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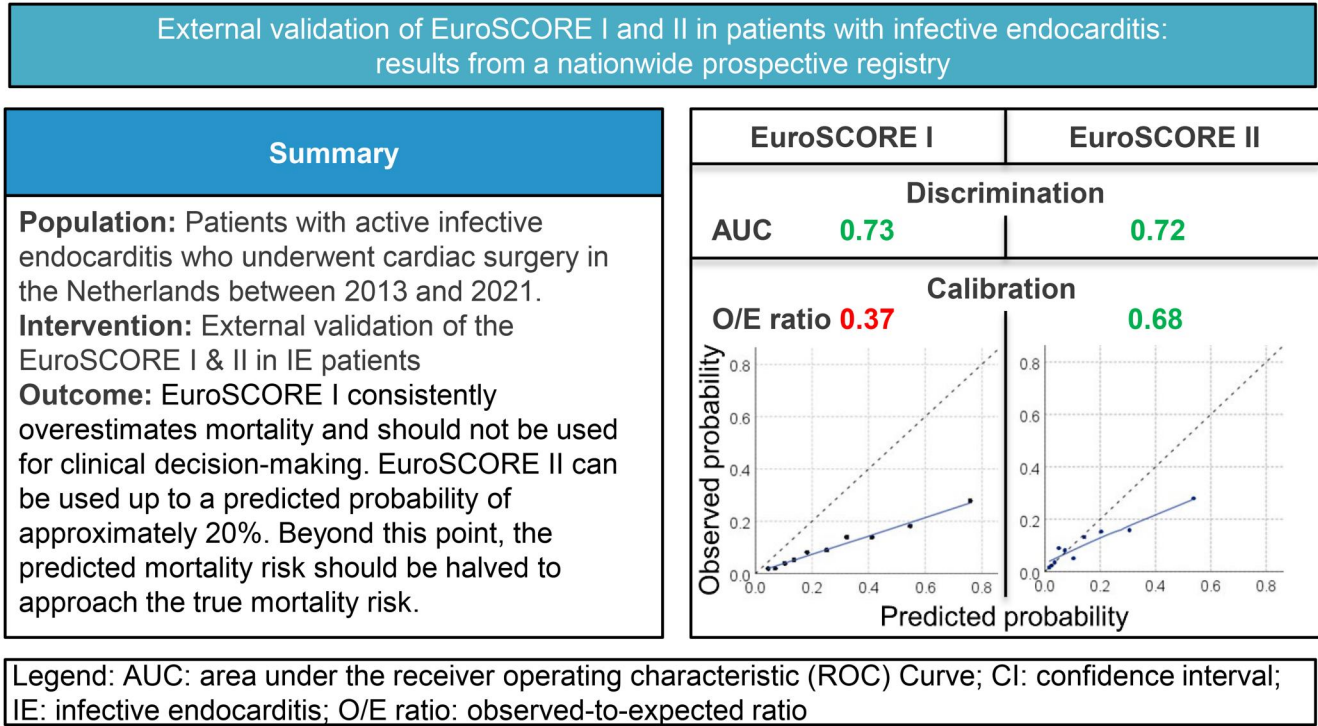
External validation of EuroSCORE I and II in patients with infective endocarditis: results from a nationwide prospective registry

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Abstract

OBJECTIVES: The primary objective was to externally validate EuroSCORE I and II in surgically treated endocarditis patients. The secondary objective was to assess the predictive performance of both models across sex, redo surgery, age, and urgency.

METHODS: Data were retrieved from the Netherlands Heart Registration. All patients with infective endocarditis who underwent cardiac surgery between 2013 and 2021 were included. Predictive performance was assessed by discrimination (area under the curve), calibration (calibration-in-the-large and calibration plots), and a decision curve analysis.

RESULTS: Two thousand five hundred and sixty-nine cases were included. Overall postoperative 30-day mortality was 10.2%. The area under the curve was 0.73 for EuroSCORE I and 0.72 for EuroSCORE II. Both models overpredict postoperative 30-day mortality, with observed-to-expected ratios of 0.37 and 0.69. EuroSCORE I overpredicts mortality across the full range, whereas EuroSCORE II overpredicts mortality only above a 20% predicted probability. We observed no significant differences in predictive performance across sex, redo surgery, or age. Discriminative capacity of EuroSCORE II was poor in emergency surgeries.

CONCLUSIONS: Both EuroSCORE models demonstrate acceptable discriminative capacity in IE patients. EuroSCORE I consistently overestimates mortality and should not be utilized in endocarditis patients. EuroSCORE II can be used in IE patients up to a predicted probability of approximately 20%, regardless of sex, redo surgery, or age. Beyond this point, the predicted mortality risk should be halved to approach the true mortality risk. EuroSCORE II should not be used for risk prediction in emergency endocarditis surgeries and patients should not be withheld from indicated surgical treatment solely based on high EuroSCOREs.

