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The COPD-augmented R₂CHA₂DS₂-VA score: development and internal assessment for predicting one-year outcomes after transcatheter aortic valve implantation

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Abstract

Background Existing CHA₂DS₂-VAsC-based scores incompletely capture the prognostic impact of chronic obstructive pulmonary disease (COPD) and of graded renal dysfunction in patients undergoing transcatheter aortic valve implantation (TAVI). We acknowledge that the score's development in a high-risk, high-comorbidity cohort may produce optimistic performance estimates that require attenuation through external validation. We aimed to develop a novel COPD-augmented R₂CHA₂DS₂-VA (COPD-R₂CHA₂DS₂-VA) score that systematically integrates quantitative renal function and COPD, and to internally assess its discriminative performance for one-year all-cause mortality and major adverse cardiovascular events (MACE).

Methods In this single-center, retrospective cohort study, 622 consecutive patients undergoing TAVI for severe aortic stenosis (2018–2024) were analyzed. The COPD-R₂CHA₂DS₂-VA score was constructed as a prespecified clinical tool by augmenting the R₂CHA₂DS₂-VA framework with COPD (1 point) and refining renal dysfunction into two graded estimated glomerular filtration rate strata (eGFR 30–59 mL/min/1.73 m²: 1 point; eGFR < 30: 2 points). Discriminative performance was evaluated using receiver operating characteristic curve analysis with bootstrap internal validation (2,000 resamples) and compared with established CHA₂DS₂-VAsC-based scores. Multivariable logistic regression assessed the independent prognostic value of the score treated as a continuous variable.

Results The COPD-R₂CHA₂DS₂-VA score demonstrated encouraging discriminative ability for one-year all-cause mortality (apparent area under the curve [AUC] 0.946, 95% CI 0.926–0.971). As a prespecified tool with fixed component weights, bootstrap internal validation confirmed negligible optimism (mean optimism –0.00014), with bias-corrected AUC identical to the apparent value. The addition of COPD significantly improved mortality discrimination over the R₂CHA₂DS₂-VA score (Δ AUC + 0.033, $p = 0.0001$). For one-year MACE, the apparent AUC was 0.806 (95% CI 0.765–0.852); the addition of COPD did not significantly enhance MACE discrimination (Δ AUC + 0.001,

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$p=0.853$). In multivariable analysis, each one-point increase in the COPD-R₂CHA₂DS₂-VA score was independently associated with 3.52-fold higher odds of one-year mortality (95% CI 2.45–5.06, $p < 0.001$) and 2.02-fold higher odds of MACE (95% CI 1.67–2.46, $p < 0.001$). The bias-corrected AUC of the full multivariable model was 0.973 (95% CI 0.962–0.984) for mortality and 0.795 (95% CI 0.752–0.841) for MACE.

Conclusions The COPD-R₂CHA₂DS₂-VA score demonstrated encouraging discriminative ability for one-year all-cause mortality after TAVI in this single-center development cohort (apparent AUC 0.946). However, this high discriminative performance is likely influenced by the elevated comorbidity burden in our cohort and the single-center design, and should be interpreted as an upper-bound estimate. The addition of COPD provides a statistically significant but clinically modest incremental improvement for mortality ($\Delta\text{AUC} + 0.033$, $p = 0.0001$), with no significant enhancement for MACE ($\Delta\text{AUC} + 0.001$, $p = 0.853$). These findings are preliminary and hypothesis-generating; urgent external validation in diverse, prospective cohorts is essential before any clinical application can be considered. At present, this score should be regarded as a development-phase, hypothesis-generating tool that complements rather than replaces guideline-recommended instruments such as STS-PROM and EuroSCORE II. The score's clinical utility remains unproven.

Keywords Transcatheter aortic valve implantation, Severe aortic stenosis, Risk stratification, Mortality, Chronic obstructive pulmonary disease, Renal dysfunction, COPD-R₂CHA₂DS₂-VA score

Introduction

Despite the paradigm shift in the management of severe aortic stenosis introduced by transcatheter aortic valve implantation (TAVI), accurate prediction of long-term individual patient outcomes remains a significant clinical challenge. Aortic stenosis is the most prevalent valvular heart disease in the elderly, associated with substantial morbidity and mortality if left untreated [1]. TAVI has revolutionized the management of severe aortic stenosis, evolving from a therapy for inoperable or high-surgical-risk patients to a standard-of-care option for selected intermediate- and even low-risk cohorts, as evidenced by major randomized trials and current guidelines [2–5].

Although TAVI indications have expanded to include intermediate- and low-surgical-risk patients, and consequently younger and less comorbid individuals, a substantial proportion of recipients in contemporary real-world registries remain elderly (mean age > 78 years) and continue to present with a high burden of both cardiovascular and non-cardiovascular comorbidities [6–8]. This complex profile contributes to persistently elevated rates of one-year mortality and major adverse cardiovascular events (MACE), underscoring the need for accurate risk prediction to guide patient selection and post-procedural management.

Current clinical practice guidelines for TAVI recommend the use of surgical risk scores, specifically the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) and the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II), for procedural risk assessment [2, 3]. However, these scores were developed and validated predominantly in surgical aortic valve replacement cohorts and have demonstrated limited calibration and only moderate discrimination for long-term outcomes in contemporary TAVI populations

[7, 8]. Moreover, they incorporate COPD and renal dysfunction as binary variables, failing to capture the graded risk associated with declining estimated glomerular filtration rate (eGFR) or the severity of airflow limitation. The CHA₂DS₂-VASc score, originally derived for thromboembolic risk prediction in atrial fibrillation, has been shown to predict mortality after TAVI in multiple observational studies, with AUCs typically between 0.60 and 0.71 [9–12]. This moderate, yet consistent, prognostic signal suggests that the CHA₂DS₂-VASc components capture fundamental cardiovascular risk that is complementary to surgical risk scores. However, the score omits two major non-cardiac determinants of late outcomes: the full spectrum of renal dysfunction and chronic obstructive pulmonary disease. Improving the CHA₂DS₂-VASc framework by systematically integrating these factors could yield a simple, bedside-accessible tool that adds prognostic granularity beyond what is offered by established surgical scores. We emphasize that the proposed score is not intended to replace STS-PROM or EuroSCORE II, but rather to complement them by providing a comorbidity-focused estimate of one-year prognosis.

In response to this need, various risk stratification tools have been proposed. However, their prognostic discrimination in the TAVI population remains suboptimal, as they fail to adequately capture the specific comorbidity burden and frailty profile inherent to these patients [9, 10]. This limitation has spurred interest in simpler, more applicable risk scores derived from routine clinical data. The CHA₂DS₂-VASc score and its derivatives possess critical limitations for this population. First, renal dysfunction, a powerful predictor of mortality, is often reduced to a binary variable, failing to capture the graded, linear risk associated with declining eGFR

[13–15]. Second, chronic obstructive pulmonary disease (COPD), which is highly prevalent and independently associated with nearly doubled mortality risk after TAVI, is not a structural component of these scores [16–21]. Consequently, existing simple scores may misestimate risk in a substantial proportion of patients, particularly those with moderate renal impairment or significant pulmonary comorbidity.

To address these specific gaps, we developed the COPD-augmented $R_2\text{CHA}_2\text{DS}_2\text{-VA}$ (COPD- $R_2\text{CHA}_2\text{DS}_2\text{-VA}$) score. This novel tool represents the first $\text{CHA}_2\text{DS}_2\text{-VASc}$ -derived framework to simultaneously: (i) quantitatively integrate renal function using graded eGFR strata (R and R_2 components), moving beyond a simplistic dichotomous approach, and (ii) systematically include COPD as a key structural element. Although both STS-PROM and EuroSCORE II include COPD as a binary variable, neither captures the severity of airflow obstruction, the intensity of pharmacotherapy, or the cumulative impact of COPD exacerbations on long-term survival. Similarly, both scores dichotomize renal function, ignoring the continuous, graded relationship between declining eGFR and mortality that has been consistently demonstrated in TAVI cohorts [13, 14]. By incorporating COPD as a structured component and replacing the binary renal variable with eGFR strata, the proposed score aims to capture a more granular risk signal from these two critical non-cardiac domains. By simultaneously capturing the graded risk of renal impairment and the significant inflammatory and hemodynamic burden of COPD, this score may more comprehensively encapsulate the multi-organ vulnerability characteristic of frail TAVI candidates. Nevertheless, we recognize that the high prevalence of comorbidities (28.3% chronic kidney disease, 24.8% COPD) in our cohort may amplify apparent discriminative performance through spectrum effects. Consequently, the observed AUC of 0.946 in this development cohort should be interpreted as an optimistic upper-bound estimate that will likely attenuate upon external validation in lower-risk, lower-comorbidity TAVI populations. We hypothesized that this comprehensive integration would provide improved discriminative ability for predicting one-year all-cause mortality after TAVI compared with existing $\text{CHA}_2\text{DS}_2\text{-VASc}$ -based models, while recognizing that the incremental value for MACE may be more limited given the primarily non-cardiovascular prognostic impact of COPD.

Methods

Study design and population

This single-center, retrospective cohort study included consecutive patients with severe symptomatic aortic

stenosis who underwent transfemoral TAVI at the Samsun University Faculty of Medicine, Samsun Training and Research Hospital Cardiology Clinic between 1 January 2018 and 31 December 2024. The indication for TAVI was determined by a multidisciplinary heart team in accordance with current guideline recommendations [2, 3]. All procedures were performed by experienced interventional cardiologists. Patient demographics, baseline clinical characteristics, laboratory parameters, echocardiographic measurements, and procedural data were extracted from the hospital's electronic health records.

Patients were excluded based on the following pre-specified criteria: (1) valve-in-valve TAVI procedures or conversion to surgical aortic valve replacement; (2) significant mental impairment preventing informed consent or follow-up; and (3) loss to one-year follow-up. Patients with acute cardiogenic shock, acute kidney injury at hospitalization, or previously implanted permanent pacemakers were retained in the primary analysis, as these characteristics reflect the real-world TAVI case mix and their exclusion would artificially inflate apparent model performance. A sensitivity analysis using multiple imputation for missing data was performed on the 634 patients who met all inclusion criteria before the exclusion of patients with missing data to confirm that exclusions did not distort the findings (Supplementary Table 3). The study conforms to the ethical standards of the Declaration of Helsinki, and ethical approval was obtained from the Samsun University Non-Interventional Clinical Research Ethics Committee (Approval number: 2025/22/8, Date: 12.11.2025). The requirement for written informed consent was formally waived due to the retrospective, fully anonymized nature of the analysis.

This was a retrospective analysis of routinely collected clinical data. A study protocol was not prepared or publicly registered. The analyses described in the Statistical Analysis section reflect the final analytical approach, and no deviations from this plan occurred.

