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RESEARCH ARTICLE

Coşer et al.: HALP and BCG failure

Pretreatment HALP score and BCG failure in non-muscle-invasive bladder cancer

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ABSTRACT

Bacillus Calmette–Guérin (BCG) is a standard adjuvant treatment for intermediate- and high-risk non-muscle-invasive bladder cancer (NMIBC), but treatment failure remains common. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score reflects hematologic, nutritional, and inflammatory status. We investigated the association between pretreatment HALP and BCG failure. This retrospective, single-center study included 138 patients with intermediate- or high-risk NMIBC who completed adequate BCG exposure or developed early high-grade failure at the 3-month evaluation after induction BCG. Failure was classified using European Association of Urology (EAU) criteria. Pretreatment HALP, other inflammatory and nutritional indices, and clinicopathological risk scores were compared between outcome groups. Logistic regression evaluated associations with documented high-grade BCG failure during the available follow-up. Forty-one patients (29.7%) experienced failure. Median HALP was lower in the failure group than among responders (34.70 [interquartile range (IQR) 22.72–56.88] vs. 53.42 [IQR 42.45–68.06]; $p < 0.001$). HALP remained associated with failure after adjustment for smoking exposure and aspartate aminotransferase (AST) in the exploratory multivariable model (odds ratio [OR] per one-point increase 0.973, 95% confidence interval [CI] 0.954–0.991; $p = 0.004$). Greater smoking exposure (OR 1.021 per pack-year; $p = 0.041$) and higher AST (OR 1.070 per U/L; $p = 0.029$) were also independently associated with failure. The apparent area under the receiver operating characteristic (ROC) curve (AUC) was 0.702 for HALP alone and 0.737 for the multivariable model. Lower pretreatment HALP was associated with BCG failure in this cohort, including after adjustment in an exploratory model. HALP warrants further study as a risk-stratification biomarker, but external validation is required before clinical use.

Keywords: Non-muscle-invasive bladder cancer, bacillus Calmette–Guérin, BCG failure, HALP, biomarkers.

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INTRODUCTION

Non-muscle-invasive bladder cancer (NMIBC) accounts for approximately 75% of bladder cancers and encompasses a heterogeneous spectrum of tumors with substantially different risks of recurrence and progression [1]. For intermediate- and high-risk disease, intravesical Bacillus Calmette–Guérin (BCG) remains a cornerstone of adjuvant treatment following transurethral resection of the bladder tumor (TURBT) [2]. Despite adequate BCG therapy, however, a considerable proportion of patients experience unfavorable clinical outcomes, most notably disease recurrence and, in some cases, progression to more advanced disease [3, 4]. Given that unresponsive disease often leads to worse oncological outcomes and frequently warrants radical cystectomy, prompt stratification of patients vulnerable to BCG failure remains a critical clinical priority [5].

Several clinicopathological risk models have been developed to estimate recurrence and progression in NMIBC, including the European Organisation for Research and Treatment of Cancer (EORTC) risk tables and the Club Urológico Español de Tratamiento Oncológico (CUETO) scoring model [6, 7]. Although these models provide useful prognostic information, their discriminatory performance in BCG-treated populations remains suboptimal, suggesting that conventional clinicopathological factors may not fully capture the heterogeneity of treatment response [8]. This has prompted increasing interest in readily available biomarkers reflecting host-related inflammatory, immune, and nutritional status. Several such indices, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and prognostic nutritional index (PNI), have been investigated as potential prognostic biomarkers in patients with cancer [9].

The hemoglobin, albumin, lymphocyte, and platelet (HALP) score is an index that reflects the interplay between hematologic status, nutritional condition, and systemic immune-inflammatory activity [10]. Although HALP has been associated with outcomes across several malignancies, including bladder cancer, data on its relationship with BCG failure in NMIBC are limited [11]. Our objective was to investigate the association between pretreatment HALP score and high-grade BCG

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failure in patients with intermediate- or high-risk NMIBC treated with intravesical BCG, alongside established risk scores and systemic inflammatory-nutritional indices.

MATERIALS AND METHODS

This retrospective, single-center cohort study included patients with intermediate- or high-risk NMIBC treated with intravesical BCG at the Department of Urology, Kütahya Health Sciences University Evliya Çelebi Training and Research Hospital between January 2015 and December 2025. Follow-up data were collected until December 2025. Follow-up duration was calculated from the date of the initial TURBT to the last documented clinical assessment. Patients without a documented high-grade BCG-failure event were required to have at least 24 months of follow-up, whereas patients with a documented high-grade BCG-failure event were eligible irrespective of follow-up duration, provided that they met the BCG-exposure eligibility criteria.

A total of 138 eligible patients were classified as BCG failure (n = 41) or BCG response (n = 97). NMIBC risk groups were retrospectively assigned according to the 2023 European Association of Urology (EAU) guidelines. Very-high-risk patients were excluded to focus the study on intermediate- and high-risk disease, as the guidelines recommend offering immediate radical cystectomy to patients with very-high-risk NMIBC. Exclusion criteria were muscle-invasive bladder cancer at initial diagnosis, low- or very-high-risk NMIBC, insufficient BCG exposure in the absence of a qualifying early high-grade failure at the 3-month evaluation following induction BCG, missing data required for eligibility assessment, outcome classification, or calculation of the HALP score, active infection or inflammatory disease at blood sampling, hematologic malignancy, autoimmune disease, chronic systemic corticosteroid or immunosuppressive therapy, concomitant malignancy, and previous intravesical therapy other than BCG. Patients were also excluded if they were lost to follow-up, died or underwent cystectomy without a preceding documented high-grade BCG-failure event, or had less than 24 months of follow-up without a documented high-grade BCG-failure event.

All patients received induction BCG. The BCG preparation used was SII-ONCO-BCG (Moscow I [Russian] strain; Serum Institute of India, India) at a dose of 40 mg per instillation. The planned regimen consisted of six weekly induction instillations

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followed by three weekly maintenance instillations at months 3, 6, 12, 18, 24, 30, and 36. No second induction course was administered. Adequate BCG exposure was defined as at least five of six induction doses plus at least two of six doses of a second induction course or at least two of three maintenance doses. Patients who developed early high-grade failure at the 3-month evaluation following induction BCG were also eligible, even if they had not completed the additional BCG required to meet this exposure definition. The planned BCG treatment protocol remained unchanged throughout the study period. Information on treatment interruptions, dose reductions, or other treatment modifications was not systematically available in the retrospective records.