Keywords: Infective endocarditis • Cardiac surgery • Risk prediction

ABBREVIATIONS

18F-FDG PET/CT	¹⁸ Fluorodesoxyglucose positron emission tomography/computed tomography
AUC	Area under the curve
CCS IV	Canadian Cardiovascular Society Angina Grade IV
CI	Confidence interval
CTA	Computed tomography angiography
eGFR	Estimated glomerular filtration rate
EuroSCORE	European System for Cardiac Operative Risk Evaluation
IE	Infective endocarditis
IQR	Interquartile range
NHR	Netherlands Heart Registration
NYHA	New York Heart Association
O/E ratio	Observed-to-expected ratio
ROC	Receiver operating characteristic
STS	Society of Thoracic Surgeons
TRIPOD	Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis

INTRODUCTION

Infective endocarditis (IE) carries substantial morbidity and mortality risk, and cardiac surgery is required in 20–50% of cases [1, 2]. Yet, not all patients qualify for cardiac surgery because of poor physical performance [3]. Subsequently, clinicians are confronted with challenging risk assessment and indicated surgery is often denied to patients with haemodynamic instability, sepsis, heart failure or stroke. However, not performing indicated surgical treatment significantly increases the mortality risk [1, 3].

The European System for Cardiac Operative Risk Evaluation (EuroSCORE) I and II are widely adopted to predict postoperative 30-day mortality [4, 5], and surgical treatment is often denied to patients with high-risk scores. Predictor variables of EuroSCORE I and II are reported in [Supplementary Material, S1](#). Active endocarditis is an individual predictor in both EuroSCORE models, which suggests both models can be applied to this patient population. However, only 497 IE patients (2.2%) were included in the development cohort [5]. Therefore, the applicability of these models to IE patients remains questionable. Previous studies have

sought to externally validate both EuroSCORE models in IE patients, with contradicting results. Some studies indicate overprediction of mortality in both models, while others suggest underprediction. A possible explanation may lie in the small sample sizes used in these validation studies [6–15].

Therefore, the aim of this study is to externally validate the EuroSCORE I and II in IE patients, based on a large nationwide prospective registry. Moreover, the performance of both models across sex, redo surgery, age, and urgency of surgery will be assessed.

PATIENTS AND METHODS

Ethical statement

This study was evaluated and approved by the Medical Ethics Committee Leiden the Hague Delft (reference number N22.053), which issued a waiver for informed consent since this study uses de-identified data only.

Study design

This study was reported in line with the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement [16]. Data were retrieved from the Netherlands Heart Registration (NHR) [17]. The NHR is a national prospective registry that contributes to maintenance, transparency, and quality improvement in cardiac care in the Netherlands. As part of the quality policies of the Dutch Society of Cardiology and Dutch Association of Cardiothoracic Surgery, a subset of patient characteristics, procedural data and outcome variables are mandatory to register for each intervention. Since 2013, EuroSCORE I and II have been registered in the NHR. However, initially not all individual predictor variables were mandatory to supply.

For this study, we performed a complete-case analysis of all patients with active IE who underwent cardiac surgery in the Netherlands between 2013 and 2021. Cases were excluded if 1) EuroSCORE I and/or II were missing or 2) the postoperative follow-up was less than 30 days for patients still alive at the end of follow-up. Multiple imputation of missing data was not performed. Predictive performance was assessed by discrimination, calibration and a decision curve analysis. Discrimination was assessed by calculating the area under the curve (AUC) of the

receiver operating characteristic (ROC) curves. Calibration was assessed by calibration-in-the-large (average observed risk versus average expected risk (O/E ratio)) and calibration plots. A perfect calibration slope was added as a reference line. A decision curve analysis was performed to assess the clinical utility of EuroSCORE I and II in surgically treated IE patients. Moreover, the predictive performance of the EuroSCORE I and II was assessed across different age groups (<70 years, 60–70 years, >70 years), sex, redo surgery, and the urgency of procedures (for definitions see [Supplementary Material, S2](#)). The predictive performance of urgency was only assessed for EuroSCORE II as this predictor was not included in EuroSCORE I.

