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ORIGINAL RESEARCH

Hematological Inflammatory Gradient Score (HIGS): A Novel Predictor of Early Mortality After Coronary Artery Bypass Grafting

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Background: Early in-hospital mortality remains an important concern after coronary artery bypass grafting. Existing risk scores, such as EuroSCORE and STS, rely mainly on demographic and clinical parameters and do not adequately incorporate routine hematological markers. This study aimed to develop and validate the Hematological Inflammatory Gradient Score (HIGS), a novel model derived from routinely available hematological indices, to predict early postoperative mortality after coronary artery bypass grafting (CABG).

Methods: A retrospective, single-center cohort of 202 patients undergoing elective isolated CABG between January 2022 and March 2024 was analyzed. HIGS was calculated using standardized z-scores of red cell distribution width (RDW), platelet distribution width (PDW), and immature granulocyte percentage (IG%). Discrimination was assessed with ROC curve analysis, while logistic regression identified independent predictors of mortality.

Results: In-hospital mortality occurred in 10.9% (22/202) of patients. Compared with survivors, non-survivors had significantly higher HIGS values (1.02 ± 0.74 vs –0.12 ± 0.43, $p < 0.001$). HIGS demonstrated the highest discriminative ability for mortality prediction among tested parameters (AUC = 0.862, 95% CI: 0.794–0.931), with 86.4% sensitivity and 78.9% specificity at the optimal cut-off (>0.44). When added to the base model consisting of age, ejection fraction, and urea, HIGS provided a modest improvement in discrimination (AUC increase from 0.639 to 0.665). In multivariate analysis, lower ejection fraction, higher IG%, and elevated urea were independent predictors of mortality, and inclusion of HIGS improved model performance.

Conclusion: HIGS is a simple, inexpensive, and biologically plausible score derived from routine blood tests that reliably stratifies early mortality risk after CABG. If confirmed in larger, prospective multicenter studies, HIGS may serve as a practical adjunct to conventional risk models in perioperative decision-making. Given the retrospective, single-center design and limited event count, these findings should be interpreted cautiously, and external validation is required.

Keywords: Coronary artery bypass grafting, CABG, Hematological Inflammatory Gradient Score, HIGS, Red cell distribution width, RDW, Platelet distribution width, PWD, Immature granulocyte percentage, IG%

Key Points

What is known about the topic?

Early postoperative mortality following coronary artery bypass grafting remains a significant clinical problem. Although existing risk scores (EuroSCORE, STS) are widely used to predict mortality, they are primarily based on demographic and clinical parameters and do not adequately incorporate routine hematological markers. While previous studies have reported associations between hematological parameters such as RDW, PDW, and IG% and cardiac surgical outcomes, no model combining these parameters into a single score has been established.

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What does this study add?

This study introduces the Hematological Inflammatory Gradient Score (HIGS), a novel prognostic score derived from RDW, PDW, and IG% values. HIGS demonstrated strong performance as an independent predictor of early mortality after CABG and showed high discriminative ability in ROC analysis. Owing to its simplicity, low cost, and reliance on routine complete blood count data, HIGS represents a practical tool that can be easily applied in clinical practice. This score provides a new approach that may complement existing risk models.

Introduction

Coronary artery disease (CAD) remains one of the leading causes of morbidity and mortality worldwide.[1] In patients with multivessel involvement, coronary artery bypass grafting (CABG) surgery is the most effective treatment modality to improve survival and reduce symptoms.[2] However, despite all technical and technological advancements, in-hospital mortality after CABG surgery continues to be a major clinical concern.[3] Currently, the reported in-hospital mortality rate following CABG remains between 1–3%, and predicting these outcomes is of critical clinical importance.[4]

To predict CABG outcomes, several risk models such as EuroSCORE and STS have been developed and are widely used.[5] These scores are based on age, sex, comorbidities, surgical complexity, and preoperative clinical variables.[5] Nevertheless, the insufficient inclusion of biochemical and hematological markers in these models poses a limitation, particularly in accurately reflecting patients' risk profiles during the acute perioperative period.[6] Despite their widespread use, EuroSCORE II and STS have shown only moderate discriminative performance in contemporary CABG cohorts, with reported AUC values typically ranging between 0.70 and 0.78.[5,6] Moreover, these models tend to underperform in subgroups such as elderly patients, individuals with preserved ventricular function, and those without significant comorbidities, where inflammatory status may play a more dominant prognostic role.[5,6]

In recent years, hematological parameters, especially indicators reflecting inflammatory processes and immune responses, have been shown to be closely associated with cardiac surgical outcomes.[7–9] Systemic inflammation has been strongly linked to adverse outcomes after CABG.[4] Inflammatory activation contributes to postoperative mortality through several interconnected mechanisms. Increased granulocytic activity and erythrocyte heterogeneity impair microcirculatory flow, promote endothelial dysfunction, and exacerbate myocardial ischemia–reperfusion injury during cardiopulmonary bypass. Platelet activation further amplifies a prothrombotic and proinflammatory milieu, potentially worsening end-organ perfusion. Together, these processes create a systemic inflammatory response that may accelerate organ dysfunction and increase susceptibility to postoperative complications, thereby elevating mortality risk.[4,7–9] Elevated inflammatory activity contributes to myocardial injury, impaired microcirculatory flow, endothelial dysfunction, and multi-organ stress responses during and after cardiopulmonary bypass, ultimately increasing perioperative mortality risk.[9] Therefore, inflammatory markers may offer prognostic information that is not captured by traditional clinical variables. Red cell distribution width (RDW) has been identified as an important biomarker of systemic inflammation and tissue hypoxia.[7] Platelet distribution width (PDW) is an indicator of platelet activation and aggregation capacity, and has been associated with thrombotic risk and complications.[8] Immature granulocyte percentage (IG%) is considered a dynamic marker of active inflammatory response and bone marrow reserve.[9]