BCG-failure categories were assigned retrospectively according to the 2026 EAU guidelines [12]. The primary endpoint was documented high-grade BCG failure during the available follow-up, rather than BCG-unresponsive disease alone. Early failure included T1 high-grade disease at the 3-month evaluation, classified as BCG-refractory/unresponsive, and Ta high-grade disease and/or carcinoma in situ (CIS) following induction alone, classified as BCG-resistant within the BCG-exposed category. Subsequent high-grade failure events were classified according to their pathological findings, timing, and preceding BCG exposure. Time to recurrence was calculated from the last BCG instillation. Among patients who were disease-free after adequate BCG, delayed relapse after adequate BCG was defined as high-grade Ta/T1 recurrence more than 6 months and up to 24 months after the last instillation, or recurrence with CIS more than 12 months and up to 24 months after the last instillation. These cases were classified as BCG-exposed. Low-grade recurrence was not considered BCG failure. Patients were classified as responders only if they had at least 24 months of follow-up without a documented high-grade BCG-failure event. Patients with documented high-grade BCG failure were classified as failures regardless of follow-up duration. Patients lost to follow-up and those who died or underwent cystectomy without a preceding documented high-grade BCG-failure event were excluded. Outcome status was determined from available clinical records, including cystoscopic, pathological, and treatment documentation.

Collected variables encompassed baseline patient characteristics [age, sex, body mass index (BMI), smoking status, and Charlson Comorbidity Index (CCI)], baseline tumor attributes (size, multifocality, pathological stage, grade, and repeat TURBT

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pathology), alongside treatment dynamics and long-term outcomes (adverse events, recurrence, progression, and overall survival).

Baseline laboratory parameters used to calculate HALP and the other inflammatory and nutritional indices were obtained from blood samples collected within seven days before the initial TURBT, prior to the initiation of intravesical BCG therapy. These included hemoglobin, hematocrit, neutrophil, lymphocyte, monocyte, and platelet counts; serum albumin; aspartate aminotransferase (AST); and alanine aminotransferase (ALT). The De Ritis ratio was calculated as AST/ALT.

Using baseline laboratory workups, host-related inflammatory and nutritional biomarkers were calculated per standard protocols [10, 13]:

HALP score:

$$\frac{\text{Hemoglobin (g/L)} \times \text{Albumin (g/L)} \times \text{Lymphocyte count } (10^9/\text{L})}{\text{Platelet count } (10^9/\text{L})}$$

(with hemoglobin values standardized to g/L).

Prognostic nutritional index (PNI):

10 × albumin (g/dL) + 0.005 × absolute lymphocyte count (/mm³), equivalent to albumin (g/L) + 5 × absolute lymphocyte count (×10⁹/L)

Cellular ratios [neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR)]: Derived by dividing absolute neutrophil and platelet counts by absolute lymphocyte counts.

Composite indices [systemic immune-inflammation index (SII) and systemic inflammation response index (SIRI)]: $\text{SII} = (\text{Platelets} \times \text{Neutrophils})/\text{Lymphocytes}$; $\text{SIRI} = (\text{Neutrophils} \times \text{Monocytes})/\text{Lymphocytes}$.

To quantify baseline clinicopathological risk profiles, we calculated the 2006 EORTC and original CUETO risk scores. The EORTC recurrence and progression scores incorporated tumor multifocality, diameter, prior recurrence rate, pathological T stage, concomitant CIS, and histological grade. Similarly, CUETO scoring was computed based on age, gender, prior recurrence history, tumor multiplicity, T category, presence of CIS, and WHO grade, in line with the primary model definitions [6, 8].

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Ethical statement

The study was approved by the Clinical Research Ethics Committee of Kütahya Health Sciences University (approval no. 2025/10-01). Given the retrospective, non-interventional nature of this study and the use of fully anonymized data, both clinical trial registration and patient informed consent were not required.

Statistical analysis

Descriptive statistics for continuous parameters are presented as medians with corresponding interquartile ranges (IQRs) and assessed via the Mann–Whitney U test. For categorical data, frequencies and proportions [*n* (%)] were calculated, with group differences evaluated through Pearson's chi-square test or an exact test when expected frequencies were low.

Candidate baseline variables potentially associated with BCG failure were restricted a priori to pretreatment variables. Post-treatment variables or variables directly related to BCG failure were excluded from association analyses and reported descriptively. Univariable logistic regression was used to examine associations between baseline variables and the binary outcome of documented BCG failure; odds ratios (ORs) and 95% confidence intervals (CIs) are reported. The binary outcome represented documented high-grade BCG failure during the available follow-up rather than failure within a fixed time horizon. Follow-up duration and censoring were not incorporated into the logistic regression analysis.

Because several inflammatory indices and clinicopathological risk scores share underlying components, collinearity was assessed before multivariable modeling. Only one representative variable from each collinear cluster, defined by an absolute correlation coefficient >0.70 or substantial overlap in component derivation, was retained. Variables with $p < 0.10$ after collinearity screening were considered for multivariable logistic regression. Forward stepwise selection based on the likelihood-ratio criterion was used, with an entry threshold of $p < 0.05$. Owing to the limited number of endpoints observed, multivariable modeling was conducted strictly on an exploratory basis. In a sensitivity analysis, HALP and the CUETO recurrence score were entered simultaneously into a logistic regression model for documented high-grade BCG failure. Apparent discrimination was evaluated in the same patients for three models: CUETO recurrence score alone, HALP alone, and CUETO recurrence

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score plus HALP. Areas under the receiver operating characteristic (ROC) curves (AUCs) and their 95% CIs were estimated using the DeLong method. The AUCs of the CUETO-only and combined models were compared using a paired DeLong test.

ROC analysis was used to describe the apparent discrimination of HALP and the final multivariable model for the binary outcome of documented BCG failure, expressed as the AUC. AUC 95% CIs were estimated using 2,000 bootstrap iterations. The events-per-variable ratio was reported to contextualize model stability. All statistical evaluations were performed utilizing IBM SPSS Statistics (v. 30, IBM Corp., Armonk, NY, USA). Two-sided testing was applied throughout, with *p*-values below 0.05 deemed statistically significant.