Statistical analyses

Analyses were performed in IBM SPSS statistics, version 27 and R studio, version 4.2.3. Normally distributed variables were reported as mean (standard deviation (SD)) and non-normally distributed variables are displayed as median (interquartile range (IQR)). Baseline characteristics were displayed as a percentage of the total cohort, in which missing values were excluded from the calculation. AUC differences across subgroups were assessed using DeLong's tests. To assess differences in categorical variables, chi-squared tests were performed. For assessing differences in continuous data, independent 2-tailed Student's *t*-tests and Mann-Whitney *U* tests were performed for normally and non-normally distributed variables. To compare mortality across age groups and urgencies, logistic regression analyses were performed.

RESULTS

Between 2013 and 2021, 2927 patients underwent cardiac surgery for IE. A total of 334 cases were excluded for missing EuroSCOREs, and 24 cases were lost to follow-up. In total, 2569 cases were eligible for analysis (Fig. 1). The median age was 64.0 years (IQR 53.0–71.0), and 76.1% were male. 37.7% of patients had previous cardiac surgery of which 84.0% had previous valve surgery. The median EuroSCORE I and II were 20.9 (IQR 10.2–40.9) and 8.8 (IQR 3.6–20.5). Baseline characteristics are presented in Table 1. Missing baseline characteristics are presented in [Supplementary Material, S3](#).

Overall, the mean postoperative 30-day mortality was 10.2% ($n = 262$). The mean mortality was significantly higher in women

compared to men (14.5% vs 8.8%, $P < 0.001$) and in redo surgery compared to index surgery (13.2% vs 8.4%, $P < 0.001$). Moreover, we observed a significant increase in 30-day mortality rates with increasing age (<60 years, 7.5%; 60–70 years, 10.1%; >70 years 14.0%, odds ratio 1.41, 95% CI 1.20–1.66, $P < 0.001$) and urgency (elective 5.1%; urgent 8.9%; emergency 18.3%; salvage 32.4%; odds ratio 1.08, 95% CI 1.06–1.10, $P < 0.001$).

In the total cohort, both EuroSCORE I and II showed acceptable discriminative performance, with AUCs of 0.73 (95% CI 0.70–0.76) and 0.72 (0.69–0.76) (Fig. 2). There was no statistical difference in AUC between EuroSCORE I and II (AUC difference 0.01, 95% CI -0.20 to 0.22 , $P = 0.45$). Calibration-in-the-large showed an O/E ratio of 0.37 (95% CI 0.21–0.55) for EuroSCORE I and an O/E ratio of 0.68 (95% CI 0.43–0.87) for EuroSCORE II (Fig. 3). The decision curve analysis suggested that the application of EuroSCORE I is beneficial up to a 15% predicted probability, while the application of EuroSCORE II remains beneficial up to a predicted probability of approximately 20% ([Supplementary Material, Fig. S1](#)). Up to a predicted probability of 20%, EuroSCORE II demonstrated excellent calibration-in-the-large with an O/E ratio of 0.92 (95% CI 0.57–0.99).

Performance of euroscore I across sex, redo surgery, and age

Stratified by sex, EuroSCORE I displayed a lower discriminative capacity in females in comparison to males, but this difference was not statistically significant (AUC difference: 0.04, 95% CI -0.03 to 0.11 , $P = 0.26$). In addition, EuroSCORE I was slightly better calibrated in females, but still overestimated mortality in general. The discriminative capacity of EuroSCORE I was slightly lower in redo surgery in comparison to index surgery; however, this difference was not statistically significant (AUC difference 0.03, 95% CI -0.03 to 0.09 , $P = 0.32$). EuroSCORE I overestimated mortality regardless of index or redo surgery, but additional overestimation was seen in index surgery with high predicted probabilities above approximately 30%. We observed a trend towards lower discriminative capacity for EuroSCORE I with increasing age. However, there was only a statistical difference in AUC between patients < 60 years and > 70 years (AUC difference 0.08, 95% CI 0.00–0.17, $P = 0.045$). Calibration-in-the-large as well as the calibration slope generally decreased with increasing age in EuroSCORE I. However, absolute differences were small.

Performance of euroscore II across sex, redo surgery, age, and urgency

Stratified by sex, EuroSCORE II demonstrated a lower discriminative capacity in females than in males (AUC difference: 0.03, 95% CI -0.04 to 0.09 , $P = 0.44$). EuroSCORE II was better calibrated in females and demonstrated an O/E ratio of 0.89 (95% CI 0.68–0.98), with a calibration slope of 0.51 and intercept at 0.06. In EuroSCORE II, AUCs were similar across index and redo surgeries but index surgery displayed overall better calibration [E/O ratio 0.89 (95% CI 0.60–0.99) versus E/O ratio 0.55 (95% CI 0.35–0.73)]. We observed a trend towards lower discriminative capacity with increasing age; however, differences were not statistically significant. Calibration was best for EuroSCORE II in patients < 60 years with an E/O ratio of 0.71 (95% CI 0.42–0.91), a calibration slope of 0.55 and the intercept at 0.018. When analyzing the