Patient selection

A flowchart detailing patient selection is shown in Fig. 1. A total of 695 consecutive patients scheduled for TAVI were screened. After applying the exclusion criteria (valve-in-valve TAVI, $n=5$; conversion to surgical aortic valve replacement, $n=4$; significant mental impairment, $n=8$; loss to one-year follow-up, $n=22$; and missing data for any study variable, $n=12$), 622 patients were included in the final analysis. A complete-case analysis was performed; there were no missing data for any variable included in the final study cohort. To evaluate the robustness of findings to potential selection bias introduced by excluding patients with missing data, a sensitivity analysis using multiple imputation (MICE, 20 imputed datasets)

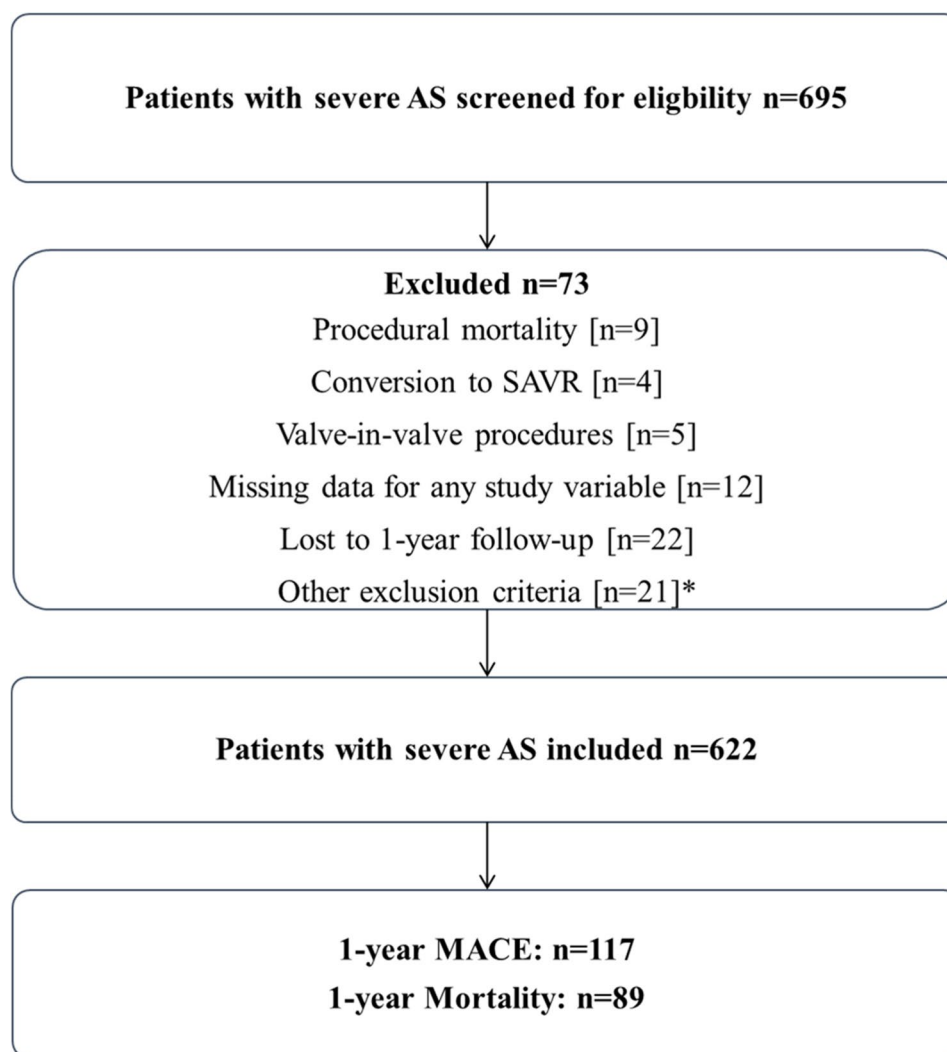


Fig. 1 Flowchart of the Patient Population. Abbreviations: SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; ViV, valve-in-valve. Notes: Other exclusion criteria (not shown individually): cardiogenic shock/hemodynamic instability ($n=10$), acute kidney injury at hospitalization ($n=8$), previously implanted permanent pacemaker ($n=3$). All exclusion criteria are detailed in Methods

was performed on the full cohort of 634 patients after applying all other exclusion criteria (Supplementary Table 3).

Data collection and definitions

Data on medical history, cardiovascular risk factors, clinical and demographic characteristics, laboratory parameters, echocardiographic measurements, procedural details, and periprocedural complications were obtained from electronic health records. Biochemical analyses were performed using venous blood samples drawn 24–48 h prior to the TAVI procedure. All periprocedural complications were defined and adjudicated according to the Valve Academic Research Consortium-3 (VARC-3) criteria [17].

Definitions of comorbidities

Hypertension: Defined as office systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on at least two separate occasions, or current use of antihypertensive medication.

Diabetes Mellitus: Defined as a documented diagnosis with corresponding ICD-10 code (E10.x–E14.x), or meeting laboratory criteria (fasting plasma glucose ≥ 126 mg/dL, HbA1c $\geq 6.5\%$, or random plasma glucose ≥ 200 mg/dL), or active use of glucose-lowering medication.

Heart Failure: Defined by a documented diagnosis with corresponding ICD-10 code (I50.x) or the presence of either: (a) history of hospitalization for decompensated heart failure within the past year, or (b) echocardiographic evidence of moderate or severe left ventricular systolic dysfunction (left ventricular ejection fraction $< 40\%$).

Vascular Disease: Defined as a history of myocardial infarction (ICD-10 I21.x–I22.x) or peripheral artery disease (ICD-10 I73.9), including prior coronary or peripheral revascularization (percutaneous intervention or surgical bypass).

Cerebrovascular Disease: Defined as a history of ischemic stroke (ICD-10 I63.x) or transient ischemic attack (TIA; ICD-10 G45.x), documented in medical records.

Chronic Obstructive Pulmonary Disease (COPD): The diagnosis of COPD was established based on a confirmed ICD-10 code (J44.x) documented in the structured electronic medical problem list prior to the TAVI procedure. To enhance diagnostic validity in this retrospective cohort, the ICD-10 diagnosis was further required to be supported by active prescription of COPD-specific maintenance inhaler therapy (long-acting beta-agonist, long-acting muscarinic antagonist, or inhaled corticosteroid) for a minimum of three months preceding TAVI. In addition, available spirometry reports demonstrating a post-bronchodilator FEV₁/FVC ratio < 0.70, in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, were available in 62% of patients classified as having COPD (95 of 154 patients).

Table 1 Components and point assignment of the COPD-R₂CHA₂DS₂-VA score

Component	Definition	Points
COPD	Chronic obstructive pulmonary disease (clinically manifest, requiring maintenance inhaler therapy; see footnote)	1
R	eGFR 30–59 mL/min/1.73 m ² (moderate renal dysfunction)	1
R ₂	eGFR < 30 mL/min/1.73 m ² (severe renal dysfunction)	2
C	Congestive heart failure (documented diagnosis or LVEF < 40%)	1
H	Hypertension (office BP ≥ 140/90 mmHg on ≥ 2 occasions, or antihypertensive use)	1
A ₂	Age ≥ 75 years	2
D	Diabetes mellitus (documented diagnosis, laboratory criteria, or glucose-lowering medication)	1
S ₂	Prior ischemic stroke or transient ischemic attack (TIA)	2
V	Vascular disease (prior myocardial infarction and/or peripheral artery disease, including revascularization)	1
A	Age 65–74 years	1
Total Possible Score		0–13

Abbreviations: BP Blood pressure, COPD Chronic obstructive pulmonary disease, eGFR Estimated glomerular filtration rate (CKD-EPI 2021 creatinine equation, without race coefficient), LVEF Left ventricular ejection fraction, TIA Transient ischemic attack

The COPD-R₂CHA₂DS₂-VA score is a prespecified clinical tool with fixed, equal component weights defined entirely a priori. The total score is the arithmetic sum of all applicable components (range: 0–13). COPD definition and eGFR thresholds are detailed in Methods

Patients with a sole diagnosis of asthma, interstitial lung disease, or other chronic pulmonary conditions without a concomitant diagnosis of COPD were not classified as having COPD. While the universal availability of spirometry is limited in elderly, frail TAVI populations, this combined definition aims to identify patients with clinically manifest COPD under active pharmacotherapy. We acknowledge that spirometric confirmation was available in only 62% of patients classified as having COPD, and that some degree of misclassification may exist. To assess the impact of this limitation, we performed a prespecified sensitivity analysis restricted to patients with spirometry-confirmed COPD.

Renal Function: Estimated glomerular filtration rate (eGFR) was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation, without the race coefficient, based on admission serum creatinine values [18]. Chronic kidney disease was defined as eGFR < 60 mL/min/1.73 m², consistent with the KDIGO classification (Stage 3–5).

Risk score calculation

Five risk scores were calculated for each patient using pre-procedural clinical and laboratory data obtained at hospitalization:

CHA₂DS₂-VA score: Age 65–74 years (1 point), Age ≥ 75 years (2 points), Heart failure (1 point), Hypertension (1 point), Diabetes mellitus (1 point), Prior stroke/TIA (2 points), vascular disease (1 point).

CHA₂DS₂-VASc score: As above, plus Female sex (1 point).

R₂CHA₂DS₂-VASc score: CHA₂DS₂-VASc plus renal dysfunction strata: eGFR 30–59 mL/min/1.73 m² (R: 1 point), eGFR < 30 mL/min/1.73 m² (R₂: 2 points).

R₂CHA₂DS₂-VA score: CHA₂DS₂-VA plus the same R and R₂ renal components.

COPD-R₂CHA₂DS₂-VA score: R₂CHA₂DS₂-VA plus COPD (1 point).

The components and point assignments for the COPD-R₂CHA₂DS₂-VA score are detailed in Table 1. The COPD-R₂CHA₂DS₂-VA score is a prespecified clinical tool: all component weights are fixed, equal (1 or 2 points), and were defined entirely a priori based on clinical judgement and prior literature. No component weights were derived from, or optimized on, the present dataset. The total score ranges from 0 to 13 and is the arithmetic sum of points for all applicable components. All scores were calculated independently by two investigators, with discrepancies resolved by consensus ($\kappa = 0.92$). The score extends the R₂CHA₂DS₂-VA framework, which applies graded renal dysfunction strata to the CHA₂DS₂-VA score [11], and builds upon prior modified CHA₂DS₂-VASc-based scores evaluated in TAVI populations [9, 10] by (i) adding COPD as an explicit structural component,

and (ii) refining the renal dysfunction domain from a single binary variable into two graded eGFR strata.

TAVI procedure

All patients underwent transthoracic echocardiography and multidetector computed tomography for pre-procedural annular sizing and vascular access assessment. TAVI procedures were performed in a standard catheterisation laboratory under conscious sedation via a transfemoral approach. Either self-expanding (Medtronic CoreValve/Evolut R/PRO; Medtronic, Minneapolis, MN, USA) or balloon-expandable (Edwards Sapien XT/3; Edwards Lifesciences, Irvine, CA, USA; Myval; Meril Life Sciences, Vapi, India) transcatheter heart valves were used at the operator's discretion. Peri-procedural anti-thrombotic therapy, post-procedural care, and discharge planning followed institutional protocols aligned with current guideline recommendations [2, 3].