Analyses were performed using available data for each variable; no imputation was undertaken. Hematocrit values were unavailable for 35 patients (25.4%) because the corresponding laboratory records could not be retrieved during retrospective data collection. Hematocrit was not included in the multivariable model because of this missingness and its overlap with hemoglobin and HALP.

RESULTS

Of 210 patients screened, 72 were excluded because of insufficient BCG exposure without a qualifying early high-grade failure (n = 19), missing data required to calculate HALP (n = 14), insufficient follow-up or loss to follow-up (n = 21), or death or cystectomy without a preceding documented high-grade failure event (n = 18). The final cohort comprised 138 patients, including eight with intermediate-risk and 130 with high-risk NMIBC. Among the 41 patients with BCG failure, 35 were classified as BCG-exposed, including six with BCG-resistant disease and 29 with delayed relapse after adequate BCG, while the remaining six were classified as BCG-unresponsive (Figure 1). Baseline characteristics are summarized in Table 1. Median follow-up was 42 months overall, 39 months in patients with BCG failure, and 44 months in BCG responders. Patients with BCG failure had greater cumulative smoking exposure and lower hematocrit, hemoglobin, lymphocyte count, and albumin levels. HALP and PNI were lower, whereas PLR and CUETO recurrence and progression scores were higher in the BCG-failure group (all $p < 0.05$). NLR, SII, SIRI, EORTC recurrence and progression scores, initial TURBT pathology, and tumor multiplicity did not differ significantly between groups.

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HALP was lower in patients with BCG failure than in responders (34.70 [IQR 22.72–56.88] vs. 53.42 [IQR 42.45–68.06]; $p < 0.001$). In univariable logistic regression, lower HALP was associated with BCG failure (OR 0.973, 95% CI 0.955–0.991; $p = 0.003$). When expressed per 10-unit increase, HALP was associated with approximately 24% lower odds of BCG failure (OR 0.761, 95% CI 0.624–0.914). Hemoglobin, hematocrit, PNI, lymphocyte count, PLR, CUETO recurrence and progression scores, and cumulative smoking exposure were also associated with BCG failure (Table 2).

Following collinearity screening, HALP, CUETO recurrence score, smoking exposure, BMI, and AST were considered for multivariable logistic regression. The final exploratory model retained HALP, smoking exposure, and AST. Lower HALP remained associated with BCG failure after adjustment for smoking exposure and AST in the exploratory model (OR 0.973, 95% CI 0.954–0.991; $p = 0.004$). Greater smoking exposure (OR 1.021 per pack-year, 95% CI 1.001–1.042; $p = 0.041$) and higher AST (OR 1.070 per U/L, 95% CI 1.007–1.137; $p = 0.029$) were also independently associated with higher odds of BCG failure. With 41 failure events and three variables in the final model, the events-per-variable ratio was 13.7.

All 138 patients were included in both the final multivariable logistic regression and ROC analyses. The multivariable model showed moderate apparent discrimination for documented BCG failure (AUC 0.737, 95% CI 0.637–0.832), while HALP alone yielded an AUC of 0.702 (95% CI 0.593–0.804). Because lower HALP values were associated with BCG failure, HALP was reverse-coded (−HALP) for the ROC analysis (Figure 2).

The CUETO sensitivity analysis included all 138 patients, of whom 41 experienced documented high-grade BCG failure. After adjustment for the CUETO recurrence score, each one-point increase in HALP was associated with lower odds of BCG failure (adjusted OR 0.979, 95% CI 0.961–0.998, $p = 0.028$). The AUC was 0.663 (95% CI 0.558–0.768) for the CUETO recurrence score alone, 0.702 (95% CI 0.595–0.808) for HALP alone, and 0.725 (95% CI 0.622–0.827) for CUETO plus HALP. Adding HALP to the CUETO-only model increased the apparent AUC by 0.062 (95% CI 0.003–0.121, paired DeLong $p = 0.040$).

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DISCUSSION

In this retrospective cohort of BCG-treated patients with intermediate- or high-risk NMIBC, lower pretreatment HALP was associated with high-grade BCG failure after adjustment for smoking exposure and AST in an exploratory multivariable model. Greater cumulative smoking exposure and higher AST levels were also independently associated with failure. The final model incorporating HALP, smoking exposure, and AST demonstrated moderate discrimination (AUC 0.737), while HALP alone yielded an AUC of 0.702. These findings suggest that HALP may reflect host-related hematologic, nutritional, and immune-inflammatory characteristics associated with BCG failure. Whether HALP adds prognostic information beyond established clinicopathological models requires formal comparative analyses and external validation.

Risk stratification in NMIBC has traditionally relied on clinicopathological characteristics. However, clinically relevant recurrence remains common despite BCG therapy, as also demonstrated by Flury-Sutter et al. in a contemporary prospective BCG-treated NMIBC cohort [14]. The original EORTC risk tables estimate recurrence and progression based on clinicopathological factors, whereas the CUETO model was specifically developed in BCG-treated patients [15, 16]. In our cohort, CUETO recurrence and progression scores were significantly higher in patients with BCG failure, whereas EORTC scores did not differ between groups. This finding is consistent with differences in the populations from which these models were derived, particularly because the original EORTC model was not developed specifically in BCG-treated patients [17, 18]. In the present cohort, EORTC and CUETO scores were calculated as established clinicopathological risk estimates. In the sensitivity analysis, lower HALP remained associated with higher odds of documented high-grade BCG failure after adjustment for the CUETO recurrence score. Adding HALP to the CUETO-only model increased the apparent AUC from 0.663 to 0.725. Both models were developed and evaluated in the same cohort, so this improvement is exploratory and requires external validation.

The biological rationale for the association between HALP and BCG response is plausible. HALP integrates hemoglobin and albumin as markers of hematologic and nutritional status, lymphocyte count as a measure of immune competence, and platelet count, which may reflect systemic inflammatory activity. Lower HALP has been

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associated with adverse outcomes across several malignancies [19], and Peng et al. demonstrated an association between lower HALP scores and poorer survival following radical cystectomy for bladder cancer [20]. In a recent retrospective study involving 428 patients with NMIBC, Utlu et al. reported significantly lower HALP scores in patients with recurrence than in those without recurrence (4.6 ± 1.4 vs. 5.9 ± 1.3, $p < 0.001$), with HALP remaining an independent predictor of recurrence in multivariable analysis [11]. They also observed significantly lower HALP values in patients who developed disease progression ($p = 0.006$). This may be particularly relevant to BCG therapy, whose antitumor activity depends on an effective immune response. In our cohort, patients with BCG failure had lower hemoglobin, lymphocyte, and albumin levels, consistent with the composite HALP association. However, these findings remain associative and do not establish a mechanistic link between HALP components and BCG efficacy.