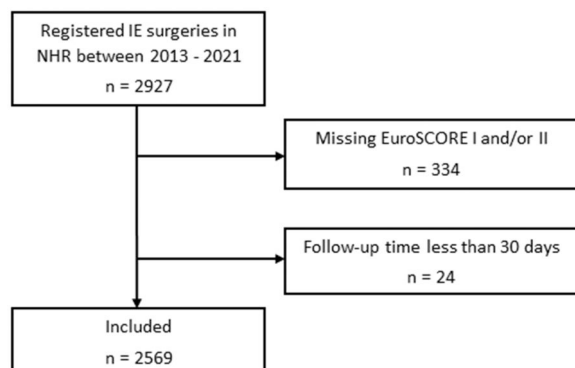


Figure 1: Flowchart of patient inclusion from NHR (Netherlands Heart Registration). IE: infective endocarditis.

Table 1: Baseline characteristics of the validation cohort

N = 2569	
Age, years, median (IQR)	64 (53–71)
Male sex, n (%)	1956 (76.1)
Body mass index, kg/m ² , mean (SD)	26.1 (13.0)
EuroSCORE I, median (IQR)	20.9 (10.2–40.9)
EuroSCORE II, median (IQR)	8.8 (3.6–20.5)
Chronic lung disease, n (%)	265 (10.3)
Extracardiac arteriopathy, n (%)	225 (8.8)
Previous stroke, n (%)	382 (14.9)
Neurological dysfunction, n (%)	253 (9.8)
Poor mobility, n (%)	263 (10.2)
Previous cardiac surgery, n (%)	968 (37.7)
Previous valve surgery, n (%)	813 (84.0)
Creatinine > 200 µmol/l, n (%)	215 (8.4)
eGFR, ml/min/1.73 m ² , mean (SD)	70.9 (32.4)
normal (eGFR > 85 ml/min/1.73 m ²), n (%)	792 (30.8)
moderate (eGFR 50–85 ml/min/1.73 m ²), n (%)	1088 (42.4)
severe (eGFR < 50 ml/min/1.73 m ²), n (%)	689 (26.8)
Dialysis, n (%)	71 (2.8)
Diabetes, n (%)	378 (14.9)
On insulin, n (%)	167 (44.2)
Critical preoperative state, n (%)	395 (15.4)
Unstable angina, n (%)	27 (1.1)
CCS IV, n (%)	73 (2.9)
Left ventricular function	
Good (LVEF > 50%), n (%)	1759 (68.5)
Moderate (LVEF 31–50%), n (%)	714 (27.8)
Poor (LVEF 21–30%), n (%)	78 (3.0)
Very poor (LVEF ≤ 20 %), n (%)	18 (0.7)
Recent myocardial infarction, n (%)	77 (3.0)
Pulmonary hypertension	
Moderate (PA systolic pressure 31–55 mmHg), n (%)	367 (14.3)
Severe (PA systolic pressure > 55 mmHg), n (%)	106 (4.1)
Functional class	
NYHA I, n (%)	542 (21.1)
NYHA II, n (%)	721 (28.1)
NYHA III, n (%)	833 (32.4)
NYHA IV, n (%)	383 (14.9)
Weight of the intervention	
Isolated CABG	NA
Single non-CABG, n (%)	1405 (54.7)
Two procedures, n (%)	834 (32.5)
Three or more procedures, n (%)	330 (12.8)
Urgency	
Elective, n (%)	331 (12.9)
Urgent, n (%)	1796 (69.9)
Emergency, n (%)	405 (15.8)
Salvage, n (%)	37 (1.4)

CCS IV: Canadian Cardiovascular Society Angina Grade IV; eGFR: estimated glomerular filtration rate; IQR: interquartile range; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PA: pulmonary artery; SD: standard deviation.

discriminative capacity across different levels of urgency, the highest AUC was observed in elective operations (0.77, 95% CI 0.69–0.86). This group consisted of 331 patients. From elective to emergency surgeries (defined as procedures within 24 hours), AUCs dropped with increasing urgency, with a statistically significant AUC difference between elective and emergency surgery (AUC difference 0.14, 95% CI 0.03–0.24, $P = 0.01$). Salvage operations were performed in 37 patients and displayed an AUC of 0.76 (0.60–0.92). Regarding calibration, the best O/E ratio was observed in emergency surgery (0.84, 95% CI 0.64–0.95). The best calibration slope was observed in salvage surgeries (0.816), but this group demonstrated poor calibration-in-the-large [O/E ratio

0.62 (95% CI 0.49–0.74)]. ROC curves and calibration plots for the subgroup analyses are presented in Figs 4 and 5.