Study endpoints and follow-up

The primary endpoint was all-cause mortality at one-year post-TAVI. The secondary endpoint was Major Adverse Cardiovascular Events (MACE), a composite of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, and rehospitalization for acute heart failure. Follow-up was conducted at hospital discharge and at one-year post-procedure using electronic health records, outpatient clinic notes, and structured telephone interviews administered by trained research personnel. Mortality was further verified against the Turkish National Death Registry. Endpoint adjudicators were blinded to the calculated COPD-R₂CHA₂DS₂-VA scores.

Statistical analysis

Statistical analyses were performed using SPSS version 31.0 (IBM Corp., Armonk, NY, USA) and R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). Data distribution was assessed for normality using the Shapiro-Wilk test, supplemented by visual inspection of Q-Q plots and histograms. Continuous variables were presented as mean $\pm$ standard deviation (SD) for normally distributed data, or as median with interquartile range (IQR) for non-normally distributed variables. Categorical variables were expressed as frequencies and percentages. For comparisons between two independent groups, the independent samples t-test was employed for normally distributed continuous variables, while the Mann-Whitney U test was used for non-normally distributed continuous variables. For comparisons of categorical variables, Pearson's chi-square test (χ^2) was applied; when expected cell frequencies were below 5, Fisher's exact test was used instead.

For the univariable score-outcome analysis, the COPD-R₂CHA₂DS₂-VA score is a prespecified clinical tool with

fixed component weights; only an intercept and a single slope are estimated at each bootstrap iteration. With 89 mortality events, the effective events-per-parameter ratio was $89/2 = 44.5$, far exceeding the recommended minimum of 10 [22]. For the multivariable logistic regression models, 9 free parameters are estimated from the data (8 predictors plus intercept). With 89 deaths, the events-per-variable (EPV) ratio was $89/9 \approx 9.9$, approaching the commonly recommended minimum of 10 [23]. For MACE (117 events, 9 parameters), the EPV was $117/9 = 13.0$, exceeding this threshold. To address potential overfitting in the data-driven multivariable models, bootstrap internal validation with 2,000 resamples was performed.

The COPD-R₂CHA₂DS₂-VA score was treated as a continuous variable in all primary logistic regression models to avoid inflation of effect estimates associated with data-driven dichotomization. Adjusted odds ratios are reported per one-point increase in the score. For descriptive stratification of baseline characteristics and unadjusted outcome comparisons, a single prespecified threshold of ≥ 5 was used. This cut-off corresponds to the upper tertile of the R₂CHA₂DS₂-VA score distribution as reported in prior TAVI cohorts and was defined prior to any analysis of the present dataset [10]. No outcome-driven optimal cut-off derivation (e.g., maximization of the Youden index) was performed.

The discriminative performance of the five risk scores for predicting one-year MACE and all-cause mortality was evaluated using receiver operating characteristic (ROC) curve analysis. For each risk score, the apparent area under the curve (AUC) with corresponding 95% confidence intervals (CI) was calculated using the DeLong method. AUC values were interpreted according to established criteria: 0.90–1.00 = strong, 0.80–0.90 = good, 0.70–0.80 = moderate, and 0.60–0.70 = limited discriminative ability. Pairwise comparisons of AUCs between risk scores were performed using the non-parametric DeLong test for correlated ROC curves, which accounts for the paired nature of the data.

We acknowledge the absence of direct comparison with guideline-recommended surgical risk scores (STS-PROM, EuroSCORE II) as a major limitation of this study. Such a comparison was not performed because these scores are not routinely collected as structured variables in our institutional registry. Consequently, the incremental prognostic value of the COPD-R₂CHA₂DS₂-VA score relative to current clinical standards remains unknown, and external validation studies should include head-to-head comparisons with both STS-PROM and EuroSCORE II.

To correct for optimism in the apparent performance estimates, bootstrap internal validation was performed with 2,000 resamples. In each bootstrap sample, a sample of size $n = 622$ was drawn with replacement from the

original data. For univariable score-outcome analyses, a logistic regression model (outcome ~ score) was fitted to the bootstrap sample. The AUC of this model, evaluated on the bootstrap sample (training performance) and on the original full dataset (test performance), was computed. Optimism for that resample was defined as $AUC_{bootstrap} - AUC_{original}$. For the multivariable models, the entire logistic regression model with all prespecified predictors was re-estimated in each bootstrap sample, and the same procedure was followed. Mean optimism was calculated as the average across 2,000 resamples. The bias-corrected $AUC = \text{apparent AUC} - \text{mean optimism}$. Bias-corrected AUCs, calibration slopes, calibration intercepts, and Brier scores are reported (Supplementary Table 2). The 95% confidence intervals for bias-corrected AUCs are percentile bootstrap intervals (2.5th and 97.5th percentiles of the bias-corrected AUC distribution across 2,000 resamples). Calibration was assessed visually with loess-smoothed calibration plots (Supplementary Figure S1) and formally with the Hosmer-Lemeshow goodness-of-fit test (10 groups).

To evaluate the independent prognostic value of the COPD- R_2 CHA₂DS₂-VA score, separate multivariable logistic regression models were constructed for one-year MACE and one-year all-cause mortality. Predictors were prespecified based on clinical relevance and prior literature, and included: COPD- R_2 CHA₂DS₂-VA score (continuous, per one-point increase), systolic pulmonary artery pressure (SPAP, per mmHg), atrial fibrillation (binary), hemoglobin (per g/dL), neutrophil-to-lymphocyte ratio (NLR, continuous), lymphocyte-to-monocyte ratio (LMR, continuous), vascular closure method (percutaneous vs. surgical), and post-procedural complications (VARC-3 major complications, binary). No stepwise, forward, or backward variable selection was performed; all predictors were entered simultaneously into the model. Components of the COPD- R_2 CHA₂DS₂-VA score (COPD, renal dysfunction [eGFR strata], heart failure, hypertension, age, diabetes mellitus, vascular disease, cerebrovascular disease) were not included as separate covariates in the model to prevent severe multicollinearity, as the score itself is a linear combination of these components. For each variable in the final models, the regression coefficient (B), standard error (SE), Wald χ^2 statistic, adjusted odds ratio (OR) with 95% confidence interval, and corresponding p value were reported. Model discrimination was assessed using the bias-corrected AUC (bootstrapped with 2,000 resamples as described above). Model fit was evaluated with $-2 \log$ likelihood, Cox and Snell R^2 , Nagelkerke R^2 , and Brier score.

Four prespecified sensitivity analyses were performed to assess the robustness of the primary findings:

Spirometry-confirmed COPD subgroup: The primary discriminative performance analysis of the continuous

COPD- R_2 CHA₂DS₂-VA score was repeated in the subset of patients who either had no COPD or had spirometry-confirmed COPD (post-bronchodilator $FEV_1/FVC < 0.70$). Patients with clinically diagnosed COPD but without spirometric confirmation ($n = 59$) were excluded. The effective sample size was 563.

Multiple imputation: To evaluate the impact of excluding patients with missing data, the primary analysis was repeated on a multiply imputed dataset (MICE, 20 imputed datasets, 10 iterations per dataset) that included all 634 patients after applying inclusion criteria but before excluding patients for missing data. Results were pooled using Rubin's rules.

Exclusion of post-procedural complications: The multivariable models were re-estimated after removing the post-procedural complications variable to assess whether this predictor, which lies on the causal pathway between the pre-procedural risk score and outcomes, influenced the adjusted OR for the score.

Continuous eGFR specification: The categorical R_2 renal components were replaced with eGFR modeled as a linear spline with a single knot at 60 mL/min/1.73 m². The C-index (a rank-based measure of discriminative ability analogous to AUC) of the continuous spline-based model was compared with the apparent AUC of the categorical R_2 -based score. This analysis assessed whether the discretization of eGFR into two strata (30–59 and < 30 mL/min/1.73 m²) resulted in meaningful information loss.

Reporting standards and transparency

This study follows the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis) statement for Type 1b studies (development and internal validation using bootstrap resampling) [24]. A completed TRIPOD checklist is provided as a supplementary file. No patients or members of the public were involved in the design, conduct, reporting, or dissemination plans of this retrospective study.

Results

The study included 622 patients with a mean age of 79.1 ± 5.2 years; 43.1% were male. Comorbidities were highly prevalent: hypertension (69.6%), hyperlipidemia (67.7%), coronary artery disease (39.1%), diabetes mellitus (29.4%), atrial fibrillation (25.4%), heart failure (30.4%), chronic kidney disease (28.3%), and COPD (24.8%). Among the 154 patients classified as having COPD, spirometric confirmation was available in 95 (61.7%). Echocardiography confirmed severe aortic stenosis (mean gradient: 49.4 ± 10.9 mmHg, aortic valve area: $0.8 [0.7–0.9]$ cm²) with preserved left ventricular ejection fraction ($50.5 \pm 8.9\%$). During a one-year follow-up, 117 patients (18.8%) experienced MACE, and 89

patients (14.3%) died from all causes. Detailed baseline characteristics are presented in Table 2.

The apparent AUCs for predicting one-year MACE are shown in Table 3; Fig. 2. The R₂CHA₂DS₂-VA score demonstrated the highest apparent AUC among the five scores (0.808, 95% CI 0.766–0.852), followed closely by the COPD-R₂CHA₂DS₂-VA score (0.806, 95% CI 0.765–0.852). Both significantly outperformed the traditional CHA₂DS₂-VAsC score (AUC 0.726, 95% CI 0.678–0.775; DeLong $p < 0.001$ for both comparisons). The addition of COPD to the R₂CHA₂DS₂-VA framework did not significantly improve MACE discrimination (Δ AUC = +0.001 vs. R₂CHA₂DS₂-VA; DeLong $p = 0.853$; Table 3). Among the comparator scores, the CHA₂DS₂-VA score yielded an apparent AUC of 0.769 (95% CI 0.725–0.815), and the R₂CHA₂DS₂-VAsC score an apparent AUC of 0.782 (95% CI 0.738–0.828). Full pairwise DeLong test results are provided in the Supplementary Table 1.

The apparent AUCs for predicting one-year all-cause mortality are shown in Table 4; Fig. 3. The COPD-R₂CHA₂DS₂-VA score demonstrated encouraging discriminative ability, with an apparent AUC of 0.946 (95% CI 0.926–0.971). This was significantly higher than the R₂CHA₂DS₂-VA score (apparent AUC 0.913, 95% CI 0.879–0.952; Δ AUC = +0.033; DeLong $z = 3.83$, $p = 0.0001$), confirming that the addition of COPD significantly improved mortality discrimination. The COPD-R₂CHA₂DS₂-VA score also significantly outperformed all other comparator scores: CHA₂DS₂-VA (AUC 0.877, $p < 0.001$), CHA₂DS₂-VAsC (AUC 0.846, $p < 0.001$), and R₂CHA₂DS₂-VAsC (AUC 0.900, $p < 0.001$). The graded improvement in AUC from CHA₂DS₂-VAsC (0.846) to R₂CHA₂DS₂-VAsC (0.900) to COPD-R₂CHA₂DS₂-VA (0.946) underscores the incremental prognostic value of first replacing a binary renal variable with eGFR strata, and then adding COPD as a structural component.