Our findings are consistent with growing evidence that systemic inflammatory and nutritional status may have prognostic value in BCG-treated NMIBC. Ye et al., in a cohort of 501 patients receiving intravesical BCG, reported that pretreatment hemoglobin, albumin, and PNI were associated with recurrence-free survival [21]. Similarly, a BCG-specific inflammation and nutrition index incorporating hemoglobin, albumin, and platelet count independently predicted recurrence after BCG therapy [22]. In our cohort, PNI was lower and PLR higher in patients with BCG failure, whereas NLR, SII, and SIRI did not differ significantly between groups. Although a recent meta-analysis associated elevated pretreatment NLR with recurrence and progression after BCG therapy [23], NLR was not associated with BCG failure in our cohort, highlighting variability among individual inflammatory markers. Given the substantial overlap among these indices, collinearity was considered before multivariable modeling, and HALP remained associated with BCG failure after adjustment for smoking exposure and AST in the exploratory model. These findings support further investigation of integrated host-related biomarkers in BCG-treated NMIBC.

Smoking exposure was also independently associated with BCG failure. A meta-analysis of 64 studies and 28,617 patients associated smoking with increased risks of NMIBC recurrence and progression, including an adverse association with progression among BCG-treated patients [24]. Greater cumulative smoking exposure

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has also been associated with worse NMIBC outcomes [25], while a BCG-treated cohort reported increasing risks of recurrence and progression with greater smoking exposure [26]. In our study, each additional pack-year was associated with a modest increase in the odds of BCG failure. However, this finding should be interpreted cautiously because changes in smoking behavior and cessation during follow-up were not assessed.

Higher baseline AST was also independently associated with BCG failure. Previous studies have linked the AST/ALT (De Ritis) ratio to recurrence or progression in NMIBC [27]. However, AST did not differ significantly between groups in our cohort, and neither ALT nor the De Ritis ratio was associated with BCG failure. Therefore, the association with AST alone should be considered exploratory and may reflect residual confounding or model-specific effects rather than a disease-specific biomarker. Independent validation is required.

From a clinical perspective, HALP is attractive because its components are routinely available and require no additional testing. Molecular studies have demonstrated biological heterogeneity in BCG response that is not fully captured by conventional clinicopathological variables [28]. A readily available host-related biomarker such as HALP warrants further evaluation alongside established risk assessment approaches. However, discrimination was moderate for both HALP alone (AUC 0.702) and the multivariable model (AUC 0.737). HALP should therefore not be used as a standalone tool to guide BCG eligibility or radical cystectomy but rather considered a candidate adjunctive biomarker requiring further validation.

This study also has several strengths. Eligibility required either adequate BCG exposure or documented early high-grade failure following induction BCG, and failure categories were assigned retrospectively using the 2026 EAU guidelines. Predictor analyses were limited to pretreatment variables, avoiding incorporation of post-treatment events related to the outcome. Multiple inflammatory and nutritional indices were evaluated alongside established clinicopathological risk scores, with collinearity considered before multivariable modeling. Derived from routine pretherapeutic laboratory testing, the HALP score provides a low-cost, objective biomarker whose accessibility supports straightforward implementation in future trials.

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Limitations

Several limitations should be acknowledged. First, the retrospective, single-center design introduces potential selection bias, residual confounding, and center-specific effects. Because patients with very-high-risk NMIBC were excluded, the findings apply primarily to BCG-treated patients with intermediate- or high-risk NMIBC, and their applicability to patients with very-high-risk disease remains uncertain. Second, the follow-up requirement differed according to outcome status. Patients with documented high-grade BCG failure could be included with less than 24 months of follow-up, whereas patients without documented failure required at least 24 months of follow-up. This may have preferentially excluded patients without documented failure who were treated near the end of the study period, leading to selection bias. The direction and magnitude of its effect on the association between HALP and BCG failure are uncertain. A time-to-event analysis was not performed. Such an analysis restricted to the included cohort would still omit patients excluded because of insufficient follow-up. The logistic regression estimates therefore describe associations with documented high-grade BCG failure during the available follow-up and do not account for differences in time at risk or censoring. Exclusion of patients lost to follow-up and those who died or underwent cystectomy without a prior documented failure event may also have contributed to selection bias. Treatment interruptions and modifications could not be systematically assessed, limiting evaluation of their potential influence on BCG outcomes.

Third, the modest sample size and the 41 BCG failure events limit model stability. Although the final stepwise model included approximately 13.7 events per retained variable, this ratio does not capture the uncertainty introduced by variable selection. Univariable screening and forward stepwise selection may have excluded clinically important covariates. In a separate sensitivity analysis, the association between HALP and BCG failure persisted after adjustment for the CUETO recurrence score. Residual confounding by other clinicopathological factors remains possible.

Fourth, inflammatory and nutritional biomarkers may be influenced by unrecognized conditions despite the predefined exclusion criteria. Fifth, laboratory parameters were assessed at a single pretreatment time point, precluding evaluation of longitudinal HALP changes during BCG therapy. Sixth, the CUETO-only, HALP-only, and combined models were fitted and evaluated in the same cohort, which may have led to

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optimistic AUC estimates. External validation is needed to determine whether the improvement in discrimination observed after adding HALP to the CUETO recurrence score is reproducible.

CONCLUSION

Lower pretreatment HALP was associated with high-grade BCG failure after adjustment for smoking exposure and AST in an exploratory model of BCG-treated patients with intermediate- or high-risk NMIBC. Greater cumulative smoking exposure and higher AST were also independently associated with failure, and the three-variable model showed moderate discrimination. HALP is a simple, readily available biomarker that warrants further evaluation in NMIBC risk-stratification research; its current performance does not support standalone clinical use. Prospective, multicenter studies with external validation and assessment of HALP's incremental prognostic value are needed before its incorporation into clinical risk-stratification strategies.