RDW, as a marker of systemic inflammation and hypoxia, has been defined as an independent predictor of mortality and complication risk following CABG.[7] PDW reflects platelet activation and has been associated with perioperative thrombosis and graft occlusion.[8] IG%, regarded as a dynamic indicator of inflammatory response, has been linked to postoperative complications and mortality when elevated.[9] The rationale for focusing on RDW, PDW, and IG% lies in their ability to capture distinct but interrelated mechanisms relevant to cardiac surgery outcomes. Several inflammation-based scores, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), have been investigated in cardiovascular diseases and cardiac surgery.[7–9] However, these scores rely primarily on cell-count ratios and do not simultaneously capture erythrocyte heterogeneity, platelet activation, and bone marrow–derived granulocytic response. Thus, none of the existing indices fully reflect the combined inflammatory, hypoxic, and pro-thrombotic pathways relevant to perioperative CABG mortality. RDW reflects anisocytosis driven by systemic inflammation and impaired erythropoiesis, PDW is a marker of platelet activation and prothrombotic potential, and IG% indicates acute inflammatory activity and bone marrow response. By integrating these three parameters, which are routinely available in a complete blood count, it is possible to construct a score that reflects inflammation, hypoxia, and thrombosis simultaneously—three major processes that critically influence CABG outcomes.[7–9]

Although these parameters individually carry prognostic value, their combined assessment into a novel scoring system has not been adequately investigated in the literature. To the best of our knowledge, HIGS represents the first composite hematological index specifically designed to integrate inflammatory, hypoxic, and thrombotic components into a single prognostic metric for early mortality after CABG. In this study, we developed the Hematological Inflammatory Gradient Score (HIGS), derived from RDW, PDW, and IG%, and evaluated its effectiveness in predicting early postoperative mortality after CABG.

Materials and Methods

Data Collection

Study Design

This study is a retrospective, single-center cohort investigation conducted at the Department of Cardiovascular Surgery, Mersin City Training and Research Hospital. Consecutive 202 patients who underwent elective isolated coronary artery bypass grafting between January 2022 and March 2024 were included. Emergency operations, cases with concomitant valve surgery, redo CABG procedures, and patients with hematological malignancy, active infection, or a history of immunosuppressive therapy were excluded. Potential confounders that might influence hematologic indices—such as preoperative anemia, occult infection, corticosteroid use, or antiplatelet/anticoagulant therapy—were assessed during data extraction. Patients with active infection, hematologic malignancy, or immunosuppressive therapy were already excluded by protocol, and hemoglobin levels were reviewed to identify clinically meaningful anemia. Although these factors were recorded, they were not included in the multivariable model due to the limited number of events. This selection was made to accurately evaluate the prognostic value of hematological parameters in a homogeneous patient population.

Data Collection

Patients' demographic characteristics (age, sex, body mass index), comorbidities (diabetes mellitus, hypertension, chronic kidney disease, chronic obstructive pulmonary disease, etc)., preoperative laboratory findings, and echocardiographic data were obtained from patient files and electronic medical records. Information on preoperative medication use—including antiplatelet agents, anticoagulants, and corticosteroids—was recorded from electronic medical files. Patients receiving chronic immunosuppressive therapy or high-dose corticosteroids were already excluded per protocol. Low-dose aspirin was routinely continued in accordance with institutional CABG practice. These variables were not included in multivariable models due to the limited number of events and the risk of model overfitting. The patient population represented a real-world, non-selected clinical cohort, characterized by a relatively high prevalence of comorbidities such as diabetes mellitus, hypertension, and renal dysfunction. These characteristics reflect the case-mix of our institution and may predispose the cohort to higher-than-expected perioperative risk profiles compared with traditional isolated elective CABG populations reported in the literature. Hematological parameters included red cell distribution width, platelet distribution width, and immature granulocyte percentage. These parameters were measured by automated hematology analyzers using complete blood samples obtained within 24 hours prior to surgery. All hematological measurements (RDW, PDW, IG%) were obtained using an automated hematology analyzer (Sysmex XN-1000, Sysmex Corporation, Kobe, Japan), which is routinely calibrated according to manufacturer and institutional quality-control standards. Perioperative data (cross-clamp time, cardiopulmonary bypass time, number of grafts) and postoperative outcomes (intensive care unit stay, mechanical ventilation time, complications, and in-hospital mortality) were retrieved from the prospectively maintained surgical database. Perioperative factors such as cardiopulmonary bypass duration, cross-clamp time, postoperative hemoglobin levels, and need for blood transfusion were also collected. However, these variables were not incorporated into the multivariable models because of the limited number of mortality events, which restricted the event-per-variable ratio and increased the risk of overfitting. As a result, residual confounding from perioperative factors cannot be completely excluded. The primary endpoint of the study was defined as in-hospital mortality. The study was reported in accordance with the RECORD (REporting of studies Conducted using Observational Routinely-collected Data) guidelines to ensure transparency and completeness in reporting observational research.

Data Analysis

Statistical Analysis

All analyses were performed two-tailed, with a p-value <0.05 considered statistically significant. The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test and q–q plots. Normally distributed variables were expressed as mean ± standard deviation, while non-normally distributed variables were presented as median (minimum–maximum). Categorical variables were expressed as numbers and percentages (%). All variables had >95% completeness; therefore, we performed a complete-case analysis without imputation. Missing data were minimal and involved only a few secondary demographic or laboratory variables, each with <5% missingness. No missingness was present in any of the primary variables used to construct HIGS (RDW, PDW, IG%), nor in key covariates such as mortality status, EF, urea, creatinine, or age. Comparisons between groups were performed using the Student's *t*-test for normally distributed continuous variables, the Mann–Whitney *U*-test for non-normally distributed variables, and the Chi-square or Fisher's exact test for categorical variables.

The HIGS developed in this study was calculated using standardized z-scores of RDW, PDW, and IG% values. The final formula was defined as follows:

$$\text{HIGS} = 0.5 \times Z_{\text{RDW}} + 0.3 \times Z_{\text{PDW}} + 0.2 \times Z_{\text{IG\%}}$$

For standardization, Z-scores were computed using the cohort-level preoperative means and standard deviations. To mitigate overfitting and outcome-driven weighting, we additionally derived data-driven coefficients via penalized logistic regression (LASSO) using 1000-bootstrap internal validation, and we report optimism-corrected discrimination (AUC), calibration intercept/slope, and Brier score. We avoided information leakage by deriving weights within cross-validation folds and, when comparing HIGS against its individual components, we fitted separate models to avert collinearity. The coefficients were determined considering biological plausibility, clinical relevance, and the discriminative contributions of each parameter obtained from ROC analysis. The final weighting scheme (0.5 for RDW, 0.3 for PDW, and 0.2 for IG%) was selected after evaluating multiple candidate models generated through exploratory logistic regression, ROC-based effect-size estimation, and penalized regression. We initially derived data-driven coefficients via LASSO and bootstrapping, and then compared their performance with clinically interpretable fixed-weight combinations. The selected weights provided the best balance between discrimination, calibration, and biological plausibility while maintaining model simplicity to facilitate bedside use. The final weighting scheme (0.5 for RDW, 0.3 for PDW, and 0.2 for IG%) was established after iterative testing of several coefficient combinations derived from exploratory logistic regression and ROC-based performance metrics. RDW was assigned the largest weight because it consistently demonstrated the strongest association with mortality across both univariate and multivariate analyses. PDW showed a moderate but clinically relevant predictive value, while IG% contributed additional information on acute inflammatory response. The chosen coefficients therefore balance statistical performance with biological plausibility, while also ensuring ease of clinical interpretability. This method was preferred over regression-based coefficients to ensure higher clinical interpretability. The prognostic performance of HIGS was evaluated using receiver operating characteristic (ROC) curve analysis; the area under the curve (AUC) was calculated, and the optimal cut-off values were determined by the Youden index.