Because the COPD-R₂CHA₂DS₂-VA score is a prespecified clinical tool with fixed, equal component weights defined entirely a priori, bootstrap internal validation (2,000 resamples) of the univariable score-outcome relationship required estimation of only an intercept and a single slope at each iteration. With 89 mortality events, the effective events-per-parameter ratio was 44.5, far exceeding conventional overfitting thresholds. Consequently, mean bootstrap optimism was negligible for all prespecified scores (mean optimism < 0.001 for all five scores; Supplementary Table 2, Panels A and B). The bias-corrected AUCs were therefore identical, or nearly identical, to the apparent AUCs (Tables 3 and 4). Nevertheless, the bias-corrected AUC of 0.973 for the multivariable mortality model should be interpreted as an upper-bound estimate pending external validation, as the events-per-variable ratio of 9.9 approaches but does not comfortably exceed the recommended minimum of 10,

and the single-center design may have introduced spectrum bias.

In contrast, the data-driven multivariable models, which estimate 9 free parameters from the data, showed measurable optimism. For the mortality model (EPV = 9.9), mean optimism was 0.00459 (0.46%), yielding a bias-corrected AUC of 0.973 (apparent AUC 0.977; Supplementary Table 2, Panel C). For the MACE model (EPV = 13.0), mean optimism was 0.01614 (1.62%), yielding a bias-corrected AUC of 0.795 (apparent AUC 0.812). These optimism values, while modest, confirm that the bootstrap procedure correctly identifies overfitting when it exists (Supplementary Table 2).

Using the single prespecified threshold of ≥ 5 , the COPD-R₂CHA₂DS₂-VA score stratified patients into low-risk (score < 5, $n = 427$, 68.7%) and high-risk (score ≥ 5 , $n = 195$, 31.3%) groups (Table 5). The high-risk group was characterized by a significantly greater burden of comorbidities, more impaired cardiac and renal function, elevated inflammatory markers, and a higher frequency of periprocedural complications compared to the low-risk group (all key comparisons $p < 0.05$; Table 5).

One-year clinical outcomes differed substantially between risk categories. In the high-risk group, MACE occurred in 48.2% of patients (94 of 195), compared with 5.4% (23 of 427) in the low-risk group ($p < 0.001$). All-cause mortality was 42.1% (82 of 195) in the high-risk group versus 1.6% (7 of 427) in the low-risk group ($p < 0.001$; Table 5).

In multivariable logistic regression analysis (Table 6), the COPD-R₂CHA₂DS₂-VA score, treated as a continuous variable, was independently associated with MACE. Each one-point increase in the score was associated with 2.02-fold higher odds of one-year MACE (adjusted OR 2.024, 95% CI 1.667–2.457, $p < 0.001$). Atrial fibrillation was also independently associated with MACE (adjusted OR 1.929, 95% CI 1.173–3.174, $p = 0.010$). Other covariates, including SPAP, hemoglobin, NLR, LMR, vascular closure method, and post-procedural complications, did not achieve statistical significance (all $p \geq 0.097$; Table 6).

The model demonstrated moderate discriminative ability (apparent AUC 0.812, 95% CI 0.763–0.859; bias-corrected AUC 0.795, 95% CI 0.752–0.841; Table 6). Calibration was suboptimal (Hosmer-Lemeshow $\chi^2 = 39.40$, $df = 8$, $p < 0.001$), with systematic overprediction of risk at high predicted probabilities, as shown in Supplementary Figure S1 (right panel). In a prespecified sensitivity analysis excluding post-procedural complications from the model, the adjusted OR for the COPD-R₂CHA₂DS₂-VA score was 2.031 (95% CI 1.675–2.462, $p < 0.001$; Supplementary Table 3), confirming the stability of the primary estimate.

In multivariable analysis for one-year all-cause mortality (Table 7), each one-point increase in the

Table 2 Baseline demographic, clinical, laboratory, and procedural characteristics of the study population

Characteristic	Value (n = 622)
Demographic Characteristics	
Age, years	79.1 ± 5.2
Male sex, n (%)	268 (43.1)
Female sex, n (%)	354 (56.9)
Body mass index, kg/m ²	27.3 ± 4.3
Current smoking, n (%)	36 (5.8)
Comorbidities	
Hypertension, n (%)	433 (69.6)
Diabetes mellitus, n (%)	183 (29.4)
Hyperlipidemia, n (%)	421 (67.7)
Coronary artery disease, n (%)	243 (39.1)
Peripheral artery disease, n (%)	76 (12.2)
Atrial fibrillation, n (%)	158 (25.4)
COPD, n (%)	154 (24.8)
— Spirometry-confirmed COPD, n (%)	95 (15.3)
Chronic kidney disease, n (%)	176 (28.3)
Cerebrovascular disease (stroke/TIA), n (%)	33 (5.3)
Heart failure, n (%)	189 (30.4)
Previous CABG, n (%)	70 (11.3)
Echocardiographic and Hemodynamic Parameters	
Left ventricular ejection fraction, %	50.5 ± 8.9
Aortic valve area, cm ²	0.8 (0.7–0.9)
Peak aortic gradient, mmHg	80.2 ± 17.9
Mean aortic gradient, mmHg	49.4 ± 10.9
Systolic pulmonary artery pressure (SPAP), mmHg	40.3 ± 8.3
Risk Scores	
CHA ₂ DS ₂ -VA score	3 (3–4)
CHA ₂ DS ₂ -VAsc score	4 (3–5)
R ₂ CHA ₂ DS ₂ -VAsc score	4 (4–5)
R ₂ CHA ₂ DS ₂ -VA score	4 (3–5)
COPD-R ₂ CHA ₂ DS ₂ -VA score	4 (3–5)
Laboratory Parameters	
Glucose, mg/dL	107 (95–134)
Creatinine, mg/dL	0.9 (0.8–1.1)
eGFR, mL/min/1.73 m ²	63.9 ± 15.0
Total protein, g/dL	6.9 ± 0.5
Total cholesterol, mg/dL	189.1 ± 42.0
Triglycerides, mg/dL	130 (98–160)
LDL cholesterol, mg/dL	115.8 ± 34.1
HDL cholesterol, mg/dL	45.6 ± 10.4
Hemoglobin, g/dL	11.9 ± 1.2
Platelet count, ×10 ⁹ /L	233.4 ± 65.8
White blood cell count, ×10 ⁹ /L	7.5 ± 1.9
Neutrophils, ×10 ⁹ /L	5.0 ± 1.6
Lymphocytes, ×10 ⁹ /L	1.6 (1.3–2.0)
Monocytes, ×10 ⁹ /L	0.6 (0.5–0.7)
Neutrophil-to-lymphocyte ratio (NLR)	2.8 (2.1–3.8)
Lymphocyte-to-monocyte ratio (LMR)	3.0 (2.2–3.8)
Procedural Characteristics	
Pre-dilatation, n (%)	406 (65.3)
Valve size, mm	28.0 ± 3.2
Self-expandable valve, n (%)	397 (63.8)
Balloon-expandable valve, n (%)	225 (36.2)

Table 2 (continued)

Characteristic	Value (n = 622)
Post-dilatation, n (%)	68 (10.9)
Percutaneous vascular closure, n (%)	579 (93.1)
Surgical vascular closure, n (%)	43 (6.9)
Post-procedural Complications (VARC-3)	
Major complications, n (%)	15 (2.4)
Permanent pacemaker implantation, n (%)	49 (7.9)
Major bleeding, n (%)	20 (3.2)
Acute kidney injury, n (%)	36 (5.8)
Stroke/TIA, n (%)	18 (2.9)
Myocardial infarction, n (%)	26 (4.2)
1-Year Outcomes	
MACE, n (%)	117 (18.8)
All-cause mortality, n (%)	89 (14.3)

Abbreviations: CABG Coronary artery bypass grafting, COPD Chronic obstructive pulmonary disease, eGFR Estimated glomerular filtration rate (CKD-EPI 2021 creatinine equation, without race coefficient), HDL High-density lipoprotein cholesterol, IQR Interquartile range, LDL Low-density lipoprotein cholesterol, LMR Lymphocyte-to-monocyte ratio, LV Left ventricular, MACE Major adverse cardiovascular events (composite of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, and rehospitalization for acute heart failure), NLR Neutrophil-to-lymphocyte ratio, SD Standard deviation, SPAP Systolic pulmonary artery pressure, TIA Transient ischemic attack, VARC-3 Valve Academic Research Consortium-3 criteria

Continuous variables are presented as mean $\pm$ SD or median (IQR); categorical variables as n (%). Comorbidity definitions are provided in Methods; risk score components are detailed in Table 1. A complete-case analysis was performed; there were no missing data for any variable in this table

Table 3 Discriminative performance and internal validation metrics of risk scores for predicting 1-year MACE

Risk Score	Apparent AUC (95% CI)	Bias-Corrected AUC (95% CI)	Bias-Corrected Calibration Slope	Brier Score
CHA ₂ DS ₂ -VA	0.769 (0.725–0.815)	0.769 (0.725–0.815)	—†	—†
CHA ₂ DS ₂ -VASc	0.726 (0.678–0.775)	0.725 (0.677–0.773)	—†	—†
R ₂ CHA ₂ DS ₂ -VASc	0.782 (0.738–0.828)	0.782 (0.737–0.827)	—†	—†
R ₂ CHA ₂ DS ₂ -VA	0.808 (0.766–0.852)	0.808 (0.766–0.852)	—†	—†
COPD-R ₂ CHA ₂ DS ₂ -VA	0.806 (0.765–0.852)	0.807 (0.765–0.852)	0.985	0.1307

Abbreviations: AUC Area under the receiver operating characteristic curve, CI Confidence interval, Cal. Calibration, COPD Chronic obstructive pulmonary disease, eGFR Estimated glomerular filtration rate, MACE Major adverse cardiovascular events

Bias-corrected estimates are from bootstrap internal validation (2,000 resamples). The prespecified descriptive threshold of ≥ 5 was not derived from the present data (see Methods). Key DeLong test result: COPD-R₂CHA₂DS₂-VA vs. R₂CHA₂DS₂-VA, Δ AUC = +0.001, p = 0.853. Full methodology and pairwise comparisons are in the Supplementary Material

† For single-predictor logistic regression models, the apparent calibration slope is identically 1.000 on the training data and is not reported. The value shown for the COPD-R₂CHA₂DS₂-VA score is the bias-corrected calibration slope

COPD-R₂CHA₂DS₂-VA score was independently associated with 3.52-fold higher odds of death (adjusted OR 3.517, 95% CI 2.446–5.058, p < 0.001). SPAP (adjusted OR 1.160 per mmHg, 95% CI 1.097–1.226, p < 0.001)

and hemoglobin (adjusted OR 0.588 per g/dL, 95% CI 0.380–0.909, p = 0.017) were also significant independent predictors. Atrial fibrillation, NLR, LMR, vascular closure method, and post-procedural complications were not independently associated with mortality (all p $\geq$ 0.106; Table 7).