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REFERENCES

1. Holzbeierlein JM, Bixler BR, Buckley DI, Chang SS, Holmes R, James AC, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline: 2024 amendment. J Urol. 2024;211(4):533–8. https://doi.org/10.1097/JU.0000000000003846

2. Kukreja JB. Non–muscle-invasive bladder cancer: side-by-side guideline comparison. Eur Urol Focus. 2023;9(6):954–6. https://doi.org/10.1016/j.euf.2023.05.004

3. Ghodoussipour S, Bivalacqua T, Bryan RT, Li R, Mir MC, Palou J, et al. A systematic review of novel intravesical approaches for the treatment of patients with non–muscle-invasive bladder cancer. Eur Urol. 2025;88(1):33–55. https://doi.org/10.1016/j.eururo.2025.02.010

4. Chehroudi AC, Black PC. Emerging intravesical therapies for the management of bacillus Calmette–Guérin (BCG)-unresponsive non-muscle-invasive bladder cancer: charting a path forward. Can Urol Assoc J. 2020;14(6):204–13. https://doi.org/10.5489/cuaj.6101

5. Taylor JI, Kamat AM, O'Donnell MA, Annapureddy D, Howard J, Tan WS, et al. Long-term outcomes of bladder-sparing therapy vs radical cystectomy in BCG-unresponsive non-muscle-invasive bladder cancer. BJU Int. 2025;135(2):260–8. https://doi.org/10.1111/bju.16509

6. Fernandez-Gomez J, Madero R, Solsona E, Unda M, Martinez-Piñeiro L, Gonzalez M, et al. Predicting nonmuscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guerin: the CUETO scoring model. J Urol. 2009;182(5):2195–203. https://doi.org/10.1016/j.juro.2009.07.016

7. Sylvester RJ, van der Meijden APM, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol. 2006;49(3):466–77. https://doi.org/10.1016/j.eururo.2005.12.031

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8. Xylinas E, Kent M, Kluth L, Pycha A, Comploj E, Svatek RS, et al. Accuracy of the EORTC risk tables and of the CUETO scoring model to predict outcomes in non-muscle-invasive urothelial carcinoma of the bladder. Br J Cancer. 2013;109(6):1460–6. https://doi.org/10.1038/bjc.2013.372

9. Chung JW, Kim JW, Lee EH, Chun SY, Park DJ, Byeon KH, et al. Prognostic significance of the neutrophil-to-lymphocyte ratio in patients with non-muscle invasive bladder cancer treated with intravesical Bacillus Calmette–Guérin and the relationship with the CUETO scoring model. Urol J. 2022;19(4):281–8. https://doi.org/10.22037/uj.v18i.6765

10. Farag CM, Antar R, Akosman S, Ng M, Whalen MJ. What is hemoglobin, albumin, lymphocyte, platelet (HALP) score? A comprehensive literature review of HALP's prognostic ability in different cancer types. Oncotarget. 2023;14:153–72. https://doi.org/10.18632/oncotarget.28367

11. Utlu A, Aksakallı T, Çelik F, Cinislioğlu AE, Altay MS, Bedir F, et al. HALP score as an independent prognostic biomarker for recurrence and progression in non–muscle-invasive bladder cancer: a retrospective cohort study. Surg Oncol. 2026;65:102357. https://doi.org/10.1016/j.suronc.2026.102357

12. Gontero P, Mariappan P, Pradere B, Rai BP, Liedberg F, Compérat E, et al. EAU guidelines on nonmuscle-invasive bladder cancer (TaT1 and CIS) – a summary of the 2026 guidelines update. Eur Urol. 2026;90(4):389–412. https://doi.org/10.1016/j.eururo.2026.04.009

13. Demirel ME, Çapkan AC, Can SS, Binzet MA. Admission inflammatory and immuno-nutritional indices and in-hospital mortality in emergency department patients admitted to intensive care: a retrospective cohort study. Front Med (Lausanne). 2026;13:1903440. https://doi.org/10.3389/fmed.2026.1903440

14. Flury-Sutter S, Heuzeroth F, Arbelaez E, Bubendorf L, Püschel H, Hayoz S, et al. Efficacy and tolerability of bacillus Calmette-Guérin strain Russia for the treatment of non-muscle-invasive bladder cancer: analysis of a prospective registry. Can Urol Assoc J. 2024;18(7):E233–9. https://doi.org/10.5489/cuaj.8552

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15. Mardelli C, Bertail T, Tachibana I, Verhoest G, Mathieu R, Pradere B, et al. Refining prognostication in non-muscle-invasive bladder cancer: from clinical models to artificial intelligence. Urol Oncol. 2026;44(5):111047. https://doi.org/10.1016/j.urolonc.2026.111047

16. Ślusarczyk A, Garbas K, Pustuła P, Zapała Ł, Radziszewski P. Assessing the predictive accuracy of EORTC, CUETO and EAU risk stratification models for high-grade recurrence and progression after Bacillus Calmette–Guérin therapy in non-muscle-invasive bladder cancer. Cancers (Basel). 2024;16(9):1684. https://doi.org/10.3390/cancers16091684

17. Oddens J, Brausi M, Sylvester R, Bono A, van de Beek C, van Andel G, et al. Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette–Guérin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. Eur Urol. 2013;63(3):462–72. https://doi.org/10.1016/j.eururo.2012.10.039

18. Gotto G, Alimohamed NS, Kulkarni GS, Black PC, Kassouf W, Kokorovic A, et al. A population-based analysis of patterns of care in patients with high-risk non-muscle-invasive bladder cancer from Alberta, Canada. Can Urol Assoc J. 2025;19(10):302–10. https://doi.org/10.5489/cuaj.9110

19. Xu H, Zheng X, Ai J, Yang L. Hemoglobin, albumin, lymphocyte, and platelet (HALP) score and cancer prognosis: a systematic review and meta-analysis of 13,110 patients. Int Immunopharmacol. 2023;114:109496. https://doi.org/10.1016/j.intimp.2022.109496

20. Peng D, Zhang CJ, Gong YQ, Hao H, Guan B, Li XS, et al. Prognostic significance of HALP (hemoglobin, albumin, lymphocyte and platelet) in patients with bladder cancer after radical cystectomy. Sci Rep. 2018;8(1):794. https://doi.org/10.1038/s41598-018-19146-y