All variables significantly associated with mortality in univariate analysis were included in a multivariate logistic regression model. Independent predictors were reported as odds ratios (OR) with 95% confidence intervals (CI). Model fit was assessed by the Hosmer–Lemeshow test, and calibration and discrimination characteristics were also reported. Given the limited number of events (n=22), we restricted multivariable modeling to prespecified parsimonious sets (≤2–3 parameters) and performed penalization (LASSO) as sensitivity analysis. Given the event-per-variable (EPV) ratio of approximately 7 for the univariate models and substantially lower for any multivariable configuration, the risk of overfitting is considerable. For this reason, we restricted all multivariable analyses to highly parsimonious models and treated coefficient estimates—especially for HIGS in the full model—with caution. The findings should therefore be interpreted as exploratory and hypothesis-generating rather than confirmatory. Variance inflation factors (VIFs) were <2 in all reported models. In addition, the prognostic power of HIGS was tested not only independently but also in comparison with

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established classical risk factors such as age, ejection fraction, renal function, and comorbidities. This approach allowed an objective evaluation of the incremental contribution of the newly developed score over existing models.

Software

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). In addition, we used R (v4.3+) with packages glmnet, rms, and pROC to perform penalized logistic regression (LASSO), bootstrap internal validation (1000 resamples), and calibration assessment (intercept, slope, Brier score). LASSO regression was performed using 10-fold cross-validation to identify the optimal penalty parameter (λ). Internal validation was conducted with 1000 bootstrap resamples. All penalized models were fitted using the "glmnet" package in R, and calibration analyses (intercept, slope, Brier score) were performed using the "rms" package. ROC analyses were conducted with the "pROC" package. ROC curves and determination of cut-off values were additionally conducted with MedCalc (MedCalc Software, Ostend, Belgium).

Results

A total of 202 patients who underwent elective isolated CABG between January 2022 and March 2024 were analyzed. The overall in-hospital mortality rate was 10.9% (22 patients), forming the Exitus group, while 180 patients survived and constituted the Alive group. Baseline demographic, clinical, and laboratory characteristics of the study population are summarized in the tables.

The data in Table 1 show that the mean age of the patients undergoing CABG was 62.2 years, with a range from 33 to 86 years. The mean ejection fraction (EF) was 52.8%, indicating a generally preserved systolic function. The mean glomerular filtration rate (GFR) was 92.7 mL/min/1.73m^2, with some patients exhibiting very high values up to 131, likely due to calculation variability in certain clinical contexts. Inflammatory markers such as CRP had a mean of 9.2 mg/L, while hematological parameters like RDW and PDW were 41.2% and 12.9 fL, respectively. The mean IG% was 0.66%. Regarding renal function, the mean urea and creatinine levels were 35.1 mg/dL and 0.86 mg/dL, respectively. Among the study population, 69.3% were male and 30.7% were female. The prevalence of diabetes mellitus and hypertension were 43.6% and 47.0%, respectively. The in-hospital mortality rate was observed to be 10.9% (Table 1).

The comparison of patients according to in-hospital mortality status presented in Table 2 shows that the Exitus group had a significantly higher mean age compared to the Alive group (66.0 ± 10.2 vs 61.8 ± 10.0 years, p = 0.024). Ejection fraction was significantly lower in the Exitus group (48.7 ± 7.2 vs 53.3 ± 6.2, p = 0.001), and glomerular filtration rate

Table 1 Distribution of Socio-Demographic and Clinical Characteristics in Patients Undergoing CABG (n = 202)

Characteristic	Mean ± SD	Median (Min–Max)
Age (years)	62.2 ± 10.1	63 (33–86)
EF (%)	52.8 ± 6.6	55 (30–65)
GFR (mL/min/1.73m^2)	92.7 ± 71.2	92 (8–131)
CRP (mg/L)	9.2 ± 12.0	5.0 (0.3–66.0)
RDW (%)	41.2 ± 4.8	40.5 (31.6–52.3)
PDW (fL)	12.9 ± 2.3	13.0 (8.2–19.5)
MPV (fL)	9.5 ± 1.1	9.4 (7.2–12.3)
IG (%)	0.66 ± 0.29	0.65 (0.1–1.6)
Urea (mg/dL)	35.1 ± 13.2	34 (15–80)
Creatinine (mg/dL)	0.86 ± 0.31	0.83 (0.45–2.1)

(*Continued*)

Table 1 (Continued).

Variable	Category	Count (n)	Percentage (%)
Gender	Male	140	69.3
	Female	62	30.7
Diabetes Mellitus	Yes	88	43.6
	No	114	56.4
Hypertension	Yes	95	47.0
	No	107	53.0
Mortality	Exitus	22	10.9
	Alive	180	89.1

Notes: Statistical tests applied include descriptive statistics, including mean ± standard deviation and median with range for continuous variables, and frequency (percentage) for categorical variables. In this table, no inferential statistical test was applied.
Abbreviations: EF, Ejection Fraction; CRP, C-Reactive Protein; RDW, Red Cell Distribution Width; PDW, Platelet Distribution Width; MPV, Mean Platelet Volume; IG, Immature Granulocyte Percentage; GFR, Glomerular Filtration Rate.