The model demonstrated encouraging discriminative ability (apparent AUC 0.977, 95% CI 0.963–0.991; bias-corrected AUC 0.973, 95% CI 0.962–0.984; Table 7) and good calibration (Hosmer-Lemeshow χ^2 = 2.32, df = 8, p = 0.970; Supplementary Figure S1, left panel). The Nagelkerke R^2 was 0.758. With an EPV of 9.9, the mean bootstrap optimism was modest (0.00459), and the bias-corrected AUC of 0.973 should be interpreted as an upper-bound estimate pending external validation. In a prespecified sensitivity analysis excluding post-procedural complications, the adjusted OR for the COPD-R₂CHA₂DS₂-VA score was 3.528 (95% CI 2.445–5.091, p < 0.001; Supplementary Table 3).

The results of the prespecified sensitivity analyses are summarized in Supplementary Table 3. In the spirometry-confirmed COPD subgroup (n = 563, excluding 59 patients with clinically diagnosed COPD lacking spirometric confirmation), the apparent AUC of the COPD-R₂CHA₂DS₂-VA score for mortality was 0.947 (95% CI 0.922–0.972), compared with 0.946 in the full cohort. For MACE, the apparent AUC was 0.813 (95% CI 0.769–0.858). These results indicate that reliance on clinical diagnosis for a subset of patients did not materially influence the score's discriminative performance.

In the multiple imputation analysis including all 634 patients, the pooled bias-corrected AUCs were 0.943 (95% CI 0.921–0.967) for mortality and 0.804 (95% CI

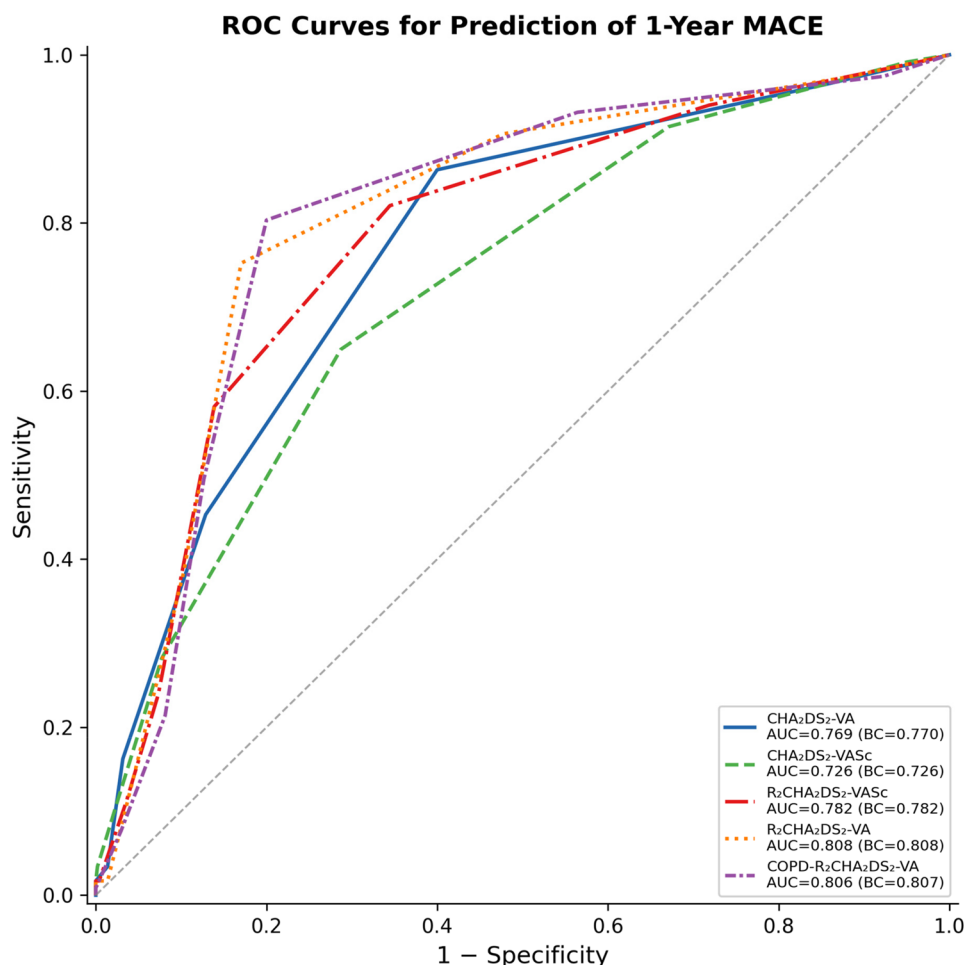


Fig. 2 ROC Curves for Prediction of 1-Year MACE. Abbreviations: AUC, area under the receiver operating characteristic curve; BC: bias-corrected; COPD, chronic obstructive pulmonary disease; MACE, major adverse cardiovascular events; ROC, receiver operating characteristic. Notes: Overlaid ROC curves for five prespecified risk scores. The diagonal dashed line represents random chance (AUC = 0.50). AUC values shown are apparent (non-corrected) estimates

0.760–0.848) for MACE, within 0.003 of the primary analysis. Replacing the categorical R/R₂ renal components with eGFR modeled as a linear spline yielded a C-index of 0.943 for mortality and 0.808 for MACE, compared with 0.946 and 0.806 for the categorical score, indicating negligible information loss from eGFR discretization.

Discussion

This study describes the development and internal assessment of the novel COPD-R₂CHA₂DS₂-VA score. To the best of our knowledge, this represents the first CHA₂DS₂-VASc-derived framework to systematically incorporate COPD as a structural component and to quantitatively integrate renal function based on graded eGFR strata for prognostic assessment after TAVI. The score demonstrates encouraging discriminative ability for one-year all-cause mortality, with a statistically significant, though clinically modest, incremental improvement over the

R₂CHA₂DS₂-VA score. For MACE, the addition of COPD does not meaningfully enhance discrimination.

Interpretation of the apparent discriminative performance. Several factors may explain the high apparent AUC of 0.946 observed in this study. First, our cohort exhibited a high prevalence of both advanced renal disease (28.3%) and COPD (24.8%), providing a broad risk spectrum that inherently amplifies discriminative capacity compared to lower-risk or lower-comorbidity populations. Second, the COPD-R₂CHA₂DS₂-VA score comprises nine components versus seven in the original CHA₂DS₂-VASc, capturing a greater proportion of outcome variance by design. Third, the single-center design may have introduced spectrum bias, as institutional referral patterns, patient selection practices, and completeness of follow-up may not reflect broader, more heterogeneous TAVI populations. Fourth, the complete-case analysis (no missing data) ensured that all 622 patients contributed full information, which may overestimate performance compared with real-world datasets where

Table 4 Discriminative performance and internal validation metrics of risk scores for predicting 1-year all-cause mortality

Risk Score	Apparent AUC (95% CI)	Bias-Corrected AUC (95% CI)	Bias-Corrected Calibration Slope	Brier Score
CHA ₂ DS ₂ -VA	0.877 (0.843–0.916)	0.877 (0.843–0.916)	—†	—†
CHA ₂ DS ₂ -VASc	0.846 (0.805–0.890)	0.846 (0.805–0.890)	—†	—†
R ₂ CHA ₂ DS ₂ -VASc	0.900 (0.864–0.940)	0.900 (0.864–0.940)	—†	—†
R ₂ CHA ₂ DS ₂ -VA	0.913 (0.879–0.952)	0.913 (0.879–0.952)	—†	—†
COPD-R ₂ CHA ₂ DS ₂ -VA	0.946 (0.926–0.971)	0.946 (0.926–0.971)	0.989	0.0507

Abbreviations: AUC Area under the receiver operating characteristic curve, CI Confidence interval, Cal. Calibration, COPD Chronic obstructive pulmonary disease, eGFR Estimated glomerular filtration rate

The negligible optimism for the COPD-R₂CHA₂DS₂-VA score reflects its prespecified nature (EPV=44.5; see Methods). The high AUC should be interpreted cautiously as a development-phase, single-center estimate requiring external validation. Key DeLong test result: COPD-R₂CHA₂DS₂-VA vs. R₂CHA₂DS₂-VA, ΔAUC = + 0.033, *p* = 0.0001

† The apparent calibration slope for single-predictor models is identically 1.000 on the training data and is not reported. The value shown for the COPD-R₂CHA₂DS₂-VA score is the bias-corrected calibration slope from bootstrap internal validation (2,000 resamples)

missing data are common. Fifth, the prespecified nature of the score, with component weights fixed a priori, means that no overfitting of the score itself occurred, but this does not protect against optimism from the cohort-specific case mix. These factors collectively suggest that the AUC of 0.946 is likely an optimistic, upper-bound estimate that will attenuate upon external validation in more diverse, unselected, and lower-comorbidity cohorts. Accordingly, all performance metrics reported here should be considered development-phase estimates rather than transportable measures of clinical utility.

Importantly, the COPD-R₂CHA₂DS₂-VA score is not proposed as a replacement for STS-PROM or EuroSCORE II, which remain the guideline-recommended instruments for procedural risk stratification and are embedded in heart team decision-making [2, 3]. Rather, it is conceived as a complementary, comorbidity-focused tool that can be rapidly calculated from clinical and laboratory data at the bedside or in the outpatient setting. Its intended use is to provide additional granularity for one-year prognostic discussions, particularly regarding non-cardiovascular mortality risk, which surgical scores may underestimate in patients with significant pulmonary or renal comorbidity.

Accurate prediction of long-term outcomes after TAVI remains a significant unmet clinical need. While various risk stratification tools have been proposed, their prognostic discrimination in the TAVI population has been suboptimal, as they fail to adequately capture the specific comorbidity burden and frailty profile inherent to these patients [6–8]. The CHA₂DS₂-VASc score, reflecting core cardiovascular risk factors, has shown consistent, albeit moderate, prognostic utility beyond atrial fibrillation in various cohorts, including TAVI patients, with AUCs typically between 0.60 and 0.71 [11, 12, 25, 26]. However, two major comorbidities strongly linked to post-TAVI outcomes, COPD and renal dysfunction, are not adequately addressed in its existing variants. Renal function is often dichotomized, neglecting the graded risk of eGFR decline, and COPD is frequently omitted as a structural component [16, 25, 26]. Our COPD-R₂CHA₂DS₂-VA score was specifically designed to bridge these gaps.