21. Ye J, Tang C, Wu R, Tang Y, Yin H, Bai Y, et al. Preoperative blood-based nutritional biomarkers as significant prognostic factors after intravesical BCG therapy in patients with non-muscle-invasive bladder cancer. World J Urol. 2024;42(1):428. https://doi.org/10.1007/s00345-024-05148-1

EARLY ACCESS

22. Li D, Wu R, Wang J, Ye J, Yu Q, Feng D, et al. A prognostic index derived from LASSO-selected preoperative inflammation and nutritional markers for non-muscle-invasive bladder cancer. Clin Genitourin Cancer. 2024;22(3):102061. https://doi.org/10.1016/j.clgc.2024.02.012

23. Huang J, Lin L, Mao D, Hua R, Guan F. Prognostic value of neutrophil-to-lymphocyte ratio in patients with non-muscle-invasive bladder cancer with intravesical Bacillus Calmette–Guérin immunotherapy: a systematic review and meta-analysis. Front Immunol. 2024;15:1464635. https://doi.org/10.3389/fimmu.2024.1464635

24. Ślusarczyk A, Zapała P, Zapała Ł, Radziszewski P. The impact of smoking on recurrence and progression of non-muscle invasive bladder cancer: a systematic review and meta-analysis. J Cancer Res Clin Oncol. 2023;149(6):2673–91. https://doi.org/10.1007/s00432-022-04464-6

25. Rink M, Furberg H, Zabor EC, Xylinas E, Babjuk M, Pycha A, et al. Impact of smoking and smoking cessation on oncologic outcomes in primary non-muscle-invasive bladder cancer. Eur Urol. 2013;63(4):724–32. https://doi.org/10.1016/j.eururo.2012.08.025

26. Andrade DL, Moretti TBC, Neto WA, Benedetti J, Reis LO. Smoke load prognostic impact on bacillus Calmette–Guérin (BCG) treated non-muscle invasive bladder cancer. Int Urol Nephrol. 2020;52(8):1471–6. https://doi.org/10.1007/s11255-020-02438-6

27. Fukui-Kawaura S, Kawahara T, Araki Y, Nishimura R, Uemura K, Namura K, et al. A higher De Ritis ratio (AST/ALT) is a risk factor for progression in high-risk non-muscle invasive bladder cancer. Oncotarget. 2021;12(9):917–22. https://doi.org/10.18632/oncotarget.27944

28. de Jong FC, Laajala TD, Hoedemaeker RF, Jordan KR, van der Made ACJ, Boevé ER, et al. Non-muscle-invasive bladder cancer molecular subtypes predict differential response to intravesical Bacillus Calmette–Guérin. Sci Transl Med. 2023;15(697):eabn4118. https://doi.org/10.1126/scitranslmed.abn4118

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TABLES AND FIGURES WITH LEGENDS

Table 1. Baseline demographic, clinicopathological, laboratory, and inflammatory and nutritional characteristics by BCG treatment outcome

Variable	BCG failure (*n* = 41)	BCG response (*n* = 97)	*p* value
Age, years	66 (58–74)	64 (60–69)	0.173
BMI, kg/m²	26.2 (23.4–28.7)	27.0 (24.8–28.9)	0.109
Smoking, pack-years	35 (30–50)	30 (15–40)	**0.012**
Hematocrit, %	39.8 (31.2–45.15)	44.05 (40.8–46.77)	**0.005**
Hemoglobin, g/dL	13.2 (12.0–14.7)	14.7 (13.3–15.7)	**0.002**
Neutrophils, ×10⁹/L	5.33 (3.31–6.39)	5.25 (4.00–6.28)	0.452
Lymphocytes, ×10⁹/L	1.73 (1.38–2.35)	2.00 (1.60–2.52)	**0.022**
Platelets, ×10⁹/L	256 (211–280)	242 (201–295)	0.865
Monocytes, ×10⁹/L	0.50 (0.40–0.62)	0.49 (0.40–0.62)	0.876
Albumin, g/L	43 (43–44)	45 (42–47)	**0.047**
AST, U/L	20 (15–24)	18 (15–22)	0.138
ALT, U/L	20 (13–29)	19 (16–25)	0.896
De Ritis ratio (AST/ALT)	1.00 (0.82–1.20)	0.91 (0.73–1.14)	0.238
EORTC recurrence score	6 (5–8)	6 (5–9)	0.597
EORTC progression score	11 (9–12)	12 (8–15)	0.835
CUETO recurrence score	11 (8–13)	8 (5–11)	**0.002**
CUETO progression score	10 (7–12)	7 (4–10)	**0.003**
HALP score	34.70 (22.72–56.88)	53.42 (42.45–68.06)	**<0.001**
Tumor size, cm	3 (3–5)	4 (3–5)	0.529
PNI	51.60 (48.50–55.50)	54.85 (52.15–58.65)	**0.005**
SII	635 (477–1,012)	625 (427–842)	0.396
PLR	169 (116–194)	119 (100–150)	**<0.001**
SIRI	1.51 (0.74–2.07)	1.27 (0.96–1.70)	0.517
NLR	2.45 (1.84–3.81)	2.40 (1.93–3.40)	0.661

Sex, *n* (%)			1.000
Male	37 (90.2)	88 (90.7)	
Female	4 (9.8)	9 (9.3)	
CCI, *n* (%)			0.632
0	22 (53.7)	58 (59.8)	
≥1	19 (46.3)	39 (40.2)	
Initial TURBT pathology, *n* (%)			0.151
CIS	1 (2.4)	1 (1.0)	
TaHG	14 (34.1)	36 (37.1)	
T1HG	21 (51.2)	52 (53.6)	
TaHG+CIS	0 (0)	5 (5.2)	
T1HG+CIS	5 (12.2)	3 (3.1)	
Tumor multiplicity, *n* (%)			1.000
Solitary	21 (51.2)	48 (49.5)	
Multiple	20 (48.8)	49 (50.5)	

Continuous variables are presented as median (IQR) and categorical variables as *n* (%). Continuous variables were compared using the Mann–Whitney U test; categorical variables were compared using Pearson's chi-square test or an exact test, as appropriate. Hematocrit values were unavailable for eight patients in the BCG-failure group and 27 patients in the BCG-response group. Two-sided p values < 0.05 were considered statistically significant and are shown in bold. **Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCG, bacillus Calmette–Guérin; BMI, body mass index; CCI, Charlson Comorbidity Index; CIS, carcinoma in situ; CUETO, Club Urológico Español de Tratamiento Oncológico; EORTC, European Organisation for Research and Treatment of Cancer; HALP, hemoglobin, albumin, lymphocyte, and platelet score; HG, high grade; IQR, interquartile range; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; SIRI,

EAU

systemic inflammation response index; TURBT, transurethral resection of bladder tumor.