DISCUSSION

This nationwide cohort study externally validated EuroSCORE I and II in 2569 IE patients; this is the largest validation study to date. Both EuroSCORE I and II had acceptable discriminative capacity in IE patients. However, both models overestimate 30-day mortality after IE surgery. EuroSCORE I overestimated mortality across the full range while EuroSCORE II only overestimated above a predicted probability of approximately 20%.

While previous validation studies indicate that both EuroSCORE models are less reliable in patients with high predicted probabilities, the performance of EuroSCORE models in IE patients has not been investigated on a large scale [18, 19]. Although it was expected that EuroSCORE II would outperform EuroSCORE I, given that it is the updated model [5], much smaller previous external validation studies have shown inconsistent performance of both EuroSCORE I and II in IE patients [6–15]. For instance, in the most recent external validation study, EuroSCORE I tended to overpredict mortality, while EuroSCORE II tended to underpredict it [15]. This validation study included 552 and 336 patients from 2 hospitals in France. Although both hospitals generally reported the same performance of EuroSCORE I and II in IE patients, calibration plots as well as AUCs differed substantially between the 2 hospitals. In another recent external validation study including 142 patients, EuroSCORE II consistently overestimated 30-day mortality, aligning with our results [6].

We hypothesize that differences in baseline characteristics of IE-specific variables, patient selection for cardiac surgery, and small sample sizes contribute to the observed difference in predictive performance of the EuroSCORE models in these validation studies. For example, there is wide variety in the incidence of the virulent microorganism *Staphylococcus aureus* in previous external validation studies. Although the presence of *S. aureus* or other IE-specific variables predict postoperative mortality, they do not influence the predicted probability provided by the EuroSCORE [20]. Consequently, variance in IE-specific variables may contribute to discrepancies between predicted and observed outcomes when externally validating the EuroSCORE models in IE patients.

Several IE-specific risk models have been developed over the last few years [21–25]. However, none have been adopted in the European practice due to the small sample sizes and inadequate performance in external validation studies [6–15, 26]. Therefore, we suggest improving and externally validating well-established prediction models, such as the EuroSCORE II, to better fit IE patients, rather than constructing new prediction models. This approach has already been taken in developing the Society of Thoracic Surgeons (STS) IE risk score and it is reported that the STS IE offers improved predicting performance over both the original STS score and EuroSCORE models [27,28]. However, other studies report contradictory findings, indicating that the STS IE was outperformed by the original STS score and the EuroSCORE models [6, 7]. We believe that the inconsistent performance of the STS IE, despite being a dedicated IE model, is due to its lack of IE-specific variables. Given that the EuroSCORE II is well established in the European practice and the STS (IE) does not seem to offer superior performance, we recommend

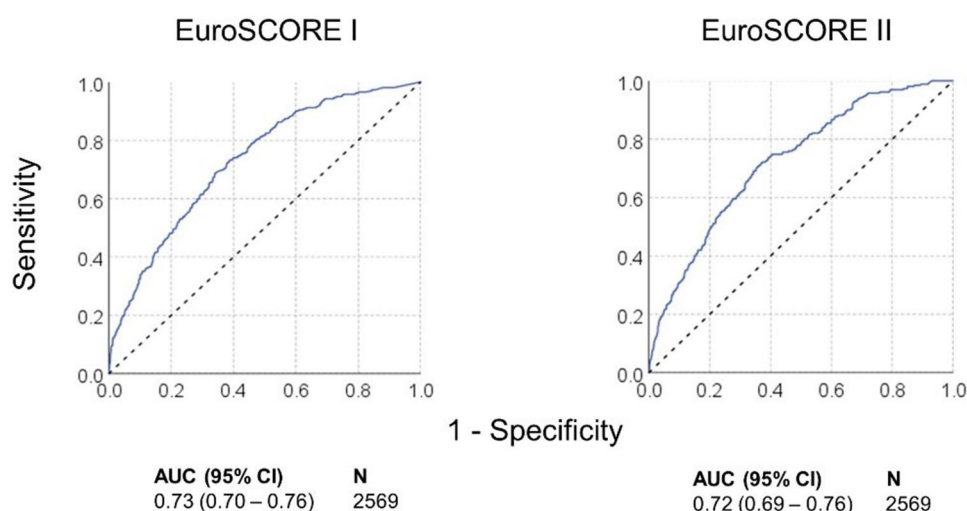


Figure 2: Receiving operating characteristic (ROC) curve of EuroSCORE I and II for the total cohort. AUC: area under the curve; CI: confidence interval; N: sample size.