Table 2 Distribution and Comparison of Clinical and Demographic Characteristics According to Mortality Status in the Study Population (n = 202)

Variable	Overall (n = 202)	Alive (n = 180)	Exitus (n = 22)	p-value
Age (years)	62.2 ± 10.2 (33–86)	61.8 ± 10.0	66.0 ± 10.2	**0.024**
EF (%)	52.8 ± 6.7 (30–65)	53.3 ± 6.2	48.7 ± 7.2	**0.001**
GFR (mL/min/1.73m^2)	92.7 ± 71.3 (8–131)	95.5 ± 74.3	68.2 ± 42.1	**0.045**
CRP (mg/L)	9.2 ± 12.0 (0.3–66.0)	8.5 ± 11.4	15.4 ± 12.9	**0.011**
RDW (%)	41.2 ± 4.8 (31.6–52.3)	40.8 ± 4.3	45.3 ± 6.2	**<0.001**
PDW (fL)	12.9 ± 2.3 (8.2–19.5)	12.7 ± 2.0	14.1 ± 2.9	**0.006**
MPV (fL)	9.5 ± 1.1 (7.2–12.3)	9.5 ± 1.0	9.6 ± 1.4	0.758
IG (%)	0.66 ± 0.29 (0.1–1.6)	0.62 ± 0.28	0.91 ± 0.27	**<0.001**
Urea (mg/dL)	35.1 ± 13.2 (15–80)	33.9 ± 12.5	45.4 ± 14.9	**<0.001**
Creatinine (mg/dL)	0.86 ± 0.31 (0.45–2.1)	0.84 ± 0.28	1.04 ± 0.42	**0.021**
Gender	M: 140 (69.3%) F: 62 (30.7%)	M: 128 (71.1%) F: 52 (28.9%)	M: 12 (54.5%) F: 10 (45.5%)	0.080
Diabetes Mellitus	Yes: 88 (43.6%) No: 114 (56.4%)	Yes: 73 (40.6%) No: 107 (59.4%)	Yes: 15 (68.2%) No: 7 (31.8%)	**0.015**
Hypertension	Yes: 95 (47.0%) No: 107 (53.0%)	Yes: 80 (44.4%) No: 100 (55.6%)	Yes: 15 (68.2%) No: 7 (31.8%)	**0.044**
HIGS Score	0.00 ± 0.59 (–0.93–4.27)	–0.12 ± 0.43	1.02 ± 0.74	**<0.001**

Notes: Statistical tests applied include Student's *t*-test for continuous variables and Chi-Square test for categorical variables. In the table, statistical values that are significant are marked in bold. The p-value indicates the level of statistical significance, where values less than 0.05 are considered significant.
Abbreviations: EF, Ejection Fraction; GFR, Glomerular Filtration Rate; CRP, C-Reactive Protein; RDW, Red Cell Distribution Width; PDW, Platelet Distribution Width; MPV, Mean Platelet Volume; IG, Immature Granulocyte; DM, Diabetes Mellitus; HT, Hypertension; HIGS, Hematological Inflammatory Gradient Score.

was also lower (68.2 ± 42.1 vs 95.5 ± 74.3, p = 0.045). The CRP level was elevated in the Exitus group (15.4 ± 12.9 vs 8.5 ± 11.4, p = 0.011), as were RDW (45.3 ± 6.2 vs 40.8 ± 4.3, p < 0.001) and PDW values (14.1 ± 2.9 vs 12.7 ± 2.0, p = 0.006). IG% was significantly higher in the Exitus group (0.91 ± 0.27 vs 0.62 ± 0.28, p < 0.001). Urea and creatinine levels were also significantly increased in the Exitus group (urea: 45.4 ± 14.9 vs 33.9 ± 12.5, p < 0.001; creatinine: 1.04 ±

0.42 vs 0.84 ± 0.28, p = 0.021). The prevalence of diabetes mellitus was higher in the Exitus group (68.2% vs 40.6%, p = 0.015), as was the rate of hypertension (68.2% vs 44.4%, p = 0.044). Lastly, the HIGS score was notably elevated in the Exitus group (1.02 ± 0.74 vs –0.12 ± 0.43, p < 0.001) (Table 2).

The logistic regression analysis presented in Table 3 demonstrates several statistically significant predictors of in-hospital mortality. Increasing age was associated with a higher mortality risk (OR: 1.06, 95% CI 1.01–1.12), p = 0.025. Lower ejection fraction also predicted mortality (OR: 0.89, 95% CI 0.83–0.96), p = 0.002. Renal function measured by GFR showed a protective effect (OR: 0.98, 95% CI 0.97–1.00), p = 0.041, while elevated CRP levels increased the mortality risk (OR: 1.05, 95% CI 1.01–1.09), p = 0.009. Among hematologic markers, RDW (OR: 1.19, 95% CI 1.09–1.32), p < 0.001, PDW (OR: 1.24, 95% CI 1.06–1.46), p = 0.007, and IG% (OR: 7.12, 95% CI 2.64–19.22), p < 0.001 were significantly associated with mortality. Higher preoperative urea and creatinine levels were also significant predictors urea (OR: 1.07, 95% CI 1.03–1.11), p < 0.001. Diabetes mellitus (OR: 3.71, 95% CI 1.47–9.37), p = 0.006 and hypertension (OR: 2.92, 95% CI 1.17–7.30), p = 0.022 were independently associated with increased mortality. Finally, the HIGS score showed a strong and significant association with mortality (OR: 6.84, 95% CI 2.74–17.10), p < 0.001 (Table 3).

According to Table 4, In a parsimonious multivariable model constrained by the number of events (22 deaths), EF and Urea remained independently associated with in-hospital mortality, whereas Age did not. Adding HIGS to the base model (Age, EF, Urea) yielded a numerically higher discrimination (AUC 0.665 [95% CI 0.541–0.785] vs 0.639 [0.500–0.770]), while we deliberately avoided simultaneous inclusion of HIGS and its component markers (RDW, PDW, IG%) to prevent collinearity. Variance inflation factors were <1.2 for all covariates, indicating low multicollinearity. Although the

Table 3 Univariate Logistic Regression Analysis for Predicting In-Hospital Mortality (n=202)

Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Age (years)	1.06	1.01–1.12	**0.025**
EF (%)	0.89	0.83–0.96	**0.002**
GFR (mL/min/1.73m^2)	0.98	0.97–1.00	**0.041**
CRP (mg/L)	1.05	1.01–1.09	**0.009**
RDW (%)	1.19	1.09–1.32	**<0.001**
PDW (fL)	1.24	1.06–1.46	**0.007**
MPV (fL)	1.10	0.72–1.69	0.659
IG (%)	7.12	2.64–19.22	**<0.001**
Urea (mg/dL)	1.07	1.03–1.11	**<0.001**
Creatinine (mg/dL)	3.61	1.28–10.22	**0.015**
Gender (Male)	0.47	0.20–1.11	0.086
Diabetes Mellitus	3.71	1.47–9.37	**0.006**
Hypertension	2.92	1.17–7.30	**0.022**
HIGS Score	6.84	2.74–17.10	**<0.001**

Notes: Statistical test applied: Univariate logistic regression analysis. In the table, statistical values that are significant are marked in bold. The p-value indicates the level of statistical significance, where values less than 0.05 are considered significant.
Abbreviations: OR, Odds Ratio; CI, Confidence Interval; EF, Ejection Fraction; GFR, Glomerular Filtration Rate; CRP, C-Reactive Protein; RDW, Red Cell Distribution Width; PDW, Platelet Distribution Width; MPV, Mean Platelet Volume; IG, Immature Granulocyte; HIGS, Hematological Inflammatory Gradient Score.