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Table 2. Univariable and multivariable logistic regression analyses of baseline variables associated with BCG treatment failure

Variable	Univariable OR (95% CI)	*p* value	Multivariable OR (95% CI)	*p* value
Hemoglobin, g/dL	0.728 (0.610–0.870)	**<0.001**	—	—
Hematocrit, %	0.885 (0.824–0.950)	**<0.001**	—	—
HALP score	0.973 (0.955–0.991)	**0.003**	0.973 (0.954–0.991)	**0.004**
CUETO recurrence score	1.204 (1.064–1.362)	**0.003**	—	—
CUETO progression score	1.213 (1.065–1.381)	**0.004**	—	—
PLR	1.012 (1.004–1.020)	**0.005**	—	—
PNI	0.904 (0.839–0.975)	**0.009**	—	—
Lymphocytes, $\times 10^9$/L	0.469 (0.257–0.857)	**0.014**	—	—
Smoking, pack-years	1.022 (1.002–1.042)	**0.029**	1.021 (1.001–1.042)	**0.041**
BMI, kg/m²	0.886 (0.781–1.005)	0.060	—	—
AST, U/L	1.052 (0.996–1.111)	0.067	1.070 (1.007–1.137)	**0.029**
ALT, U/L	1.018 (0.994–1.043)	0.132	—	—
Albumin, g/L	0.924 (0.834–1.025)	0.135	—	—
Age, years	1.029 (0.987–1.073)	0.181	—	—
SII	1.000 (1.000–1.001)	0.209	—	—
NLR	1.139 (0.929–1.396)	0.210	—	—
SIRI	1.173 (0.897–1.532)	0.243	—	—
De Ritis ratio (AST/ALT)	1.488 (0.674–3.284)	0.325	—	—
Neutrophils, $\times 10^9$/L	0.922 (0.757–1.123)	0.421	—	—
EORTC recurrence score	0.951 (0.824–1.098)	0.494	—	—
Monocytes, $\times 10^9$/L	0.641 (0.178–2.312)	0.497	—	—
CCI ≥1 (ref. 0)	1.284 (0.615–2.681)	0.505	—	—
Platelets, $\times 10^9$/L	1.001 (0.995–1.006)	0.799	—	—
EORTC progression score	1.009 (0.923–1.102)	0.847	—	—

Multiple tumors (ref. solitary)	0.933 (0.449–1.937)	0.852	—	—
Female sex (ref. male)	1.057 (0.306–3.649)	0.930	—	—
Tumor size, cm	0.996 (0.836–1.188)	0.967	—	—

Univariable logistic regression included baseline pretreatment variables; post-treatment variables and variables directly related to the definition or consequences of BCG failure were excluded a priori. Collinearity was assessed because several inflammatory and nutritional indices share components and the EORTC and CUETO recurrence and progression scores were highly correlated. One representative variable from each collinear cluster was retained. Following this screening, HALP, CUETO recurrence score, smoking exposure, BMI, and AST were eligible for entry into the forward stepwise multivariable model. CUETO recurrence score and BMI did not meet the likelihood-ratio entry criterion; the final model included HALP, smoking exposure, and AST. With 41 failure events and three retained variables, there were approximately 13.7 events per variable. Multivariable results are exploratory and require external validation. Statistically significant *p* values are shown in bold. — indicates a variable not included in the final multivariable model. **Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCG, bacillus Calmette–Guérin; BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; CUETO, Club Urológico Español de Tratamiento Oncológico; EORTC, European Organisation for Research and Treatment of Cancer; HALP, hemoglobin, albumin, lymphocyte, and platelet score; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index.

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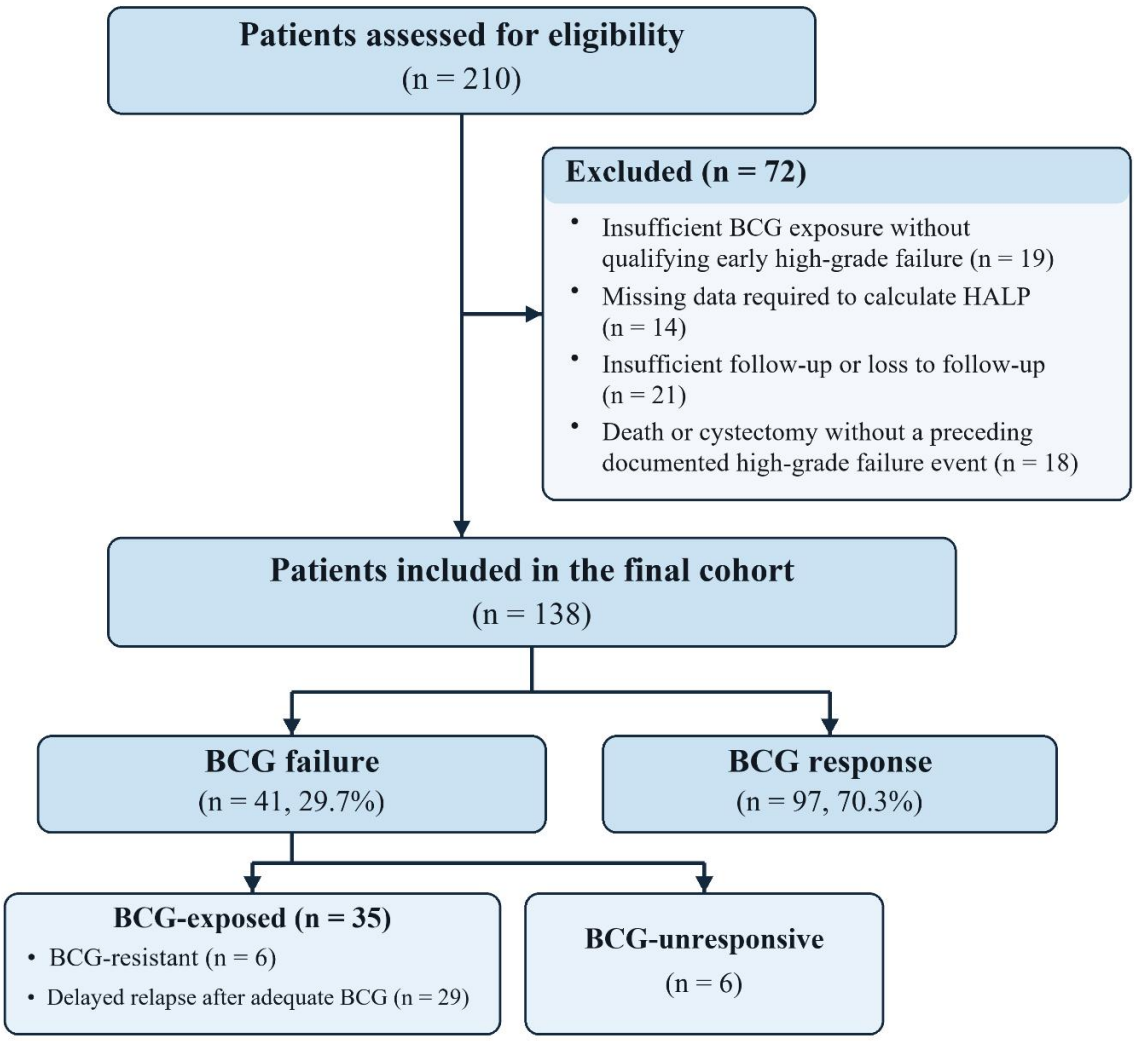