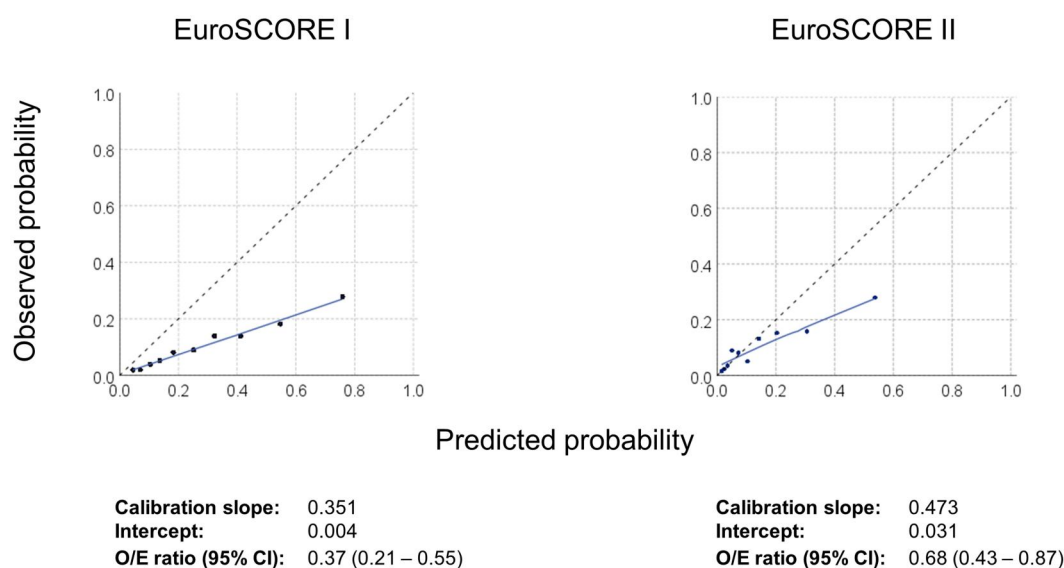


Figure 3: Calibration plots for EuroSCORE I and II for the total cohort. CI: confidence interval; N: sample size; O/E ratio: observed-to-expected ratio.

continuing the use of EuroSCORE II up to a predicted probability of approximately 20%, based on its adequate performance demonstrated in the current study. In addition, we advocate to include IE specific variables in the EuroSCORE II to enhance its predictive performance. IE-specific variables might include *S. aureus* infection, previous peripheral embolization, presence of periannular extension and the duration of preoperative antibiotic therapy.

In our subgroup analyses, we observed no significant differences in predictive performance of EuroSCORE I and II across sex, redo surgery or age. Nevertheless, we observed a trend to lower discriminative capacity of EuroSCORE I and II in females than in males. We hypothesize that, because our cohort was predominantly male (76.1%), the AUC estimation may have been less stable for the smaller female sample size (23.9%) making the female population more susceptible to differences in baseline characteristics. In line with previous research, postoperative 30-day mortality rates were significantly higher in females than in males, possibly due to increased frailty, more severe IE presentations

and more virulent causative microorganisms [1, 29]. However, data on sex differences in IE are limited and more research is needed. With increasing age, we observed a gradual decrease in AUC. This decrease may be attributed to the heterogeneity in the physical condition of the elderly, making it more difficult to accurately predict postoperative mortality.

In our cohort, the majority of patients underwent urgent surgery (69.9%), which is defined as procedures performed during the current hospital admission, but not within 24 hours. We hypothesize that the inherent prolonged hospital admission times of IE patients are responsible for this overrepresentation. The heterogeneity in preoperative hospital admission times, ranging from just 2 days until many weeks, complicates the interpretation and comparison of results with other external validation studies. The calibration slope of EuroSCORE II improved across urgency. However, sample sizes for emergency and salvage operations were very small. Therefore, we discourage clinical decision-making with EuroSCORE II for emergent IE surgeries.