Our findings must be interpreted in the context of prior studies that evaluated CHA₂DS₂-VASc-based scores in TAVI cohorts. Hamid et al. reported that the original CHA₂DS₂-VASc score predicted one-year mortality with an AUC of 0.62 in 308 patients [9]. Orvin et al. observed an AUC of 0.70 in a multicenter registry of 1,260 patients [12]. Kalyoncuoglu et al. found that the R₂CHA₂DS₂-VASc score achieved an AUC of 0.71 for late mortality in 302 patients [10]. The markedly higher AUC of 0.946 observed in the present study may be attributable to several factors. First, the R₂ component replaces a binary renal dysfunction variable with graded eGFR strata, capturing the well-established continuous, log-linear relationship between declining renal function and post-TAVI mortality, a relationship that is substantially attenuated when renal function is dichotomized [14, 15]. Second, the incorporation of COPD adds a second major non-cardiac prognostic domain that is absent from traditional CHA₂DS₂-VASc-based scores. Third, our cohort exhibited a high prevalence of both advanced renal disease (28.3% CKD) and COPD (24.8%), providing a broad risk spectrum that amplifies discriminative capacity. Fourth, the score comprises 9 components versus 7 in CHA₂DS₂-VASc, inherently capturing a greater proportion of outcome variance. However, direct comparisons across studies are confounded by differences in case mix, endpoint definitions, and follow-up completeness. The true incremental value of these modifications can only be determined through external validation in populations with varying comorbidity profiles.

A noteworthy finding of this study is the differential incremental value of COPD for mortality versus MACE. Adding COPD to the R₂CHA₂DS₂-VA score significantly improved mortality discrimination (ΔAUC + 0.033, *p* = 0.0001) but did not meaningfully enhance MACE prediction (ΔAUC + 0.001, *p* = 0.853). This divergence is

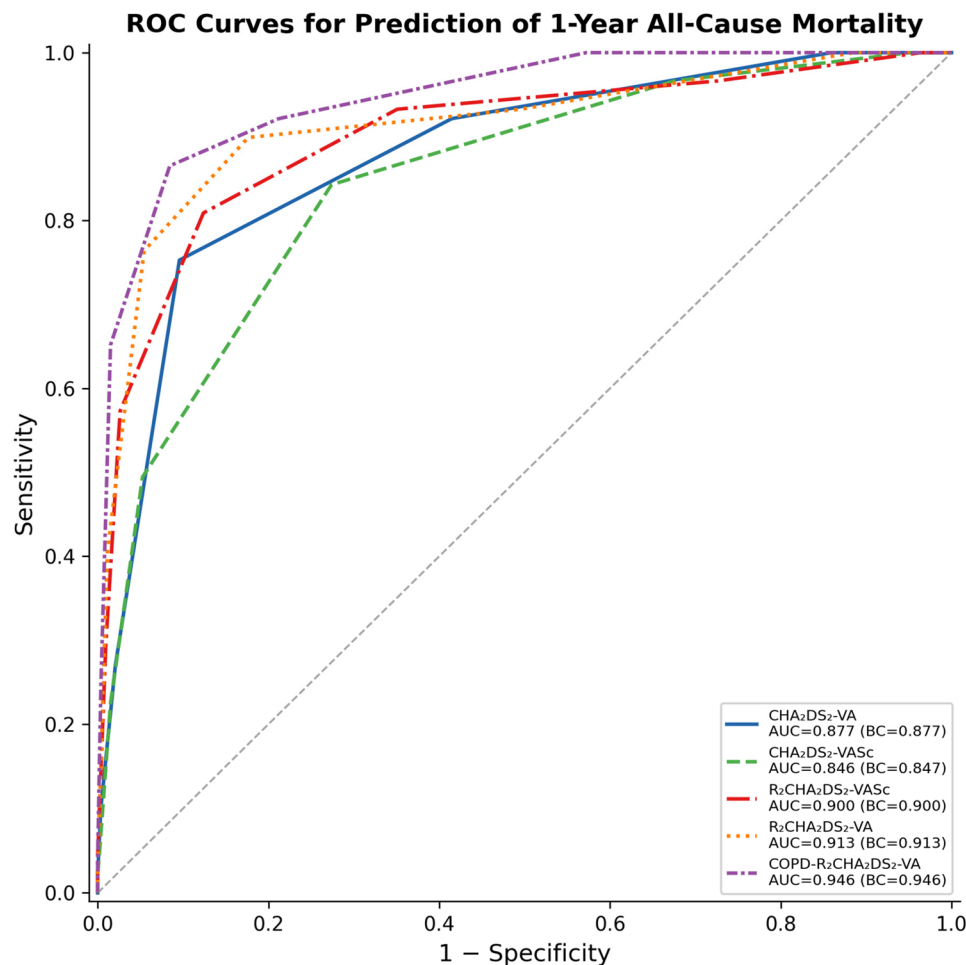


Fig. 3 ROC Curves for Prediction of 1-Year All-Cause Mortality. Abbreviations: AUC, area under the receiver operating characteristic curve; BC: bias-corrected; COPD, chronic obstructive pulmonary disease; ROC, receiver operating characteristic. Notes: Overlaid ROC curves for five prespecified risk scores. The diagonal dashed line represents random chance (AUC=0.50)

biologically plausible and likely reflects the fact that all-cause mortality captures non-cardiovascular deaths, particularly respiratory failure, pneumonia, sepsis, and pulmonary malignancy, to which COPD contributes directly. In contrast, MACE is a composite of cardiovascular events (myocardial infarction, stroke, and heart failure hospitalization) that are less directly influenced by the presence of COPD. Comparable patterns have been noted for other non-cardiac comorbidities in TAVI cohorts [16, 25]. This finding has implications for how the score should be interpreted clinically: it may be more informative for counselling patients about overall one-year survival than for predicting cardiovascular event risk. However, we acknowledge that cause-specific mortality was not adjudicated in this study, and this hypothesis requires prospective validation with detailed cause-of-death ascertainment.

The encouraging discriminative performance of the score for mortality is attributable to its comprehensive capture of key pathophysiological pathways. Beyond

chronic hypoxemia and pulmonary hypertension, COPD induces a state of persistent systemic inflammation. Elevated interleukin-6, tumour necrosis factor- α , and C-reactive protein levels in these patients accelerate vascular senescence and may impair myocardial recovery post-TAVI [19, 20]. The lung-heart-kidney axis in COPD involves shared inflammatory pathways that simultaneously affect pulmonary vasculature, myocardial function, and renal perfusion, collectively impairing hemodynamic adaptation [21]. Furthermore, the graded risk associated with eGFR decline reflects not only reduced filtration but also endothelial dysfunction and uremic toxin accumulation. Renal dysfunction also modifies the pharmacodynamics of essential post-TAVI medications [13–15, 27]. The independent association of SPAP with mortality in our study aligns with previous reports highlighting the prognostic importance of pulmonary hypertension in patients undergoing TAVI [28, 29]. Similarly, the independent association of lower hemoglobin levels with increased mortality is consistent

Table 5 Baseline characteristics according to COPD-R₂CHA₂DS₂-VA risk score categories (prespecified threshold ≥ 5)

Variable	Low Risk (< 5) n = 427	High Risk (≥ 5) n = 195	p value	Test
Continuous Variables, Median (IQR)				
Age, years	79.0 (75.0–82.0)	80.0 (77.0–84.0)	< 0.001	MWU
BMI, kg/m ²	26.7 (24.0–29.5)	25.9 (23.9–30.4)	0.390	MWU
LVEF, %	55.0 (50.0–60.0)	45.0 (40.0–54.0)	< 0.001	MWU
Aortic Valve Area, cm ²	0.8 (0.7–0.8)	0.8 (0.7–0.9)	0.055	MWU
Peak Gradient, mmHg	80.0 (70.0–92.0)	74.0 (65.5–84.5)	< 0.001	MWU
Mean Gradient, mmHg	48.0 (43.0–55.5)	45.0 (41.0–52.0)	< 0.001	MWU
SPAP, mmHg	38.0 (35.0–40.0)	46.0 (40.0–53.0)	< 0.001	MWU
eGFR, mL/min/1.73 m ²	68.5 (61.3–78.0)	50.0 (44.0–62.0)	< 0.001	MWU
Hemoglobin, g/dL	12.0 (11.4–13.0)	11.0 (10.4–11.9)	< 0.001	MWU
Glucose, mg/dL	103.0 (94.0–123.0)	123.0 (100.0–163.5)	< 0.001	MWU
Total Cholesterol, mg/dL	187.0 (162.0–216.0)	178.0 (158.5–203.5)	0.052	MWU
HDL, mg/dL	45.0 (39.0–52.0)	44.0 (38.0–48.5)	0.031	MWU
LDL, mg/dL	112.8 (92.0–138.0)	109.0 (91.6–132.0)	0.228	MWU
Triglycerides, mg/dL	129.0 (98.0–161.0)	132.0 (97.5–158.0)	0.928	MWU
WBC, 10 ³ /μL	7.1 (6.1–8.2)	7.8 (6.7–9.4)	< 0.001	MWU
NLR	2.5 (2.1–3.2)	3.8 (2.7–5.2)	< 0.001	MWU
LMR	3.2 (2.6–4.1)	2.4 (1.8–3.2)	< 0.001	MWU
Platelet, 10 ³ /μL	230.0 (188.0–274.0)	223.0 (188.5–266.0)	0.702	MWU
Valve Size, mm	29.0 (26.0–29.0)	27.5 (26.0–29.0)	0.985	MWU
Categorical Variables, n (%)				
Female sex	253 (59.3%)	101 (51.8%)	0.098	χ ²
Current Smoking	17 (4.0%)	19 (9.7%)	0.008	χ ²
Hypertension	273 (63.9%)	160 (82.1%)	< 0.001	χ ²
Diabetes Mellitus	84 (19.7%)	99 (50.8%)	< 0.001	χ ²
Hyperlipidemia	283 (66.3%)	138 (70.8%)	0.308	χ ²
Coronary Artery Disease	116 (27.2%)	127 (65.1%)	< 0.001	χ ²
Peripheral Artery Disease	12 (2.8%)	64 (32.8%)	< 0.001	χ ²
Atrial Fibrillation	70 (16.4%)	88 (45.1%)	< 0.001	χ ²
COPD	66 (15.5%)	88 (45.1%)	< 0.001	χ ²
Chronic Kidney Disease	46 (10.8%)	130 (66.7%)	< 0.001	χ ²
Cerebrovascular Disease	3 (0.7%)	30 (15.4%)	< 0.001	Fisher
Heart Failure	85 (19.9%)	104 (53.3%)	< 0.001	χ ²
Previous CABG	43 (10.1%)	27 (13.8%)	0.213	χ ²
Pre-dilatation	281 (65.8%)	125 (64.1%)	0.746	χ ²
Percutaneous Vascular Closure	408 (95.6%)	171 (87.7%)	< 0.001	χ ²
Post-dilatation	43 (10.1%)	25 (12.8%)	0.378	χ ²
Major Complications (VARC-3)	5 (1.2%)	10 (5.1%)	0.007	χ ²
Permanent Pacemaker	27 (6.3%)	22 (11.3%)	0.049	χ ²
Major Bleeding	7 (1.6%)	13 (6.7%)	0.002	χ ²
Acute Kidney Injury	6 (1.4%)	30 (15.4%)	< 0.001	χ ²
Risk Scores, Median (IQR)				
CHA ₂ DS ₂ -VA	3.0 (3.0–4.0)	5.0 (4.0–5.0)	< 0.001	MWU
CHA ₂ DS ₂ -VAsC	4.0 (3.0–4.0)	5.0 (5.0–6.0)	< 0.001	MWU
R ₂ CHA ₂ DS ₂ -VAsC	4.0 (3.0–4.0)	6.0 (5.0–7.0)	< 0.001	MWU
R ₂ CHA ₂ DS ₂ -VA	3.0 (3.0–4.0)	5.0 (5.0–6.0)	< 0.001	MWU
COPD-R ₂ CHA ₂ DS ₂ -VA	3.0 (3.0–4.0)	6.0 (5.0–7.0)	< 0.001	MWU
1-Year Outcomes, n (%)				