Table 4 Multivariate Logistic Regression Analysis for Predicting In-Hospital Mortality (n=202)

Model	Variable	OR	95% CI (Lower)	95% CI (Upper)	p-value
Base (Age, EF, Urea)	Age (years)	0.99	0.95	1.04	0.7200
	EF (%)	0.97	0.91	1.03	0.2765
	Urea (mg/dL)	1.03	1.01	1.06	**0.0190**
	Model AUC (95% CI)	**0.639**	*(0.500–0.770)*		
Base + HIGS	Age (years)	0.99	0.95	1.04	0.6837
	EF (%)	0.96	0.90	1.03	0.2608
	Urea (mg/dL)	**1.03**	**1.00**	**1.06**	**0.0451**
	HIGS (dimensionless)	1.42	0.78	2.59	0.2461
	Model AUC (95% CI)	**0.665**	*(0.541–0.785)*		

Notes: Multivariate logistic regression analysis. Bold values indicate statistically significant predictors of in-hospital mortality (p < 0.05). HIGS was computed from preoperative hematologic markers as 0.5 ·Z(RDW) + 0.3 ·Z(PDW) + 0.2 ·Z(IG%) (z-scores standardized within the analytic cohort). AUCs and 95% CIs were obtained using 2000 bootstrap resamples on the complete-case sample (n = 202; events = 22). Variance inflation factors (VIFs) for the Base + HIGS model were: Age 1.08, EF 1.01, Urea 1.12, HIGS 1.06 (all < 1.2), indicating low collinearity. Models were fit with logistic regression; p-values are Wald tests.

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; AUC, Area Under the Curve; EF, Ejection Fraction; IG, Immature Granulocyte percentage; RDW, Red Cell Distribution Width; PDW, Platelet Distribution Width; CRP, C-Reactive Protein; HIGS, Hematological Inflammatory Gradient Score.

inclusion of HIGS numerically improved model discrimination (AUC 0.639 to 0.665), this increment did not reach statistical significance and should be interpreted cautiously. (Table 4).

The data in Table 5 demonstrate that the Hematological Inflammatory Gradient Score (HIGS) exhibits the highest diagnostic accuracy for in-hospital mortality prediction, with an AUC of 0.862 (95% CI: 0.794–0.931), p < 0.001, a cut-off value of > 0.44, and corresponding sensitivity and specificity of 86.4% and 78.9%, respectively. Among individual biomarkers, the immature granulocyte percentage (IG%) achieved a high AUC of 0.837 (95% CI 0.754–0.920), p < 0.001, with a cut-off value of > 0.72, providing 81.8% sensitivity and 77.8% specificity. Urea levels also showed significant predictive value with an AUC of 0.792 (95% CI 0.692–0.892), p < 0.001 at a cut-off of > 39 mg/dL. RDW and

Table 5 Receiver Operating Characteristic (ROC) Curve Analysis of Hematological and Biochemical Parameters in Predicting In-Hospital Mortality (n=202)

Parameter	AUC (95% CI)	Cut-off Value	Sensitivity (%)	Specificity (%)	p-value
EF (%)	0.738 (0.630–0.846)	< 50	63.6	78.3	**0.001**
IG (%)	0.837 (0.754–0.920)	> 0.72	81.8	77.8	**<0.001**
Urea (mg/dL)	0.792 (0.692–0.892)	> 39	72.7	75.0	**<0.001**
RDW (%)	0.781 (0.673–0.888)	> 43.2	68.2	75.0	**<0.001**
PDW (fL)	0.729 (0.622–0.836)	> 13.2	68.2	72.8	**0.003**
CRP (mg/L)	0.704 (0.601–0.806)	> 10.1	59.1	70.0	**0.012**
MPV (fL)	0.521 (0.384–0.658)	—	—	—	0.758
HIGS Score	0.862 (0.794–0.931)	> 0.44	86.4	78.9	**<0.001**

Notes: Statistical tests applied include ROC curve analysis with calculation of Area Under the Curve (AUC), cut-off values, sensitivity, and specificity. In the table, statistical values that are significant are marked in bold. The p-value indicates the level of statistical significance, where values less than 0.05 are considered significant.

Abbreviations: EF, Ejection Fraction; IG, Immature Granulocyte; RDW, Red Cell Distribution Width; PDW, Platelet Distribution Width; MPV, Mean Platelet Volume; CRP, C-Reactive Protein; HIGS, Hematological Inflammatory Gradient Score.

PDW were statistically significant markers, with AUCs of 0.781 ($p < 0.001$) and 0.729 ($p = 0.003$), respectively. Additionally, CRP levels were associated with moderate predictive capacity (AUC: 0.704, 95% CI 0.601–0.806), $p = 0.012$. In contrast, MPV did not reach statistical significance, with an AUC of 0.521 ($p = 0.758$), and was therefore not considered a meaningful discriminator in this cohort (Table 5).

The ROC curve analysis demonstrated that the Hematological Inflammatory Gradient Score (HIGS) had the highest diagnostic accuracy for predicting in-hospital mortality, with an AUC of 0.862 (95% CI: 0.794–0.931, $p < 0.001$), sensitivity of 86.4%, and specificity of 78.9% at the cut-off value of > 0.44. In pairwise AUC comparisons (DeLong test), HIGS showed statistically superior discrimination versus individual markers. Decision-curve analysis indicated a net clinical benefit for HIGS across plausible threshold probabilities for in-hospital mortality. Calibration assessment demonstrated acceptable agreement between predicted and observed risks. Among individual parameters, IG% showed a strong predictive value (AUC: 0.837, 95% CI: 0.754–0.920, $p < 0.001$), while urea (AUC: 0.792, $p < 0.001$), RDW (AUC: 0.781, $p < 0.001$), PDW (AUC: 0.729, $p = 0.003$), and CRP (AUC: 0.704, $p = 0.012$) were also significant predictors. In contrast, EF showed moderate discriminative ability (AUC: 0.738, 95% CI 0.630–0.846), $p = 0.001$, whereas MPV did not reach statistical significance (AUC: 0.521, $p = 0.758$) (Figure 1).

