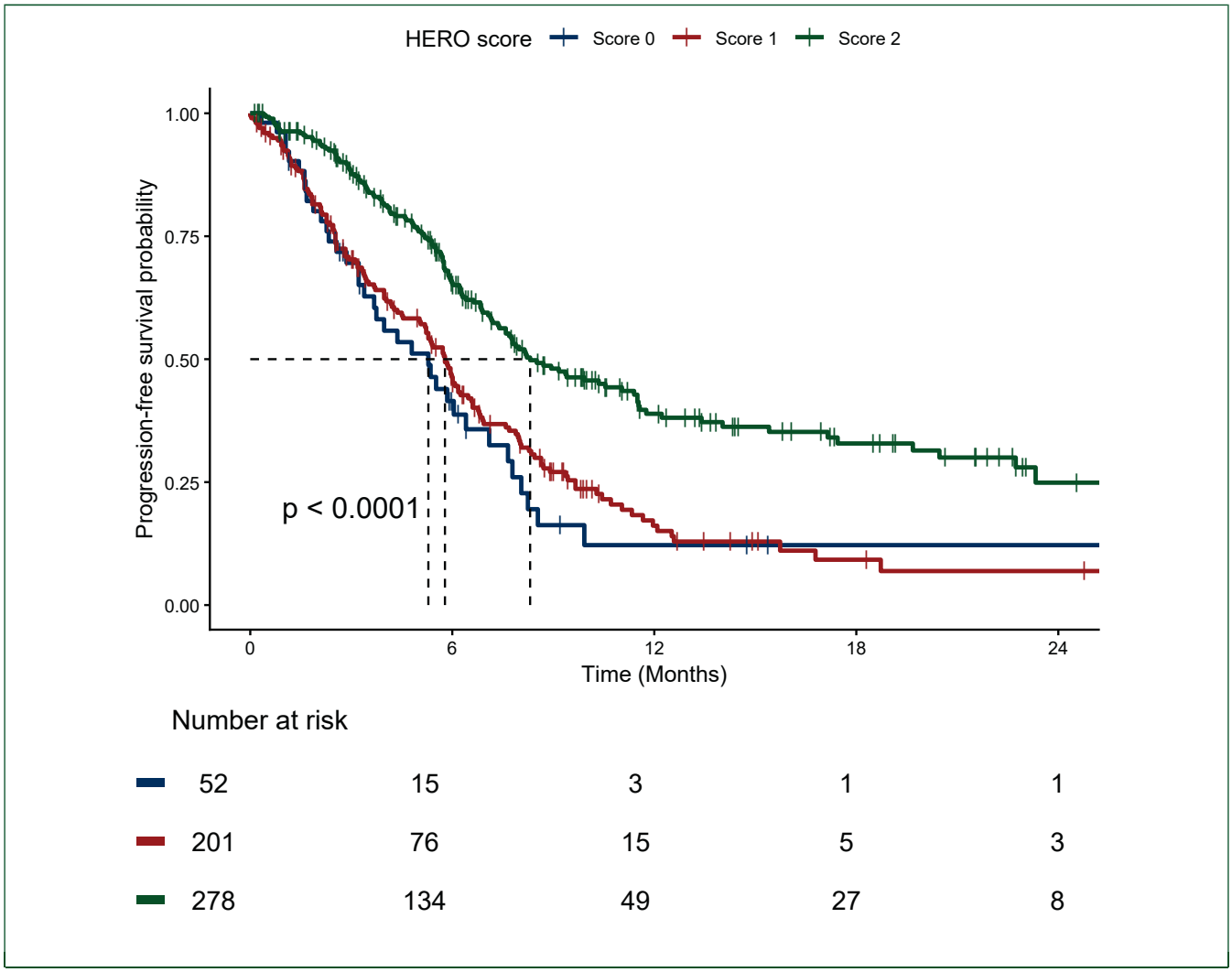

Figure 3. **Kaplan–Meier survival curve of progression-free survival according to HERO score.**