Table 5 (continued)

Variable	Low Risk (< 5) n = 427	High Risk (≥ 5) n = 195	p value	Test
MACE	23 (5.4%)	94 (48.2%)	< 0.001	χ^2
All-Cause Mortality	7 (1.6%)	82 (42.1%)	< 0.001	χ^2

Abbreviations: BMI Body mass index, CABG Coronary artery bypass grafting, COPD Chronic obstructive pulmonary disease, eGFR Estimated glomerular filtration rate (CKD-EPI 2021 equation), HDL High-density lipoprotein cholesterol, IQR Interquartile range, LDL Low-density lipoprotein cholesterol, LMR Lymphocyte-to-monocyte ratio, LVEF Left ventricular ejection fraction, MACE Major adverse cardiovascular events, MWU Mann-Whitney U test, NLR Neutrophil-to-lymphocyte ratio, SPAP Systolic pulmonary artery pressure, VARC-3 Valve Academic Research Consortium-3 criteria, WBC White blood cell count, χ^2 Pearson's chi-square test, Fisher Fisher's exact test

The threshold of ≥ 5 was prespecified and was not derived from the present dataset (see Methods). It is used exclusively for descriptive stratification; in all primary regression analyses, the score is treated as a continuous variable. Continuous variables are presented as median (IQR) and compared using the Mann-Whitney U test. Categorical variables are presented as n (%) and compared using Pearson's chi-square or Fisher's exact test. All p values are two-sided and unadjusted for multiplicity

Table 6 Multivariable logistic regression analysis for predictors of 1-year major adverse cardiovascular events (MACE)

Variable	B	SE	Wald χ^2	Adjusted OR (95% CI)	p value
COPD-R ₂ CHA ₂ DS ₂ -VA Score (per one-point increase)	+ 0.705	0.099	50.66	2.024 (1.667–2.457)	< 0.001
SPAP (per mmHg)	-0.027	0.016	2.76	0.974 (0.943–1.005)	0.097
Atrial Fibrillation	+ 0.657	0.254	6.70	1.929 (1.173–3.174)	0.010
Hemoglobin (per g/dL)	-0.055	0.109	0.25	0.947 (0.765–1.171)	0.614
NLR	-0.041	0.077	0.28	0.960 (0.825–1.117)	0.600
LMR	-0.048	0.117	0.17	0.953 (0.758–1.200)	0.684
Vascular Closure (Percutaneous vs. Surgical)	+ 0.112	0.362	0.10	1.118 (0.550–2.272)	0.758
Post-procedural Complications (VARC-3)	-1.280	0.800	2.56	0.278 (0.058–1.333)	0.110

Model Fit and Performance Indices: Number of events: MACE = 117 (18.8% of cohort); Events-per-variable (EPV) ratio: 117 / 9 = 13.0; -2 Log Likelihood = 491.475; Cox & Snell R^2 = 0.203; Nagelkerke R^2 = 0.261; Hosmer-Lemeshow χ^2 = 39.40, df = 8 (p < 0.001); Apparent AUC = 0.812 (95% CI: 0.763–0.859); Bias-Corrected AUC = 0.795 (95% CI: 0.784–0.816); Brier Score = 0.1255

Abbreviations: AUC Area under the receiver operating characteristic curve, B Unstandardized regression coefficient, CI Confidence interval, COPD Chronic obstructive pulmonary disease, df Degrees of freedom, LMR Lymphocyte-to-monocyte ratio, MACE Major adverse cardiovascular events, NLR Neutrophil-to-lymphocyte ratio, OR Odds ratio, SE Standard error, SPAP Systolic pulmonary artery pressure, VARC-3 Valve Academic Research Consortium-3 criteria

The COPD-R₂CHA₂DS₂-VA score was treated as a continuous variable; the adjusted OR represents the multiplicative increase in odds per one-point increment. Predictors were prespecified based on clinical relevance; individual score components were not included as separate covariates to prevent multicollinearity (see Methods). Bootstrap internal validation details and optimism values are in Supplementary Table 2. Calibration was suboptimal (Hosmer-Lemeshow p < 0.001; see Supplementary Figure S1 for calibration plot). In a sensitivity analysis excluding post-procedural complications, the adjusted OR for the score was 2.031 (95% CI 1.675–2.462, p < 0.001)

with studies demonstrating the adverse impact of anemia on outcomes after TAVI [30, 31]. Our observed one-year mortality (14.3%) and MACE (18.8%) rates are consistent with those reported in contemporary real-world TAVI registries, supporting the generalizability of our cohort [6–8].

Table 7 Multivariable logistic regression analysis for predictors of 1-year all-cause mortality

Variable	B	SE	Wald χ^2	Adjusted OR (95% CI)	p value
COPD-R ₂ CHA ₂ DS ₂ -VA Score (per one-point increase)	+ 1.258	0.185	46.05	3.517 (2.446–5.058)	< 0.001
SPAP (per mmHg)	+ 0.148	0.028	27.29	1.160 (1.097–1.226)	< 0.001
Atrial Fibrillation	+ 0.657	0.406	2.61	1.929 (0.870–4.277)	0.106
Hemoglobin (per g/dL)	-0.531	0.222	5.70	0.588 (0.380–0.909)	0.017
NLR	+ 0.032	0.117	0.08	1.033 (0.821–1.299)	0.783
LMR	-0.206	0.219	0.89	0.814 (0.529–1.250)	0.347
Vascular Closure (Percutaneous vs. Surgical)	-0.190	0.662	0.08	0.827 (0.226–3.029)	0.775
Post-procedural Complications (VARC-3)	-0.188	0.756	0.06	0.828 (0.188–3.648)	0.803

Model Fit and Performance Indices: Number of events: All-cause mortality = 89 (14.3% of cohort); Events-per-variable (EPV) ratio: 89 / 9 = 9.9; -2 Log Likelihood = 166.789; Cox & Snell R^2 = 0.561; Nagelkerke R^2 = 0.758; Hosmer-Lemeshow χ^2 = 2.32, df = 8 (p = 0.970); Apparent AUC = 0.977 (95% CI: 0.963–0.991); Bias-Corrected AUC = 0.973 (95% CI: 0.970–0.977); Brier Score = 0.0405

Abbreviations: AUC Area under the receiver operating characteristic curve, B Unstandardized regression coefficient, CI Confidence interval, COPD Chronic obstructive pulmonary disease, df Degrees of freedom, LMR Lymphocyte-to-monocyte ratio, NLR Neutrophil-to-lymphocyte ratio, OR Odds ratio, SE Standard error, SPAP Systolic pulmonary artery pressure, VARC-3 Valve Academic Research Consortium-3 criteria

The COPD-R₂CHA₂DS₂-VA score was treated as a continuous variable. The EPV ratio of 9.9 is borderline; the bias-corrected AUC of 0.973 should be interpreted as an upper-bound estimate pending external validation. In a sensitivity analysis excluding post-procedural complications, the adjusted OR for the score was 3.528 (95% CI 2.445–5.091, p < 0.001)

Neither NLR nor LMR remained an independent predictor in the multivariable models, despite their known prognostic value in cardiovascular disease. This may be attributable to the comprehensive nature of the COPD-R₂CHA₂DS₂-VA score, which likely captures the systemic inflammatory burden through its components, particularly COPD and renal dysfunction. Both conditions are associated with chronic inflammation, and their inclusion in the score may have captured the predictive information carried by NLR and LMR.

Limitations

Several limitations of this study warrant careful consideration. The most critical limitation is the absence of external validation. All performance metrics reported here, including the AUC of 0.946 for mortality and the bias-corrected multivariable model AUC of 0.973, were obtained from a single center and a single cohort. Although we employed rigorous bootstrap internal validation with 2,000 resamples, this technique cannot substitute for evaluation in an independent sample with a different case mix, practice patterns, and outcome prevalences. External validation in geographically, ethnically, and clinically diverse TAVI populations is a prerequisite before the COPD-R₂CHA₂DS₂-VA score can be considered for clinical use. Such studies should assess not only discrimination and calibration but also measures of clinical utility, including decision curve analysis and net reclassification improvement compared with established instruments such as STS-PROM and EuroSCORE II. In accordance with the TRIPOD statement, the present study represents the development and internal assessment phase (Type 1b); progression to TRIPOD Type 3 (external validation) is essential. Furthermore, the high comorbidity burden of the present cohort (28.3% CKD, 24.8% COPD) provides a broad risk spectrum that amplifies discriminative capacity. As TAVI indications continue to expand toward lower-risk populations, the transportability of this score to cohorts with lower comorbidity prevalence requires specific evaluation.

Second, the retrospective, single-center design may introduce selection bias and limit the generalizability of findings to other healthcare settings. Although we used standardized VARC-3 definitions and national registry verification for endpoint adjudication, retrospective data collection inherently carries the risk of misclassified event recording.

Third, the ethnically homogeneous cohort from a single country (Türkiye) necessitates caution when extrapolating these results to diverse geographic or ethnic populations.

Fourth, the definition of COPD warrants careful consideration regarding misclassification bias. Although we employed a combined definition requiring both an ICD-10 diagnosis and active maintenance inhaler therapy, spirometric confirmation (post-bronchodilator FEV₁/FVC ratio < 0.70) was available in only 62% of patients classified as having COPD (95 of 154 patients). This limitation reflects a realistic challenge in elderly, frail TAVI populations, where pre-procedural spirometry is often not performed due to logistical constraints, patient immobility, acute dyspnea, or the prioritization of procedural planning over pulmonary function testing. Nonetheless, we acknowledge that the absence of universal spirometric confirmation may have introduced misclassification bias,

potentially misclassifying patients with asthma, bronchiectasis, heart failure-related pulmonary congestion, or other chronic pulmonary conditions as having COPD, while missing patients with undiagnosed airflow obstruction who do not yet require maintenance inhaler therapy. To address this concern, we performed a prespecified sensitivity analysis restricted to patients with either no COPD or spirometry-confirmed COPD ($n = 563$, excluding 59 patients with clinically diagnosed COPD lacking spirometric confirmation). In this analysis, the apparent AUC of the COPD-R₂CHA₂DS₂-VA score for mortality was 0.947 (95% CI 0.922–0.972), compared with 0.946 in the full cohort; for MACE, the apparent AUC was 0.813 (95% CI 0.769–0.858), compared with 0.806 in the full cohort. These nearly identical results suggest that reliance on clinical diagnosis for the subset without spirometry did not materially influence the score's discriminative performance. Nevertheless, future external validation studies should mandate pre-procedural spirometry whenever feasible and should explore whether incorporating GOLD stage, exacerbation history (frequency of moderate/severe exacerbations in the preceding year), or COPD phenotype (emphysematous vs. chronic bronchitis predominant) enhances the score's prognostic performance beyond a simple binary COPD indicator.