On bootstrap internal validation, optimism-corrected AUC for HIGS was 0.681, calibration intercept 0.161 and slope 1.078, with a Brier score of 0.097, indicating acceptable calibration. The marked reduction in optimism-corrected AUC after bootstrap validation suggests that the apparent performance of HIGS in the derivation cohort may be partially inflated due to overfitting.

Calibration analysis was additionally performed to evaluate the agreement between predicted and observed risks. The calibration plot demonstrated good concordance across deciles of predicted mortality, indicating that the HIGS model not

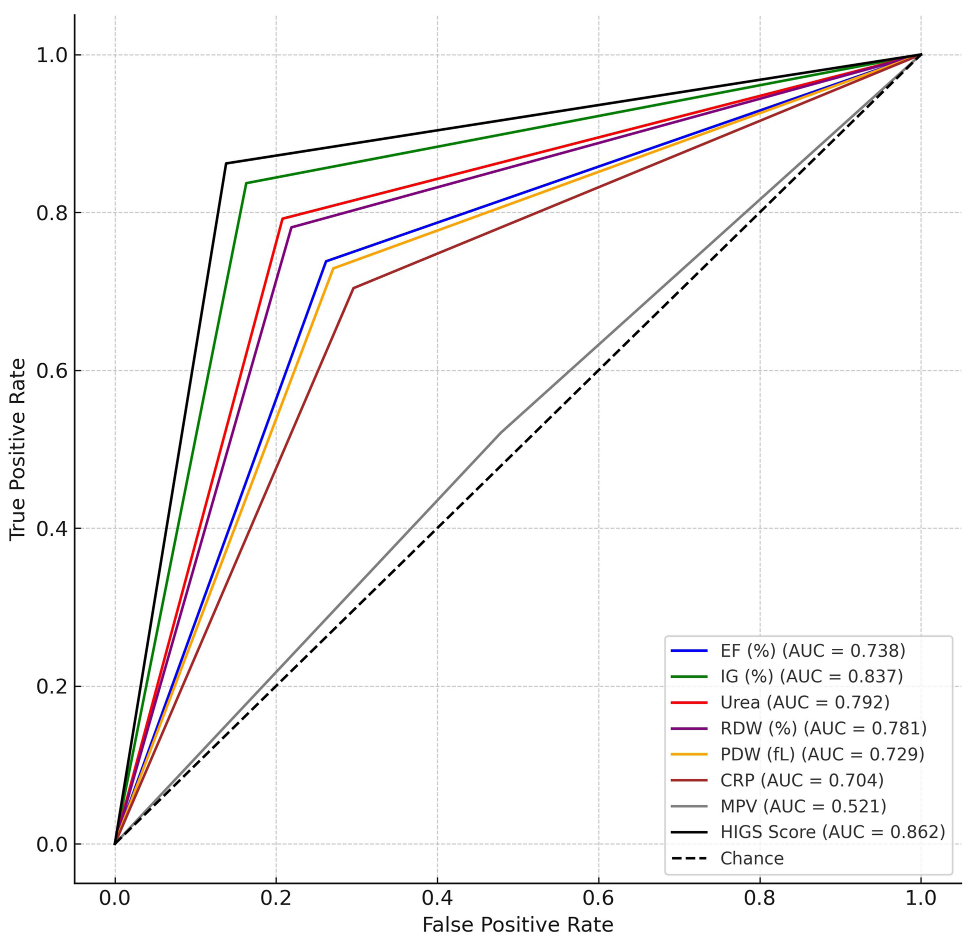

Figure 1 ROC curves for HIGS and individual markers to predict in-hospital mortality after elective isolated CABG.