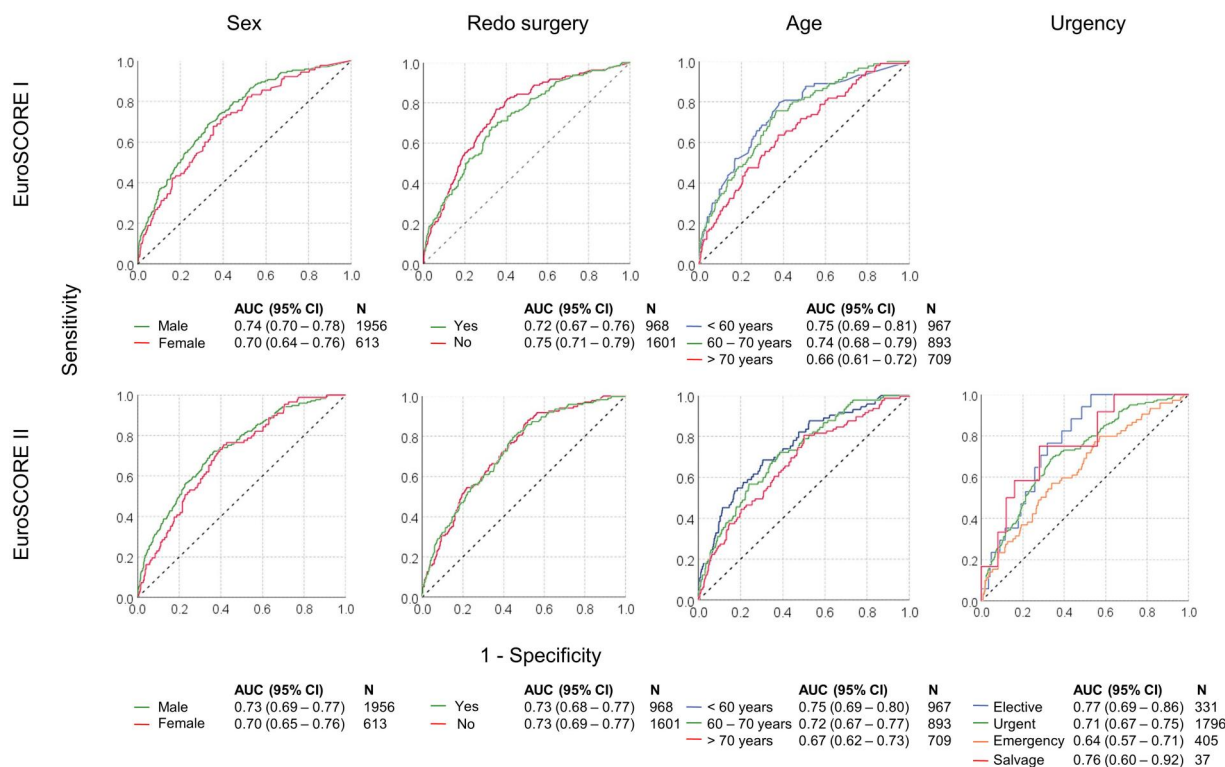


Figure 4: Receiving operating characteristic (ROC) curve of EuroSCORE I and II across sex, redo surgery, age, and urgency. AUC: area under the curve; CI: confidence interval; N: sample size.