Fifth, a further methodological consideration concerns the interpretation of the bootstrap internal validation results for the score itself. Because the COPD-R₂CHA₂DS₂-VA score is entirely prespecified, with component weights fixed a priori, bootstrap resampling of the univariable score-outcome relationship estimates only an intercept and a single slope. The effective events-per-parameter ratio was 44.5, far exceeding conventional thresholds, and the mean bootstrap optimism was -0.00014 (effectively zero). This confirms that the apparent AUC of 0.946 is not driven by overfitting of the score itself. By contrast, the multivariable models, which estimate 9 free parameters from the data and have EPV values of 9.9–13.0, showed measurable optimism. These results illustrate the critical distinction between validating a prespecified clinical tool and validating a data-driven model. Nonetheless, the high apparent AUC may also reflect the specific case mix of our cohort, and external validation is essential to determine the true, transportable discriminative performance.

Sixth, for the multivariable mortality model, the events-per-variable ratio of 9.9 approaches but does not comfortably exceed the commonly recommended minimum of 10 to 20. While bootstrap internal validation estimated modest optimism (0.00459), the bias-corrected AUC of 0.973 should be viewed as an upper-bound estimate. The adjusted odds ratios, particularly for covariates with wide confidence intervals, should be interpreted

with caution. External validation in cohorts with substantially higher event counts is needed to obtain stable, unbiased estimates of predictor effects. Additionally, the MACE model demonstrated suboptimal calibration, with systematic overprediction of risk at high predicted probabilities. This miscalibration may reflect the heterogeneity of the composite MACE endpoint, whose components (cardiovascular death, myocardial infarction, stroke, and heart failure hospitalization) have different predictor profiles. The MACE model should therefore be interpreted with caution for individualized risk prediction.

Seventh, although we adjusted for key covariates in our multivariable models, unmeasured confounders, including objective frailty metrics and medication adherence, may have influenced the clinical outcomes. The COPD-R₂CHA₂DS₂-VA score does not incorporate frailty, a multidimensional geriatric syndrome that is among the strongest independent predictors of adverse outcomes after TAVI [32, 33]. Frailty captures physiological reserve and vulnerability beyond the cumulative burden of individual comorbidities, and its omission may limit the score's prognostic accuracy, particularly in the very elderly. Future prospective studies should investigate whether combining the COPD-R₂CHA₂DS₂-VA score with a validated frailty instrument (e.g., Essential Frailty Toolset, Clinical Frailty Scale) provides incremental discriminative value.

Eighth, cause-specific mortality was not adjudicated in this study. The differential performance of COPD for all-cause mortality versus MACE, while biologically plausible, would be strengthened by demonstrating that excess mortality in COPD patients is indeed driven by non-cardiovascular causes.

Ninth, as with any study evaluating one-year outcomes, patients who died before completing follow-up are included in the analysis. While this is inherent to the study design and endpoint definition, the potential for immortal time bias should be acknowledged. This bias is unlikely to materially affect the discriminative performance of the prespecified score, but may influence the calibration of time-dependent risk estimates.

Tenth, the COPD-R₂CHA₂DS₂-VA score does not incorporate any objective frailty metric. Frailty is a multidimensional geriatric syndrome encompassing physiological reserve, nutritional status, mobility, cognitive function, and vulnerability to stressors. Multiple studies, including the landmark FRAILTY-AVR study, have demonstrated that frailty is among the strongest independent predictors of adverse outcomes after TAVI, often outperforming conventional comorbidity-based risk scores. The absence of frailty from our score is a meaningful limitation because frailty may be discordant with the cumulative burden of individual comorbidities: a patient with few comorbidities but significant frailty may have worse

outcomes than a patient with multiple comorbidities but preserved physiological reserve. Consequently, our score may systematically underestimate risk in frail patients with relatively few CHA₂DS₂-VASc components and overestimate risk in robust patients with multiple comorbidities. Furthermore, COPD, which we have added as a component, may itself be a partial surrogate for certain frailty domains, but it does not capture nutritional status, mobility, cognitive impairment, or exhaustion. Future prospective studies should investigate whether combining the COPD-R₂CHA₂DS₂-VA score with a validated frailty instrument, such as the Essential Frailty Toolset (EFT), Clinical Frailty Scale (CFS), Fried Frailty Criteria, or the Hospital Frailty Risk Score, provides incremental discriminative value and improves net reclassification. Until such studies are performed, the score should be used with particular caution in very elderly (aged ≥ 85 years) or obviously frail patients.

Eleventh, the absence of direct comparison with guideline-recommended surgical risk scores (STS-PROM and EuroSCORE II) is a major limitation. These scores are embedded in current clinical practice guidelines (ACC/AHA 2020 and ESC/EACTS 2021) and are routinely used by multidisciplinary heart teams for procedural risk stratification and treatment decision-making. Without a head-to-head comparison within the same cohort, the incremental prognostic value of the COPD-R₂CHA₂DS₂-VA score relative to these established instruments remains entirely unknown. It is possible, indeed plausible, that STS-PROM or EuroSCORE II achieves similar or superior discriminative performance for one-year mortality in our cohort, which would substantially diminish the clinical utility of our proposed score. Furthermore, direct comparison would permit assessment of net reclassification improvement (NRI), integrated discrimination improvement (IDI), and decision curve analysis, all of which are essential for determining whether adding COPD and graded renal strata meaningfully improves clinical decision-making beyond current standards. The absence of these analyses means that we cannot claim any incremental value over existing tools. We strongly recommend that external validation studies include prospective collection of STS-PROM and EuroSCORE II components to enable such comparisons. Until these analyses are performed, the COPD-R₂CHA₂DS₂-VA score should be regarded strictly as a hypothesis-generating tool that is complementary to, rather than a replacement for, established surgical risk scores.

Conclusion

In conclusion, the COPD-R₂CHA₂DS₂-VA score, a prespecified clinical tool integrating graded renal dysfunction and COPD, demonstrates encouraging discriminative ability for one-year all-cause mortality

after TAVI in this single-center development cohort (apparent AUC 0.946), with negligible optimism on internal validation. The addition of COPD provides a statistically significant, though clinically modest, incremental improvement over the R₂CHA₂DS₂-VA score for mortality (Δ AUC + 0.033, $p = 0.0001$), but does not meaningfully enhance MACE discrimination (Δ AUC + 0.001, $p = 0.853$). The score's simplicity and reliance on routinely available clinical and laboratory data are appealing features for a bedside tool. However, the high apparent AUC likely reflects spectrum effects from the elevated comorbidity burden in our cohort and the single-center design. Moreover, the absence of frailty metrics and of direct comparison with guideline-recommended surgical risk scores (STS-PROM, EuroSCORE II) are major limitations that preclude any claim of clinical utility at this stage. External validation in large, prospective, multicenter cohorts with diverse geographic and ethnic representation is mandatory before any implementation in clinical practice. Until such validation is available, this score should be regarded strictly as a development-phase, hypothesis-generating tool, not as a replacement for STS-PROM or EuroSCORE II, and not for clinical decision-making. Future studies should also evaluate the incremental value of adding objective frailty measures to the score, incorporate cause-specific mortality adjudication to validate the hypothesis that COPD exerts its prognostic impact primarily through non-cardiovascular pathways, and perform head-to-head comparisons with established surgical risk scores using decision curve analysis.

Abbreviations

AKI	Acute Kidney Injury
AS	Aortic Stenosis
AUC	Area Under the Curve
CABG	Coronary Artery Bypass Grafting
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COPD	Chronic Obstructive Pulmonary Disease
eGFR	Estimated Glomerular Filtration Rate
HDL	High-Density Lipoprotein
IQR	Interquartile Range
LDL	Low-Density Lipoprotein
LMR	Lymphocyte-to-Monocyte Ratio
LV	Left Ventricular
MACE	Major Adverse Cardiovascular Events
NLR	Neutrophil-to-Lymphocyte Ratio
OR	Odds Ratio
PAD	Peripheral Artery Disease
ROC	Receiver Operating Characteristic
SAVR	Surgical Aortic Valve Replacement
SD	Standard Deviation
SPAP	Systolic Pulmonary Artery Pressure
TAVI	Transcatheter Aortic Valve Implantation
THV	Transcatheter Heart Valve
TIA	Transient Ischemic Attack
VARC-3	Valve Academic Research Consortium-3
VIV-TAVI	Valve-in-Valve Transcatheter Aortic Valve Implantation

Supplementary Information

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Supplementary Material 1.

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Artificial intelligence statement

Artificial intelligence-assisted technology was used solely to improve the readability and language of the manuscript, including the correction of grammar, spelling, punctuation, and stylistic issues in text originally written by the authors. No artificial intelligence tools were used for the generation of scientific content, data analysis, interpretation of results, or conclusions. The authors reviewed and edited the output as necessary and take full responsibility for the final content of the manuscript, confirming that it accurately reflects their original work and intellectual contributions.

Authors' contributions

Conceptualization: F.B., M.K.S., M.A.; Methodology: F.B., M.K.S., M.A., A.Y.; Software: M.K.S.; Validation: F.B., M.K.S., M.A., A.Y., M.Y., O.O.S.; Formal analysis: F.B., M.K.S.; Investigation: F.B., M.K.S., M.A., A.Y., M.Y., O.O.S., M.U., H.I.K., B.O., E.K., H.C., M.Y., E.F.O., H.C.; Resources: F.B., M.A., A.Y., M.Y., O.O.S.; Data curation: M.U., H.I.K., B.O., E.K., H.C., M.Y., E.F.O., H.C.; Writing - original draft: F.B., M.K.S.; Writing - review & editing: F.B., M.K.S., M.A., A.Y., M.Y., O.O.S.; Visualization: F.B., M.K.S.; Supervision: F.B., M.K.S., M.A.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The ethical approval for this retrospective analysis was obtained from the Samsun University Non-Interventional Clinical Research Ethics Committee (Approval number: 2025/22/8, Date: 12.11.2025). The study conforms to the ethical standards of the Declaration of Helsinki, the Turkish Regulation on Non-Interventional Clinical Research, and the Law on the Protection of Personal Data. All data extracted from clinical records were irreversibly anonymized prior to analysis, with all direct and indirect identifiers removed. Consequently, the ethics committee formally waived the requirement for obtaining written informed consent from participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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