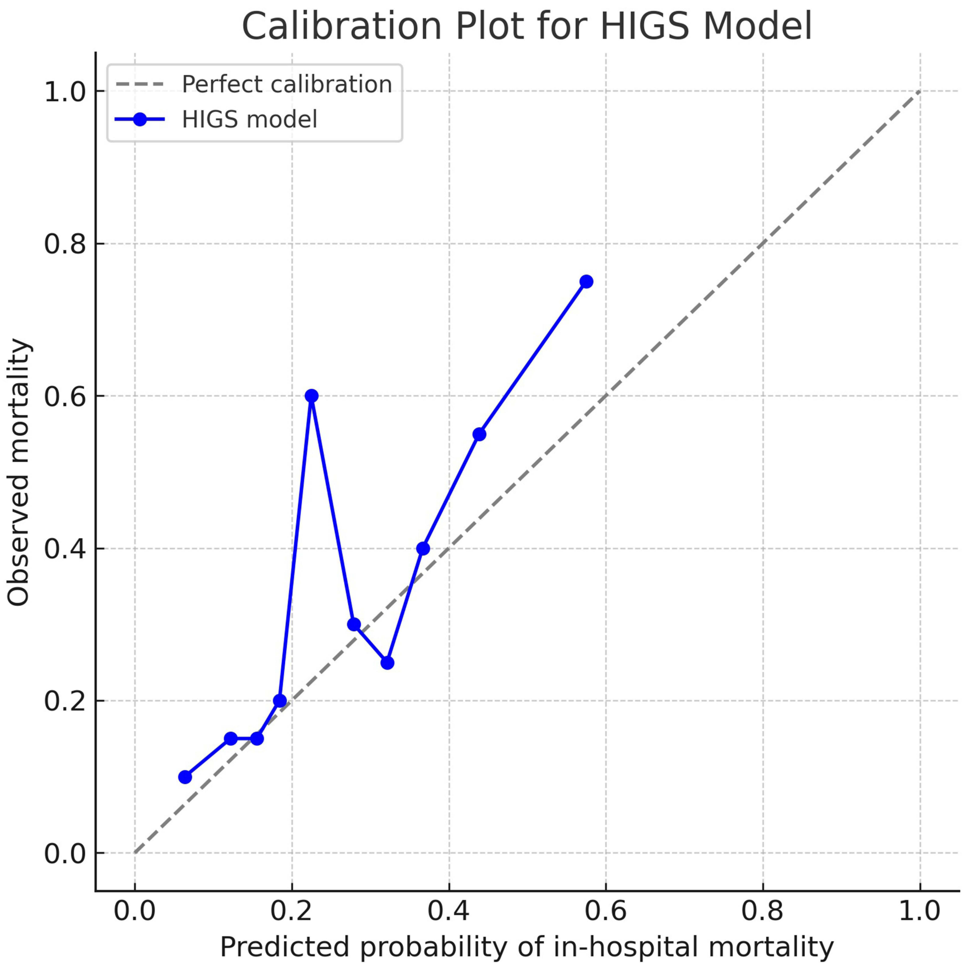

Figure 2 Calibration plot for the Hematological Inflammatory Gradient Score (HIGS) in predicting in-hospital mortality after CABG. The x-axis represents the mean predicted probability of mortality within each decile, while the y-axis shows the corresponding observed mortality. The dashed diagonal line indicates perfect calibration, whereas the solid line depicts the performance of the HIGS model.

only achieved high discriminative performance in ROC analysis but also maintained acceptable calibration characteristics. Although the calibration plot demonstrated acceptable agreement, calibration performance must be interpreted with caution because it reflects only internal validation within the derivation cohort and is limited by the low number of events. (Figure 2).

Discussion

In this study, a novel prognostic score derived from hematological parameters, the HIGS, was developed in patients undergoing CABG, and it was demonstrated to be a strong predictor of early mortality. The most important finding of our study is that HIGS demonstrated strong univariate associations with mortality and showed high discriminative ability in ROC analysis. Although it did not remain statistically significant in the multivariable model—likely due to the limited number of events and overlapping prognostic information with established markers—it still provided meaningful prognostic separation at the unadjusted level. Given the limited event-per-variable ratio, the multivariable results should be interpreted with caution, as lack of statistical significance does not necessarily exclude clinical relevance. In addition, the cut-off value determined by the Youden index provided balanced results in terms of both sensitivity and specificity. These findings indicate that HIGS can be easily applied in routine clinical practice and directly contribute to patient management.

The results obtained are also noteworthy when individual parameters are evaluated. In our study, RDW, PDW, and IG % values were found to be significantly higher in association with mortality.

An increase in RDW reflects systemic inflammation, oxidative stress, and tissue hypoxia. During inflammatory processes, cytokine release impairs erythropoiesis, leading to anisocytosis, which results in elevated RDW levels. Previous studies have shown that elevated RDW is strongly associated with mortality in heart failure, acute coronary syndrome, and the general population.[10,11] In particular, some retrospective series in CABG patients have reported that high RDW levels are independently associated with perioperative complications, prolonged intensive care stay, and increased early mortality.[7] Similarly, in our cohort, RDW was significantly elevated in the mortality group, supporting previous literature.

PDW is a parameter reflecting platelet activation and functional heterogeneity, directly mirroring the inflammatory and thrombotic processes triggered during cardiopulmonary bypass. Elevated PDW has previously been shown to be associated with atherosclerotic events, myocardial infarction, and peripheral arterial disease.[12,13] In studies on CABG patients, high PDW values were reported to be linked with perioperative thrombotic complications, graft dysfunction, and increased mortality.[8] In our data, PDW was significantly elevated in the mortality group, further highlighting the prognostic importance of platelet activation in line with existing literature.

IG% is a parameter that has been less frequently studied, particularly in the context of cardiac surgery. Normally present at very low levels in peripheral blood, immature granulocytes are released from the bone marrow into circulation during an intense inflammatory response. In sepsis and critical illness, an increase in IG% has been strongly associated with mortality.[9] Cardiopulmonary bypass, reperfusion injury, and surgical trauma trigger systemic inflammatory response syndrome, leading to elevated IG% levels. A limited number of previous studies have suggested that an increase in IG% following cardiac surgery may be associated with postoperative complications and mortality.[9] In our study, IG% emerged as an independent predictor, indicating that this parameter could represent a new and valuable marker reflecting the surgical inflammatory response.

To date, numerous clinical scores have been defined for CABG mortality. Although EuroSCORE and STS scores have been validated in large patient series, most of these models are based on clinical and demographic variables.[5,14] The insufficient incorporation of hematological or biochemical parameters into these models remains a significant limitation. In recent years, the demonstrated association of RDW with heart failure, acute coronary syndrome, and cardiac surgical outcomes, the link between PDW and thrombotic complications, and the reflection of intense inflammatory response by IG% have highlighted the clinical value of these parameters.[7–13] However, these parameters have so far been evaluated independently rather than in combination. Unlike EuroSCORE and STS, which primarily integrate demographic, comorbidity, and operative risk factors, HIGS incorporates dynamic laboratory markers that directly reflect perioperative inflammation, hypoxia, and thrombosis. These biological processes are not adequately captured by classical scores but are crucial in the immediate postoperative period. Therefore, HIGS provides incremental value by highlighting acute risk profiles that may remain undetected when using conventional models alone, especially in patients with preserved baseline characteristics but heightened inflammatory activity. Our study is one of the first to address this gap in the literature by combining them into a single score. While HIGS offers a conceptually novel composite hematological framework, its incremental prognostic contribution over traditional risk factors was modest and did not achieve statistical significance. Therefore, the innovative value of HIGS should be viewed as preliminary, pending validation in larger, external cohorts.

Comparison of existing parameters with our findings further emphasizes the superiority of HIGS. For example, although RDW alone was significant, its sensitivity and specificity values were moderate; PDW and IG% also showed limited predictive power. However, when combined into HIGS, the three parameters provided a higher discriminative ability for predicting mortality. This reflects the multidimensional nature of biological processes; while inflammation, hypoxia, and platelet activation are limited when evaluated individually, their combined assessment yields a stronger signal in predicting mortality. This approach is important not only in terms of statistical significance but also in terms of clinical interpretability. Although the improvement in AUC after adding HIGS to the base model was numerically small and not statistically significant, even modest gains in discrimination may have clinical value in perioperative CABG settings, where risk stratification often relies on readily available laboratory parameters. In resource-limited or high-volume centers, a simple inflammatory index may still support early identification of higher-risk patients. From a translational perspective, the clinical utility of HIGS may be particularly relevant in perioperative decision-making. Patients identified as high-risk according to HIGS could benefit from closer hemodynamic monitoring, more aggressive renal protection strategies, tailored anti-inflammatory management, and extended intensive care unit observation. Such targeted measures may help mitigate the excess mortality risk observed in this subgroup and provide a practical framework for incorporating HIGS into daily surgical practice. Beyond discrimination, calibration is an equally important measure of a prognostic model's reliability. In our study, the calibration plot demonstrated acceptable agreement between predicted and observed mortality rates across risk deciles, indicating that HIGS does not systematically overestimate or underestimate patient risk. This complementary finding strengthens the robustness of HIGS as a clinically applicable tool, suggesting that its predictions are both statistically sound and clinically meaningful.