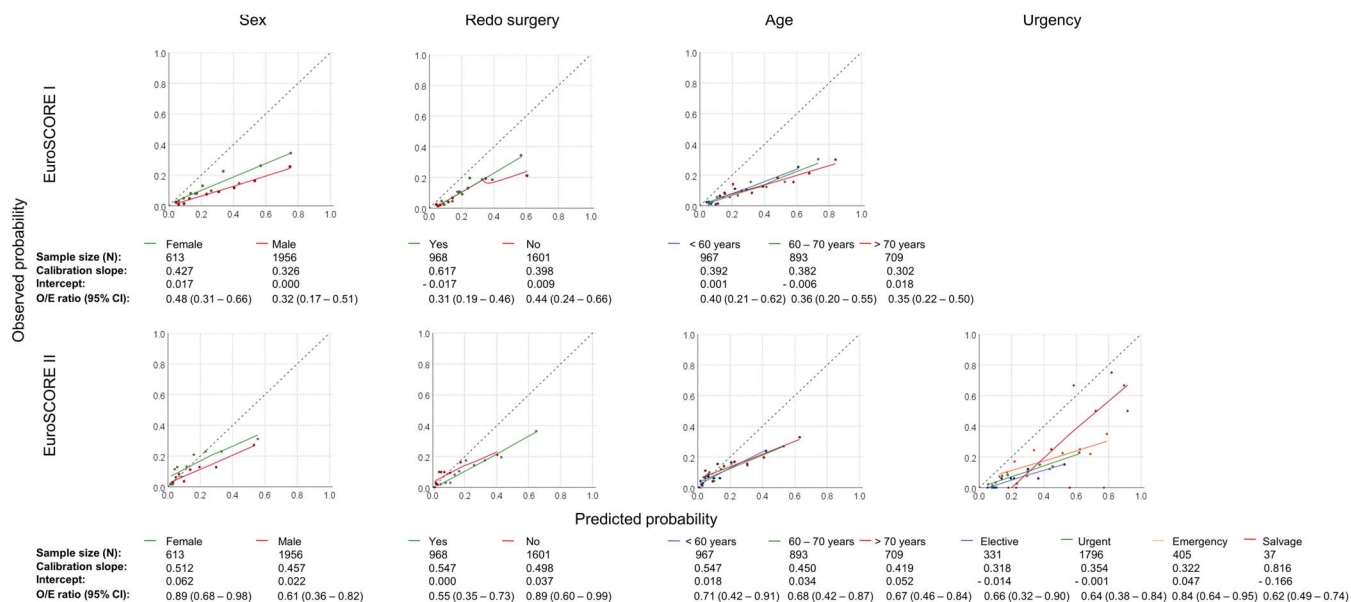


Figure 5: Calibration plots for EuroSCORE I and II across sex, redo surgery, age, and urgency. CI: confidence interval; N: sample size; O/E ratio: observed-expected ratio.

Strengths and limitations

The main strength of this study is the comprehensiveness of the prospectively collected data provided by the NHR. For 2569 patients with confirmed IE, both EuroSCORE I and II as well as the 30-day mortality rates were accurately collected. Considering that IE patients were underrepresented in the

development cohort of EuroSCORE models [5], we believe our study with 2569 confirmed IE patients provides a distinctive insight into the performance of both models in this specific patient population. However, we must keep in mind that underlying demographic differences as well as differences in patient selection between the multinational developmental cohort and the Dutch nationwide cohort used in this external validation

study may account for differences in study results. We observed a postoperative 30-day mortality rate of 10.2%, whereas other cohort studies report rates of up to 26% [30]. In terms, leading to differences in calibration.

The first limitation of our study is that IE-specific variables are not registered in the NHR, prohibiting comparison to previous validation studies. Secondly, this study did not analyze temporal trends in the predictive performance of the EuroSCORE models. Since the data collection for EuroSCORE II in 2010, advancements in cardiac imaging modalities such as ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) and computed tomography angiography (CTA), combined with earlier surgical treatment and implementation of multidisciplinary endocarditis teams, have resulted in lower postoperative mortality rates for IE patients [3]. Consequently, calibration of the EuroSCORE models in IE patients decreases as therapeutic strategies improve. This stresses the need for a new EuroSCORE model which not only includes more IE patients in the development cohort, but also consists of IE patients that were treated according to the most recent endocarditis guidelines. Lastly, we want to emphasize that because our data solely consisted of surgically treated patients, our decision curve analysis reflects how well the EuroSCORE models predict postoperative 30-day mortality in this group but does not reflect whether these models are useful in determining who should or should not undergo surgery.

CONCLUSION

Both EuroSCORE models demonstrate acceptable discriminative capacity in IE patients. EuroSCORE I consistently overestimates mortality and should not be applied to IE patients. EuroSCORE II can be used in IE patients, regardless of sex, redo surgery or age, up to a predicted probability of approximately 20%. Beyond this point, the predicted mortality risk should be halved to approach the true mortality risk. The EuroSCORE II should not be used for risk prediction in emergency surgeries and reliance on EuroSCORE models may lead to disadvantageous decision-making if patients with a high-predicted probability are withheld from indicated surgical treatment.

SUPPLEMENTARY MATERIAL

[Supplementary material](#) is available at *EJCTS* online.

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COLLABORATORS

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DATA AVAILABILITY

The data underlying this article will be shared on reasonable request to the corresponding author and the Netherlands Heart Registration.

Author contributions

Floris J. Heinen, MD: Conceptualization; Formal analysis; Investigation; Project administration; Visualization; Writing—original draft; Writing—review & editing. **Annelot J.L. Peijster, MD:** Investigation; Project administration; Resources; Writing—original draft. **Edouard L. Fu, PhD:** Formal analysis; Investigation; Methodology; Software; Writing—review & editing. **Otto Kamp, MD, PhD:** Investigation; Supervision; Writing—review & editing. **Steven A.J. Chamuleau, MD, PhD:** Investigation; Supervision; Writing—review & editing. **Marco C. Post, MD, PhD:** Investigation; Supervision; Writing—review & editing. **Michelle D. van der Stoel, MSc:** Data curation; Formal analysis; Resources; Validation; Writing—review & editing. **Mohammed-Ali Keyhan-Falsafi, MD, PhD:** Investigation; Supervision; Writing—review & editing. **Cees van Nieuwkoop, MD, PhD:** Investigation; Supervision; Writing—review & editing. **Robert J.M. Klautz, MD, PhD:** Investigation; Supervision; Writing—review & editing. **Wilco Tanis, MD, PhD:** Conceptualization; Investigation; Supervision; Validation; Writing—original draft; Writing—review & editing.

Reviewer information

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