Figure 1. Patient selection and classification by BCG treatment outcome. Of 210 patients assessed for eligibility, 72 were excluded for the reasons shown and 138 were included in the final cohort. Documented high-grade BCG failure occurred in 41 patients (29.7%), while 97 (70.3%) were classified as responders. The failure group comprised 35 patients with BCG-exposed disease, including six with BCG-resistant disease and 29 with delayed relapse after adequate BCG, and six patients with BCG-unresponsive disease. **Abbreviations:** BCG, bacillus Calmette–Guérin; HALP, hemoglobin, albumin, lymphocyte, and platelet score.

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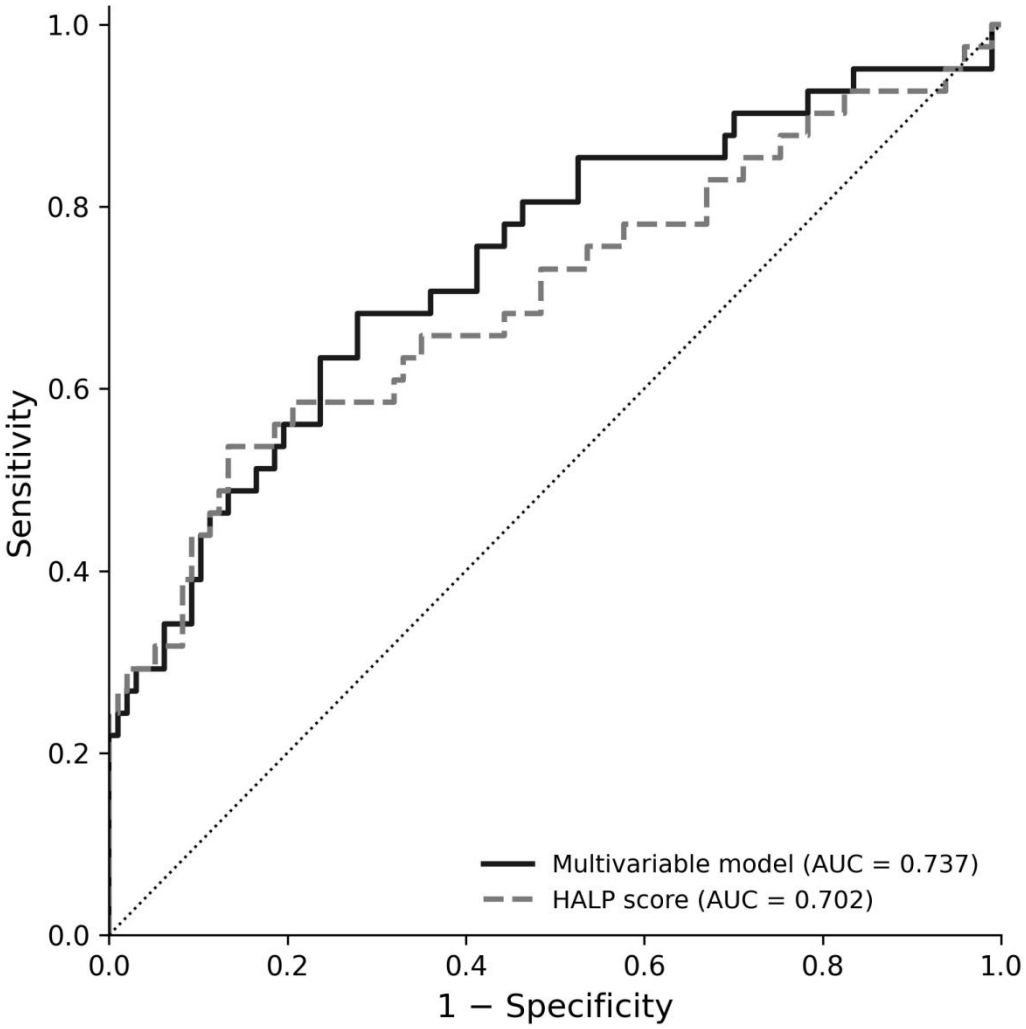


Figure 2. ROC curves for discrimination of documented high-grade BCG failure. Analyses included all 138 patients. The solid black curve represents the exploratory multivariable model comprising HALP score, smoking exposure, and AST (AUC 0.737, 95% CI 0.637–0.832). The dashed gray curve represents HALP alone (AUC 0.702, 95% CI 0.593–0.804). HALP was reverse-coded (−HALP) because lower scores were associated with BCG failure. The 95% CIs were estimated using 2,000 bootstrap iterations. The dotted diagonal line indicates chance-level discrimination. **Abbreviations:** AST, aspartate aminotransferase; AUC, area under the curve; BCG, bacillus Calmette–Guérin; CI, confidence interval; HALP, hemoglobin, albumin, lymphocyte, and platelet score; ROC, receiver operating characteristic.