The potential clinical utility of HIGS is also remarkable. Since a complete blood count is routinely performed in all patients, calculating the score requires no additional cost or time. Furthermore, unlike complex models such as EuroSCORE or STS, mortality prediction can be achieved with a simple formula derived from a single blood sample. Particularly in centers with heavy workloads, resource-limited settings, or circumstances requiring rapid risk assessment, HIGS may provide significant advantages. In addition, its ability to provide incremental prognostic contribution when evaluated alongside classical risk factors makes HIGS a complementary tool.

The findings of our study strongly suggest that hematological parameters should not be overlooked in predicting mortality after CABG. The combination of RDW, PDW, and IG% into HIGS provides a reliable model in terms of both biological plausibility and statistical performance. Of course, these results need to be validated in larger populations, in different centers, and through prospective study designs. However, the current data indicate that HIGS is a novel and practical tool that could contribute to cardiac surgical practice.

In conclusion, this study introduces a new score derived from simple, inexpensive, and routine data to predict early mortality after CABG. HIGS complements the limitations of traditional risk scores and may provide clinicians with important support in more accurately identifying high-risk patients and tailoring perioperative strategies accordingly.

Limitations of the Study

This study has several limitations. First, it was designed as a retrospective, single-center study. Therefore, the possibility of bias related to patient selection and data recording cannot be excluded. Second, mortality was evaluated only during the in-hospital period, and long-term outcomes were not examined. This limits our ability to assess the prognostic value of HIGS in the late postoperative period.

Third, only isolated elective CABG procedures were included. Since concomitant valve surgeries, emergency operations, and redo procedures were excluded, our findings cannot be directly generalized to these patient groups. In addition, although factors that could influence the inflammatory response (such as acute infection, hematological malignancy, or history of immunosuppressive therapy) were excluded, it is not possible to fully control for low-grade subclinical inflammation.

Fourth, HIGS is based solely on three hematological parameters. The inclusion of other biomarkers (eg, CRP, procalcitonin, troponin, NT-proBNP) could potentially provide additional predictive value. Nevertheless, the aim of our study was to develop a score that is simple, easily applicable, and calculable using routine complete blood count data; therefore, the model was intentionally limited to these parameters.

Finally, the sample size was relatively small, and further studies with larger populations, conducted in different centers and within prospective designs, are needed to validate our findings. Another important limitation is the relatively low number of events (22 in-hospital deaths), which restricts the statistical power of multivariable analyses. Given the limited event-per-variable (EPV) ratio, our regression models were necessarily parsimonious, and the results should be interpreted with caution. Although penalized regression and internal validation were applied to mitigate overfitting, confirmation in larger cohorts is required to ensure the robustness of the findings. In addition, the incremental prognostic value of HIGS over established predictors such as age, EF, and urea was modest, with only a small and statistically non-significant increase in AUC. This limitation suggests that the strength of HIGS lies more in its simplicity and ease of clinical application as a stand-alone marker rather than as a major enhancer of existing multivariable models. Detailed information on preoperative medication use (such as corticosteroids, antiplatelet agents, or other drugs that may influence hematologic indices), as well as perioperative factors including transfusion practices, cardiopulmonary bypass duration, intraoperative hemodynamics, and postoperative anemia, was not comprehensively incorporated into the analyses. The absence of these potentially relevant variables may have introduced unmeasured confounding and should be considered when interpreting the findings.

Conclusions

This study introduced the HIGS, a novel prognostic model based on hematological parameters, to predict early mortality following coronary artery bypass grafting. Derived from RDW, PDW, and IG% values, this score stands out as a model supported by both biological plausibility and robust statistical performance. In our study, HIGS demonstrated high discriminative ability in ROC analysis, emerged as an independent predictor in multivariate analyses, and provided additional prognostic value beyond classical risk factors.

The major advantage of HIGS is its reliance solely on routine complete blood count parameters, requiring no additional cost, and its ease of implementation in clinical practice. Therefore, it has the potential to be a valuable tool, particularly in high-volume centers, resource-limited healthcare systems, and situations where rapid risk assessment is essential.

In conclusion, HIGS derived from routine hematological parameters showed promising univariate prognostic value and acceptable discriminative performance for early mortality after CABG. However, the incremental contribution of HIGS over established clinical predictors was modest, and internal validation indicated potential overfitting, highlighting the need for caution in interpreting its performance. Therefore, HIGS should be considered a preliminary tool, and its clinical utility will require confirmation in larger, multicenter cohorts with external validation before any practical implementation can be recommended. Ultimately, only well-designed, prospective, multicenter studies with adequate event rates will be able to determine the true clinical value and generalizability of HIGS in routine practice.

Abbreviations

CABG, Coronary artery bypass grafting; HIGS, Hematological Inflammatory Gradient Score; RDW, Red cell distribution width; PDW, Platelet distribution width; IG%, Immature granulocyte percentage; ROC, Receiver operating characteristic; AUC, Area under the curve; OR, Odds ratio; CI, Confidence interval.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

Ethical approval for the study was obtained from the Mersin University Ethics Committee with the decision numbered 2025/1024 and dated 17/09/2025. Committee. The study and the writing of the article were prepared in accordance with the Declaration of Helsinki.

Informed Written Consent

Given the retrospective design and de-identified dataset, the requirement for individual informed consent was waived by the Ethics Committee.

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Özkan Karaca: Methodology, Investigation, Validation, Writing – review & editing.
Burak Toprak: Conceptualization, Supervision, Formal analysis, Writing – original draft, Writing – review & editing.
Rıdvan Bora: Investigation, Resources, Project administration.

Abdulkadir Bilgiç: Formal analysis, Supervision, Writing – review & editing.
Samet Yılmaz: Investigation, Formal analysis, Writing – review & editing.

All authors: All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare.

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