Notably, a retrospective study by Jindal et al[19] identified somatic alterations in tumor protein p53 (TP53) and mouse double minute 2 (MDM2) as potential biomarkers of improved response to EV. In this cohort, patients harboring TP53 or MDM2 alterations exhibited significantly higher response rates and prolonged PFS, with TP53 alterations remaining independently associated with improved outcomes in multivariable analyses. The composite TP53/MDM2 biomarker was particularly enriched among responders, suggesting a potential role of the p53 protein (p53) pathway in modulating sensitivity to EV. These findings are particularly intriguing given the well-established role of TP53 alterations as negative prognostic factors in UC. The observation that TP53-mutated tumors may derive enhanced benefit from EV suggests a possible shift from prognostic to predictive relevance in the context of antibody–drug conjugates. Mechanistically, it has been hypothesized that alterations in the p53–MDM2 axis may increase tumor vulnerability to cytotoxic payloads such as monomethyl auristatin E, although this remains speculative and warrants further investigation.[19]

Importantly, the integration of genomic biomarkers with clinical indices such as the HERO score could represent a future direction for more refined risk stratification. While the HERO score captures host-related factors and systemic inflammation, genomic alterations may provide complementary information on tumor biology. The combination of these dimensions could potentially lead to more accurate prediction models and personalized treatment strategies.

Beyond genomic factors, additional host-related characteristics have been associated with EV outcomes. For instance, higher BMI has been correlated with improved response rates and survival in patients treated with EV, possibly reflecting metabolic and pharmacokinetic influences.[20] Similarly, baseline albumin levels and ECOG PS have consistently emerged as independent prognostic factors across multiple studies, including both our analysis and prior reports.[19] These findings further emphasize the multifactorial nature of treatment outcomes in mUC.

The contemporary therapeutic landscape of UC is evolving rapidly, particularly with the increasing use of EV-based combinations and earlier-line treatment strategies.[21,22] Accordingly, the present findings should be interpreted within the specific context of a real-world cohort treated with EV monotherapy after prior platinum-

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based chemotherapy and ICI therapy. Whether the HERO score retains similar prognostic performance in patients treated with EV-based combinations or in earlier disease settings remains to be determined.

This study has several limitations. Firstly, its retrospective design introduces the possibility of selection bias, missing data, and uncontrolled confounding. In addition, the analysis was based on a complete-case approach including patients with available data required for HERO score calculation and outcome assessment, which may have introduced additional selection bias related to missing data. Secondly, treatment assessments were carried out according to local practice across multiple international centers, potentially introducing heterogeneity in follow-up schedules and response evaluations. Thirdly, although the HERO score was associated with survival outcomes, its predictive role for EV-specific benefit cannot be established in the absence of a comparator arm.

Furthermore, the present study did not include formal discrimination and calibration metrics commonly recommended for prognostic model validation, such as Uno's C-index or calibration analyses. Therefore, the findings should be interpreted as a real-world clinical prognostic assessment rather than a comprehensive formal validation study. Similarly, multivariable analyses were exploratory in nature and were not intended for formal prognostic model development or validation; accordingly, these findings should be interpreted cautiously and primarily as supportive analyses. In addition, the relatively limited number of patients in the HERO score 0 subgroup compared with the other categories may have reduced the discriminatory power between lower score groups. Finally, genomic data were not available in our cohort, limiting the possibility of integrating molecular biomarkers into the present analysis.[23,24]

Conclusion

This large international real-world study evaluated the clinical prognostic performance of the HERO score in patients with mUC treated with EV. The HERO score was associated with survival and response outcomes, particularly through the identification of a subgroup of patients with a more favorable prognosis (score 2). However, the discriminatory performance between lower score categories was less pronounced, suggesting that the score may be more effective in identifying favorable-risk patients rather than providing clear separation across all risk groups. Further prospective refinement and evaluation of the HERO score are warranted, particularly in the context of contemporary EV-based combination strategies.

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DATA AVAILABILITY

The datasets generated and analyzed during the current study are not publicly available due to privacy regulations but are available from the corresponding author on reasonable request.

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